Journal of Neuroradiology 46 (2019) 25–28

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Original Article

Relationships between aneurysmal wall enhancement and conventional risk factors in patients with intracranial aneurysm: A high-resolution MRI study

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ARTICLE INFO

Article history:
Available online 30 October 2018

Keywords:
Intracranial aneurysm
Magnetic resonance imaging
Aneurysmal wall enhancement
Inflammation

ABSTRACT

Background and purpose. – Aneurysmal wall enhancement (AWE) is thought to reflect wall inflammation and is a novel imaging biomarker for intracranial aneurysm (IA) risk evaluation. However, the relationship between AWE and other conventional risk factors (e.g., size) remains unclear. The aim of this study was to investigate the relationship between AWE and other risk factors.

Material and methods. – Seventy-six consecutive patients from February 2016 to April 2017 with 88 unruptured IAs were reviewed. Patients and IAs were divided into with AWE and without AWE groups according to high-resolution magnetic resonance imaging (HRMRI) images. In addition to the patients' clinical characteristics, the features of the IAs (e.g., size and aspect ratio (AR)) were evaluated via computed tomography angiography. Multiple logistic regression analysis was used to identify the association between AWE and other risk factors. A receiver operating characteristic curve analysis was performed for the final model to obtain optimal thresholds.

Results. – IAs with an irregular shape (OR 12.544) and a high AR (OR 32.891) were associated with AWE. The threshold value of the AR was 1.05.

Conclusions. – AWE on contrast-enhanced HRMRI was correlated with IAs with an irregular shape and a high AR. AWE may be a marker of instability and even risk of rupture.

Introduction

Recently, aneurysmal wall enhancement (AWE) visualized using gadolinium enhanced high-resolution magnetic resonance imaging (HRMRI) has been reported in several studies [1–8]. The results of these studies have suggested that AWE is a novel imaging biomarker for risk evaluation and is considered to be caused by wall inflammation, vasa vasorum, increased permeability, intraaneurysmal thrombus, stagnation, or leakage of the contrast agent [1–9]. However, AWE has not been sufficiently investigated. For example, the relationships between AWE and other risk factors (e.g., aneurysm size and shape) remain unclear. However, only a few studies have focused on the relationship of AWE with other risk factors, and these works have had different results [2,3,5]. Therefore, this study was conducted to identify the relationship between AWE and other risk factors, including personal clinical factors and imaging characteristics.

Methods

This retrospective study was approved by our institutional ethics committee. Data of the patients were collected from hospital information system.

Patients

One hundred and six patients with saccular intracranial aneurysms (IAs) diagnosed by computed tomography angiography (CTA) were recruited to undergo enhanced HRMRI between February 2016 and April 2017. Exclusion criteria were as follows: children, pregnancy and patients who had contraindications for undergoing MRI and contrast agent usage; patients with a recent history of using aspirin or nonsteroidal anti-inflammatory drugs, because these drugs may reduce the degree of AWE and lead to incorrect diagnosis; patients with traumatic, fusiform, dissecting

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https://doi.org/10.1016/j.neurad.2018.09.007
0150-9861/

