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Comparison of radiological and clinical characteristics between blood blister-like aneurysms (BBAs) and non-blister aneurysms at the supraclinoid segment of internal carotid artery

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Abstract

Blood blister-like aneurysms (BBAs) were considered a therapeutic challenge for both microsurgeons and endovascular therapists. While a great deal of efforts had been put to refining the treatment of BBAs, the diagnostic criteria had not been established yet. In this study, we reviewed data of 43 suspicious, small (< 1 cm), broad-necked aneurysms at supraclinoid segment of internal carotid artery (ICA) in 41 patients who had been treated with microsurgery in our hospital during the past 5 years. Diagnosis of BBAs and non-blister aneurysms was based on intraoperative findings. Epidemiological, clinical, and radiological features of BBAs and non-blister aneurysms were compared. Subtypes of BBAs were also compared. Discriminant analysis was used to generate a differentiating model for BBAs. Seventeen aneurysms were diagnosed as BBAs and 26 were diagnosed as non-blister aneurysms. No significant difference regarding age, gender, association of multiple aneurysms, or location on ICA was found between the groups. Dome/neck ratio and distal angle (intersection angle of aneurysm with ICA, distal to ophthalmic artery branching site) of BBAs were smaller than those of non-blister aneurysms ($P = 0.009$ and $P = 0.002$). A discriminant function including aforementioned factors with an overall accuracy of 76.2% was yielded ($P = 0.005$). BBAs and non-blister aneurysms were difficult to differentiate by clinical and radiological features as they share many characteristics in common. Dome/neck ratio < 1 did not guarantee accurate diagnosis of BBAs. A discriminant function incorporating dome/neck ratio and degree of distal angle as factors might increase the accuracy of pre-surgical diagnosis of BBAs.

Keywords Blood blister-like aneurysms · BBAs · Non-blister aneurysms · Ophthalmic segment aneurysms · Diagnosis · Discriminant analysis · Dome/neck ratio

Introduction

Blood blister-like aneurysms (BBAs) of internal carotid artery (ICA) are a rare but treacherous entity of cerebral aneurysms with extremely thin, fragile walls and a wide, poorly defined neck, usually appearing at the non-branching segment of ICA [12, 21]. Their propensity to spontaneous rupture has led to high morbidity and mortality, raising challenges for both

surgeons and interventionalists whoever attempted to treat these lesions [1]. Recent studies have been focusing on the exploration of microsurgical and endovascular methods to determine the optimal treatment for BBAs [8, 17, 22]; however, the clinical identification of BBAs remains ambiguous.

Theoretically, the diagnosis of BBAs should be made from histopathological examinations with evidence of degenerated internal elastic lamina and abnormal adventitia [7, 15]. Nevertheless, obtaining histological samples for BBAs is not always feasible; therefore currently, the most acknowledged diagnosis of BBAs is based on intraoperative inspection, during which the extremely friable aneurysmal wall can be observed by a surgeon [16]. A growing literature of endovascular methodologies identifies BBAs by digital subtraction angiography (DSA), where features including specific localization, small dimension, hemispherical shape, and radiological dome/ratio < 1 had been adopted in the diagnosis of BBAs [5, 9, 14, 18].

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Notably, previous studies had demonstrated that not all small aneurysm locating at the non-branching site of ICA were BBAs, and that non-blister aneurysms were also found at the same segment [13]. Therefore, it is reasonable to postulate that current diagnosis based on radiology alone might not be accurate enough. More importantly, such inconsistency might lead to misinterpretations of effects achieved by different treatments. In this study, we retrospectively reviewed all aneurysms presenting with suspicious radiological features (< 1 cm, broad-based and located at non-branching sites of the ICA [6]) treated in our hospital in the past 5 years, in order to identify clinical and radiological characteristics of BBAs and formulate a possible pre-surgical diagnostic criterion for BBAs.

Methods

Clinical materials

We retrospectively reviewed medical and surgical records, and radiological imaging of suspicious small (< 1 cm), hemispherical, wide-necked aneurysms at supraclinoid segment of ICA that had been treated by microsurgery at our institute from January 2012 to August 2017. Endovascular cases were not included because the aneurysm wall could not be inspected for to confirm the diagnosis. After ruling out cases with incomplete information or ambiguous description of aneurysmal quality, 41 patients with 43 aneurysms (mean 51.33 ± 9.88 years; range 31.0 to 74.0 years) were included in this study. Diagnosis of BBAs was based on intraoperative findings of extremely fragile aneurysm wall and purple-red color of an integral, blister-like bulge. Aneurysms with comparatively firm walls were recognized as ordinary non-blister aneurysms (Fig. 1).