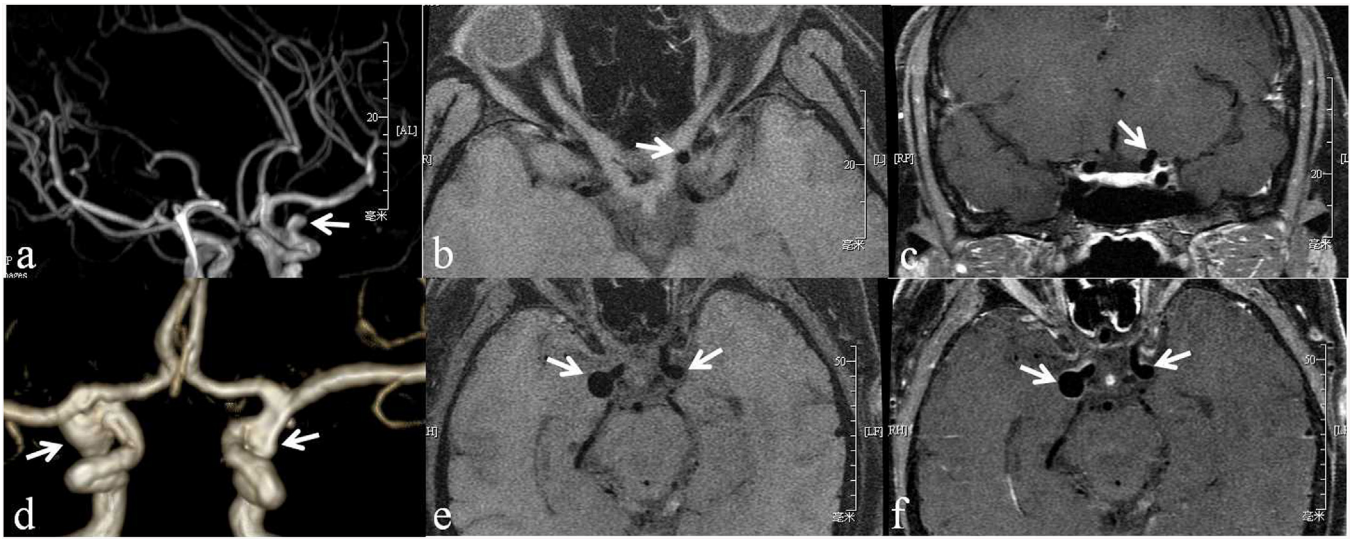

Fig. 1. MRA (first column), pre-contrast (second column), and post-contrast T1-weighted (third column) of two patients with and without aneurysmal wall enhancement. (a-c): Female, 50 years old, with a left internal carotid artery terminus unruptured aneurysm and no symptoms. (a): 3D MIP by MRA exhibits the aneurysm (arrow). Post-contrast MRI (c) shows no enhancement of the aneurysmal wall (arrows) compared with the pre-contrast image (b). (d-f): A 64-year-old female patient presented with sentinel headache due to bilateral aneurysms in the posterior communicating artery. (d): 3D VR by MRA exhibits the two aneurysms (arrow). Post-contrast MRI (f) shows entire wall enhancement (arrows) compared with the pre-contrast image (e).

and ruptured aneurysm; and patients who were unable to cooperate during the MRI examination or with poor image quality. Of note, some patients had multiple IAs, among which the ruptured one was excluded, but the unruptured ones were included. Finally, 76 patients with 88 IAs were available for analysis. The patients' clinical data (e.g., age, hypertension) were collected using their electronic medical records.

Imaging protocol and analysis

CTA

The patients initially underwent CTA on a 64-slice CT machine (GE LightSpeed VCT; GE Healthcare, Milwaukee, Wisconsin, USA). After the contrast agent (Visipaque 320; GE Healthcare) was injected into the antecubital vein at a rate of 4–4.5 mL/s, three-dimensional (3D) volume-rendered (VR) images were obtained. The IA morphological indices were measured by two experienced readers, and the average value was used for subsequent statistical analyses. The readers identified the best view angle to measure the depth (the longest diameter between the neck and dome), neck width (the largest cross-sectional diameter of the aneurysm neck), maximum size (Dmax, the largest measurement in terms of maximum dome diameter or width), and the diameter of the parent artery (DP). Two secondary geometric indices, including the aspect ratio (AR, depth/neck width) and size ratio (SR, depth/DP), were also calculated. In addition, the readers also identified IA location (anterior circulation or posterior circulation), bifurcation (presence or absence) and shape (simple, lobed or irregular). These variables have been previously defined and described clearly in the literature [10,11].

MRI

MRI was performed on a 3.0T scanner (Signa HDx, GE Healthcare, Milwaukee, Wisconsin, USA) with an 8-channel head coil. First, a 3D-TOF-MRA was performed using the following parameters for the localization of subsequent scans: repetition time (TR), 25 ms; echo time (TE), 3.4 ms; flip angle, 15°; field of view (FOV), 22 × 19.8 cm; acquired matrix, 384 × 160; slice thickness, 1.2 mm; and layer spacing, 0 mm. Then, the pre- and post-contrast HRMRI were performed using a 2D black-blood T1-weighted sequence that using the following parameters: TR/TE, 580/11 ms; FOV, 16 × 16 cm; acquired matrix, 384 × 224; slice thickness, 1.2 mm; and layer spacing, 0 mm. All patients were administered a single dose (0.1 mmol/kg) of Gd-BOTPA (MultiHance; Bracco, Shanghai, China) by intravenous injection. After the contrast agent was injected, given that a single 3D T1-weighted sequence could not be obtained through the MR examination, each aneurysm scan was performed four times: axial, coronal, sagittal and axial planes. The total scan time was 25 minutes. The two readers subsequently determined whether there was an AWE on the post-contrast image, using the pre-contrast image as reference (Fig. 1). Controversial cases were resolved through discussion and consensus.

Statistical analysis

Variables are expressed as the median and interquartile range or as a percentage (%) where appropriate. The agreement between two observers for the presence of AWE was evaluated by a kappa value. Categorical data were compared using the chi-squared test and continuous data were compared using the Mann–Whitney *U*-test. All variables were entered into univariate analysis if $P \leq 0.2$. Forward multiple logistic regression was used to calculate the 95% confidence interval (CI) and odds ratio (OR) for the AWE for those features that achieved univariate statistical significance ($P \leq 0.05$). Then, a receiver operating characteristic (ROC) curve analysis was performed for the final model and the cutoff value of the variable with the best sensitivity and specificity was determined using the Youden's index. All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) and a *P*-value <0.05 was considered statistically significant.

Results

In total, 76 patients with 88 IAs were available for analysis (Table 1). Ten patients had multiple IAs (22 IAs). The mean age of the patients was 56.99 ± 9.10 years. No clinical characteristics were significantly different between patients with IAs with or without AWE.

Table 1
The clinical characteristics of patients with and without AWE.

Clinical data	Without AWE ($n=23$)	With AWE ($n=65$)	P
Male	8(34.8%)	19(29.2%)	0.610
Age (years)	57 (48,61)	59 (51.5,64)	0.213
Hypertension	7(30.4%)	31(47.7%)	0.129
Diabetes mellitus	0(0.0%)	8(12.3%)	0.105
Cerebral atherosclerosis	4(17.4%)	12(18.5%)	1.000
Current alcohol	6(26.1%)	9(13.8%)	1.000
Current smoking	5(21.7%)	12(18.5%)	0.763
Multiple aneurysms	5(21.7%)	17(26.2%)	0.784

Table 2
The morphological characteristics of aneurysms with and without AWE.

Morphologic parameters	Without AWE ($n=23$)	With AWE ($n=65$)	P
Anterior circulation	23(100.0%)	62(95.4%)	1.000
Bifurcation[a]	4(17.4%)	34(52.3%)	0.006
Irregular shape[a]	1(4.3%)	35(53.8%)	<0.001
Thrombosis	0(0%)	3(4.6%)	0.564
Neck width (mm)	3.9 (3.4, 4.9)	4.3 (3.4, 5.3)	0.467
Depth (mm)[a]	3.4 (2.3, 3.8)	4.9 (3.7, 6.55)	<0.001
Maximal Size (mm)[a]	4.4 (3.6, 5.2)	6.1 (4.7, 7.9)	<0.001
Aspect ratio[a]	0.83 (0.59, 1.00)	1.12 (0.91, 1.57)	<0.001
DP (mm)	3.6 (2.9, 4.1)	3.4 (2.7, 3.95)	0.218
Size ratio[a]	0.96 (0.62,1.2)	1.48 (1.12,2.26)	<0.001

DP, the diameter of the parent artery.
[a] Variables showing significant difference by univariate analysis ($P<0.05$).

Table 3
Binary logistic regression analysis for AWE.