This study was approved by the institutional review board of Beijing Tiantan Hospital, Capital Medical University. All patients included in this study had consent with their information being used for clinical investigation anonymously.

Evaluation of patients

Modified Rankin Scale (mRS) was used to evaluate neurological status at admission and discharge. "Deterioration" was defined by a score of mRS at discharge higher than that at admission. Hunt-Hess grading system was used for the evaluation of patients with subarachnoid hemorrhage (SAH) onset.

Radiological examinations

All 41 patients received at least one kind of angiography before surgery. Thirty-two patients underwent digital subtraction angiography (2D-DSA or two-plane DSA), on that basis 29 of them had three-dimensional rotational digital subtraction angiography

(3D-DSA) reconstruction imaging. Twenty-two patients underwent computed tomography angiography (CTA). Among them, 12 patients were examined by both DSA and CTA.

Measurements of aneurysms

Measurements of aneurysms were taken from radiological examinations in order of 3D-DSA, 2D-DSA, and CTA, on the panel with best vision of aneurysm. Angle size of the apex angle and two side angles (proximal and distal to the ophthalmic artery), as well as the length of aneurysmal neck and dome, were measured as demonstrated in Fig. 2. Dome/neck ratio was calculated by the length of dome to the length of neck. In this study, 42 out of 43 aneurysms were measured except for one that did not develop on any kind of angiography, which was incidentally found next to another ruptured blister-like aneurysm during surgery.

Classification of BBAs

BBAs were categorized into four subtypes based on their configuration as described in previous literature [2, 10]: type I, minimal bulge involving part of ICA wall; type II, berry-like blister aneurysms with a sac and a large neck; type III, longitudinal blister aneurysms; and type IV, circumferential blister aneurysm involving a large portion of ICA wall.

Statistical analysis

Statistical analysis was carried out using SPSS software (v.22.0; IBM Corp., Chicago, IL, USA). Group data were compared using unpaired t test and χ^2 test as appropriate. Fisher's exact test was adopted when any value in a fourfold table was less than 5. Linear discrimination analysis was used to construct a model of predictions for blood blister-like aneurysms. A value of P less than 0.05 was considered statistically significant.

Results

Comparing clinical characteristics of blister-like aneurysms to non-blister aneurysms

A total of 43 small (diameter < 1 cm), hemispherical, broad-based aneurysms arising from the non-branching site of ICA were recruited from our database, all of which had been visually examined during microsurgery. Among them, 17 (39.5%) aneurysms of 16 patients were diagnosed as blister-like aneurysms and 26 aneurysms (60.5%) of 25 patients were diagnosed as ordinary non-blister aneurysms. Clinical characteristics of BBAs and non-blister aneurysms were compared as seen in Table 1.
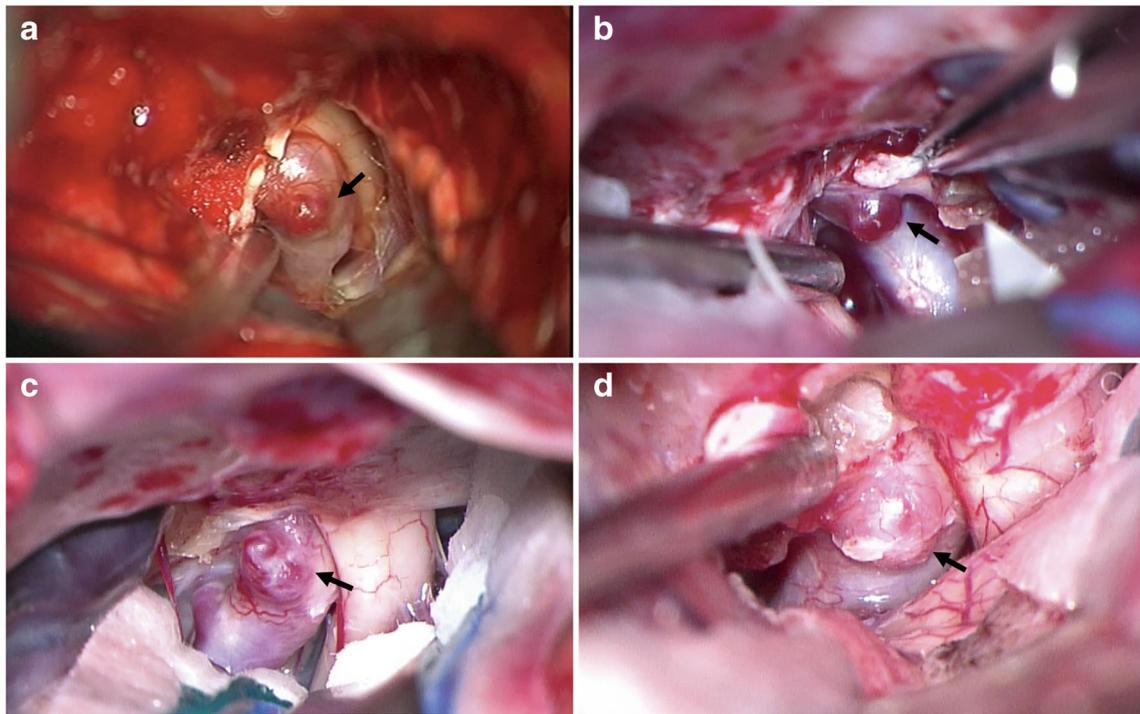
Fig. 1 Diagnosis of blister-like aneurysms (BBAs) and non-blister aneurysms based on intraoperative findings. **a**, **b** Diagnosed as BBAs based on extremely fragile aneurysmal wall; **c**, **d** Diagnosed as non-blister aneurysms as they have comparatively firm walls