Variable	Odds ratio	P	95% CI	B
AR	32.891	0.012	2.143–504.777	3.493
Irregular shape	12.544	0.021	1.461–107.730	2.529

CI: confidence intervals; B: partial regression coefficient.

Table 4
Area under the curve for aspect ratio.

Characteristics	Area	Threshold value	P	Sen (%)	Spe (%)	95% CI
Aspect ratio	0.812	1.05	<0.001	60.0	91.3	0.720–0.904

Sen: sensitivity; Spe: specificity; CI: confidence intervals; Threshold value: the cut off for the aspect ratio.

The level of agreement between the two observers for AWE was satisfactory, with κ coefficients of 0.807 ($P<0.001$). Discordances between the two observers were resolved by discussion and consensus in 7 IAs. The geometric and morphological characteristics of IAs with and without AWE are presented in Table 2. IAs located at the bifurcation, with an irregular shape, depth, maximal size, AR and SR were significantly different between IAs with and without AWE.

These variables ($P \leq 0.2$) were subsequently entered into a univariate logistic regression model. Then, variables ($P \leq 0.05$) were entered into a forward conditional multiple logistic regression model. IAs with an irregular shape (OR 12.544) and a high AR (OR 32.891) were associated with IAs with AWE (Table 3)..

ROC analysis (Fig. 2) indicated that the most reliable cutoff values of the AR to differentiate between IAs with or without AWE was 1.05, and the sensitivity and specificity were 0.60 and 0.913, respectively (Table 4).

Discussion

AWE is believed to reflect wall inflammation [1–4] and is a new imaging biomarker for risk evaluation. However, the relationships between AWE and other risk factors (e.g., aneurysm size and shape) remain unclear. In this study, we used 3T gadolinium-enhanced HRMRI to demonstrate that AWE is more frequently observed in IA with an irregular shape and a high AR.

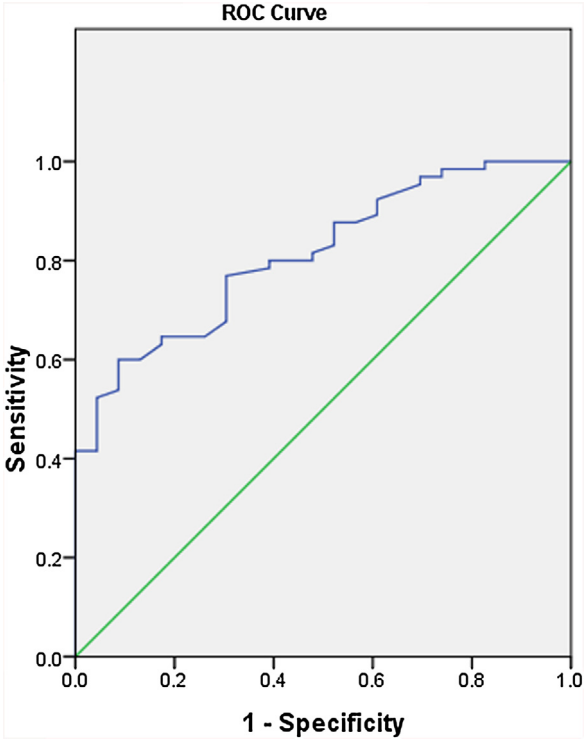

Fig. 2. The area under the receiver operating characteristic curve for the AR is 0.812 (95% confidence interval, 0.720–0.904). The cut-off point for the AR is 1.05, the sensitivity is 60.0%, and the specificity is 91.3%.

Irregular shape was defined as an aneurysm with a lobular shape or daughter sacs [10–12]. Most but not all previous retrospective studies have reported that IAs with irregular shape were associated with a higher risk of rupture [10–13]. Abboud et al. [13] investigated 420 IAs and suggested that risk of rupture might increase according to extent of morphological change. Recently, two prospective studies have indicated that irregularly shaped IAs are more likely to rupture [14,15]. The higher risk of rupture may be because the irregular shape, which leads to instability in the blood flow pattern. Our previous study showed that partial enhancement was more commonly found in the ruptured aneurysm cohort, and all of the partial enhancement was present in the irregularly shaped portion or in daughter sacs [9]. We hypothesize that AWE might be a marker of aneurysmal wall inflammation and of inflammation associated with the rupture of IAs. To this end, IAs with irregular shape may be one of the reasons of AWE.

IA size has been studied extensively as a parameter for rupture risk prediction. Traditionally, the risk of rupture of IAs is higher in larger IAs. The American Heart Association/American Stroke Association suggest that IA size should be considered as the main parameter evaluated before making treatment decisions regarding IAs [16]. Amenta et al. [17] demonstrated that a dome diameter larger than 10 mm is associated with aneurysm rupture. Kang et al. [18] demonstrated that maximum aneurysm height greater than 7 mm is associated with aneurysm rupture. Liu et al. [5] evaluated 61 unruptured IAs and demonstrated that aneurysm size was independently associated with AWE; however, they also demonstrated that some small IAs did exhibit AWE, suggesting that AWE may provide additional information regarding aneurysm instability. Although in our clinical experience ruptured IAs tend to be larger than unruptured IAs [19,20], size was not significantly dif-

ferent between the ruptured and unruptured groups, which is similar to findings from previous studies [20,21]. Recent HRMRI studies have also demonstrated no significant differences in IA size between wall enhancement and non-enhancement groups [2,3].

Most but not all previous studies have shown that IAs with a higher AR are significantly more prone to rupture [10,11,17–19]. In the present study, AR was significantly and positively correlated with AWE on contrast enhanced black-blood HRMRI. Although the depth, maximal size and SR were found to be higher in IAs with AWE, no definitive relationship was established during multivariate analysis. The reason may be that AR is related to these parameters, but the relationship to AWE is much stronger. In addition, the present data show that the threshold value for AR was 1.05, which is close to the value for risk of rupture prediction [10,11].

IAs usually occur at Willis' or arterial bifurcations, and many cases of subarachnoid hemorrhage (SAH) arise from bifurcation aneurysms [10]. In this study, bifurcation IAs were defined as lesions originating from major bifurcations [21]. A recent study showed that IAs located at bifurcations are a risk factor for rupture of small IAs [12]. According to previous studies, bifurcation areas of arteries are known to be vulnerable sites where the arterial wall is weak and associated with hemodynamic stress changes [12,22]. In this study, IAs located at bifurcations were more likely to showed AWE, whereas it exhibited no relationship upon multiple analysis.

In this study, we also investigated the relationship between thrombosis within IAs and AWE. Thrombosis was reported to be a sign of inflammation [3,23]. Although only 3 IAs were of partially thrombosis, all cases showed AWE on HRMRI in our study, which may arise from the inflammation of the IA wall from thrombosis. However, there is no significant correlation between thrombosis and AWE, a larger sample size is needed to study their relationship.

This study had several limitations. First, this study has patient recruitment bias because the data were collected from a single center and patients with larger IAs were more willing to participate, which may explain the high prevalence of AWE. Second, the data were collected from a single center, and there were a relatively small number of included subjects. Third, we did not investigate the relationship between AWE and inflammation in the aneurysm wall using histopathological analysis because of the difficulty in obtaining pathology specimens. In the future, a prospective study with a larger number of patients is necessary. In addition, the relationship between AWE and inflammation in the aneurysm wall requires confirmation in future studies.

In conclusion, our study demonstrates that AWE in contrast-enhanced HRMRI was correlated with IAs with an irregular shape and a high AR. These factors are independently associated with the risk of IA rupture, suggesting that AWE may be a marker of instability and even a risk factor for IA rupture. In clinical practice, more attention should be paid to IAs with AWE.

Funding statement

The study was supported by the Research Project of Third Military Medical University (2016YLC22).

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

The authors thank American Journal Experts (AJE) for assisting in the preparation of this paper. We thank Ru-fu Xu, professor of epidemiology of the Xinqiao hospital, Third Military Medical University for statistical advice.

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