Age, gender distribution, and history of hypertension were not significantly different between the two groups, though female domination was apparent in both groups. Association with multiple aneurysms was frequent in both groups (41.2 versus 38.5%, respectively) with no significant difference. Association of multiple ophthalmic artery (OA) aneurysms was not significantly different either, regardless of bilateral or unilateral multiple OA aneurysms.

Seven (41.2%) cases in the BBA group and four (15.4%) in the non-BBA group presented with SAH. BBAs presented a higher incidence of spontaneous bleeding and intraoperative rupture than non-blister aneurysms ($P = 0.058$, $P = 0.026$), but Hunt-Hess grading for SAH-onset patients was not significantly different between the two groups. Other onset symptoms in the BBA group included headache in four (23.5%) cases, dizziness in two (11.8%) cases, and ptosis in one (5.9%) case, and three (17.6%) cases were found by accident. Forty-two aneurysms were treated with direct clipping and one non-blister aneurysm was treated with wrapping. No death or postoperative re-bleeding occurred in this series. Postoperative ischemic events and deterioration rate (mRS ≥ 2 at discharge) were similar between the groups.

Comparing locations of blister-like aneurysms to non-blister aneurysms

The most common location for BBAs and non-blister aneurysms on ICA was both on the anterior wall (64.7 and 42.3%,

respectively). The second most common location was on the medial wall of ICA (29.4 and 34.6%, respectively). One (5.9%) BBA was found on the anterolateral wall. Notably, five non-blister aneurysms (19.2%) were located on the posterior wall of ICA on the posteromedial wall, but no blister-like aneurysm was found on this site ($P = 0.054$). The distribution of aneurysms on ICA was not significantly different between the two groups (Fig. 3 and Table 2). No significant difference between the two groups was detected regarding which side the aneurysms were located on, either (Table 2).

Two kinds of relationships between the ophthalmic artery and the aneurysms were noticed (Fig. 4): three (17.6%) BBAs and eight (30.7%) non-blister aneurysms were located around the bifurcation of ophthalmic artery (OA) from ICA. Fourteen (82.4%) BBAs and 18 (69.2%) non-blister aneurysms were located distal to the branching site of ophthalmic artery. No significant difference was found between the two groups (Table 2).

Comparison of radiological measurements between the two groups

We calculated the dome/neck ratio of every aneurysm based on their measurements obtained from radiological imaging, except for one aneurysm that was not found on any type of angiography. Dome/neck ratio ranged from 0.42 to 0.95 (mean 0.62 ± 0.15) in the BBA group and 0.40 to 1.21 (mean 0.76 ± 0.17) in the non-blister aneurysm group. Among 43
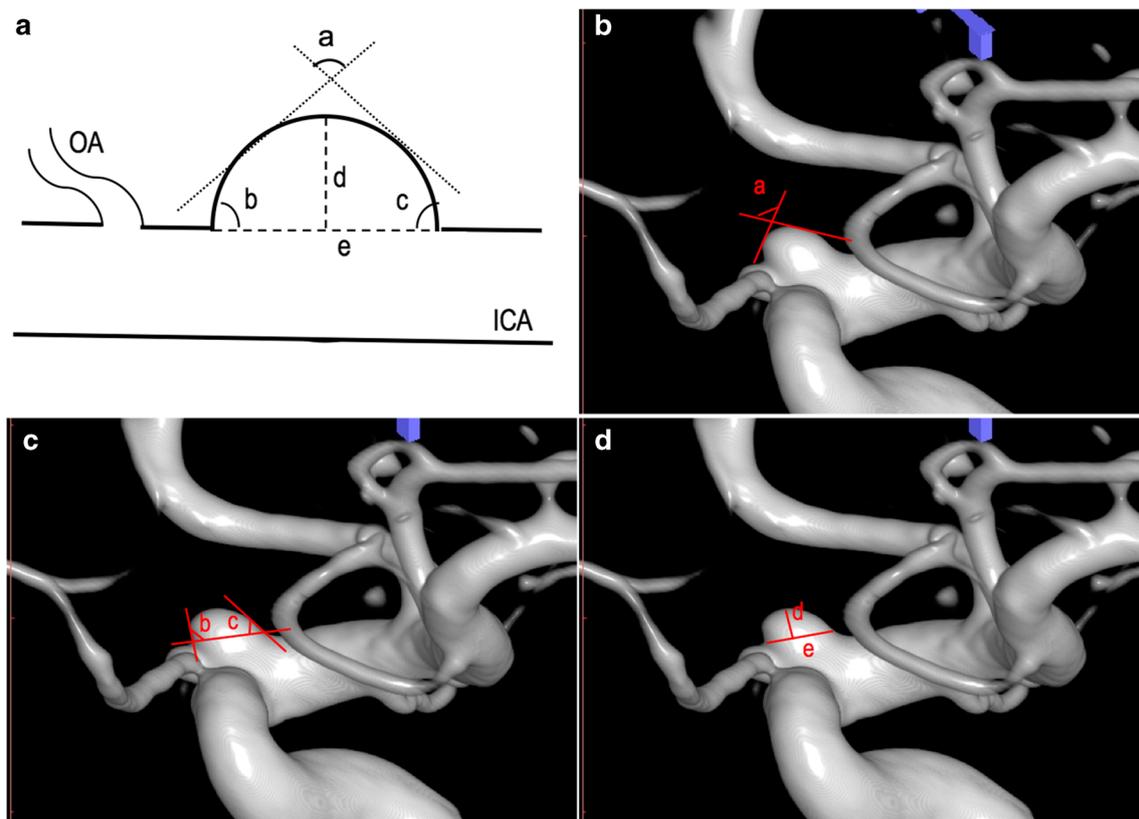
Fig. 2 Measurements of aneurysms acquired from digital subtract angiography (DSA). **a** A schematic diagram of measurements. a (apex angle), the intersection angle between two straight lines tangent to the aneurysmal bulge, with point of contact at the midpoint of the curve from aneurysm doom to base at each side; b (proximal angle) and c (distal angle), the intersection angle between the bulge and the base, proximal and distal to the ophthalmic artery, respectively. d (dome), the length of aneurysmal dome to the base; e (neck), the length of aneurysmal base. **b–d** Measuring apex angle, proximal angle, distal angle, dome, and neck on DSA, respectively (OA, ophthalmic artery; ICA, internal carotid artery)

values, only one non-blister aneurysm had a dome/neck ratio > 1. Average dome/neck ratio of BBAs was significantly lower comparing to that of non-blister aneurysms ($P =$ 0.009, distribution shown in Fig. 5a).

Table 1 Comparison of clinical characteristics between BBAs and non-blister aneurysms

	Blister-like ($n = 17$)	Non-blister ($n = 26$)	P value
Epidemiology			
Female	13 (76.5%)	23 (88.5%)	NS
Age (year)	53.2 ± 10.8	50.1 ± 9.3	NS
Medical history			
History of hypertension	11 (64.7%)	11 (42.3%)	NS
Rupture	7 (41.2%)	4 (15.4%)	0.058
Hunt-Hess grading			
I	4	3	NS
II	3	1	NS
Intraoperative Rupture	3 (17.6%)	0 (0.0%)	0.026
Postoperative Ischemia	3 (17.6%)	2 (7.7%)	NS
mRS ≥ 2 at discharge	2 (11.8%)	2 (7.7%)	NS
Association with			
Multiple aneurysms	7 (41.2%)	10 (38.5%)	NS
Bilateral OA aneurysms	1 (5.9%)	4 (15.4%)	NS
Unilateral multiple OA aneurysms	3 (17.6%)	1 (3.8%)	NS

mRS, Modified Rankin Scale; *OA*, ophthalmic artery; *NS*, not significant

Fig. 3 The distribution of blood blister-like aneurysms (BBAs) and non-blister aneurysms on internal carotid artery (ICA). The most common location of BBA and non-blister aneurysms was both on the anterior wall of ICA, followed by the medial wall. Five non-blister aneurysms but no BBAs were located on the posterior wall of ICA whereas five non-blister aneurysms located at this site. The overall distribution of BBAs and non-blister aneurysms was not significantly different
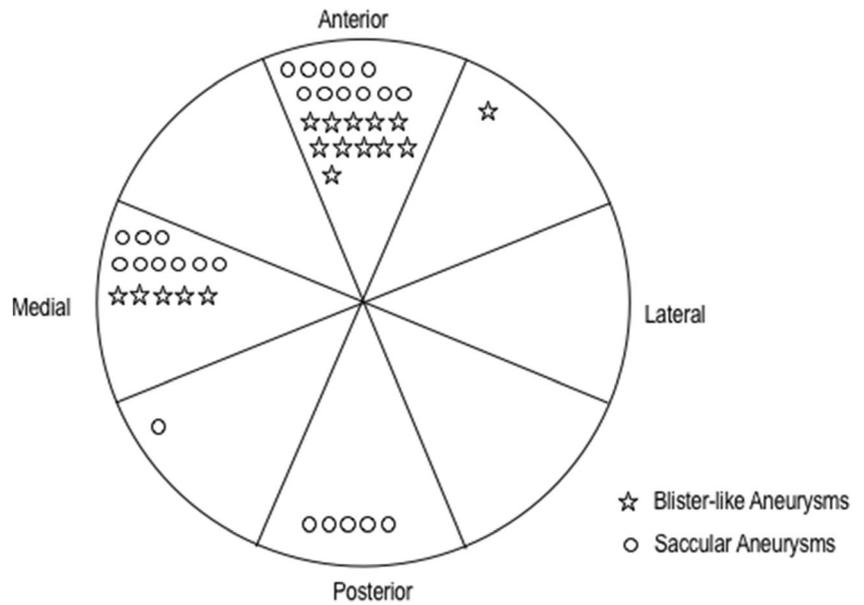
Regarding measurements of angles, degree of apex angle, and proximal angle were not significantly different between the groups (Fig. 5b, c). Notably, distal angles of BBAs were significantly smaller than those of non-blister aneurysms ($P = 0.002$, Fig. 5d).

Discriminant function for pre-surgical diagnosis of BBAs

Discriminant analysis yielded a linear function ($P = 0.005$) with an overall accuracy of 76.2%. Dome/neck ratio and distal angle were included as significant and unique contributors in the function. The final discriminant function was calculated according to the following equation:

$$y \;=\; 2.824 \;\times\; \text{dome/neck ratio} + \; 0.031$$
$$\times \; \text{distal angle (degree)} - 4.633$$

where -4.633 was the constant of the equation.

Table 3 summarizes the results of classification by discriminant analysis. The rate of correct prediction was 81.3% for blister-like aneurysms (sensitivity) and 73.1% for control subjects (specificity).

Categorization of blister-like aneurysms and comparison between different types

The majority of BBAs were type II (52.9%), followed by type I (35.3%) and type III (11.8%). Type IV BBAs were not found in the current series. Clinical characteristics of different types of BBAs were listed in Table 4. Because the amount of type III BBAs was very small ($n = 2$), we only compared features between type I and type II. Results showed that all cases of postoperative ischemic events occurred in the group of type II BBAs (33.3%, $P = 0.028$). Apart from this, no significant difference was found between type I and type II BBAs regarding demographic, clinical, or morphological characteristics.

Table 2 Comparison of locations between BBAs and non-blister aneurysms

	Blister-like ($n = 17$)	Non-blister ($n = 26$)	P value
Side (L/R)	8 (47.1%)	12 (46.2%)	NS
Location (around/distal to OA)	3/14	8/18	NS
Location on ICA			
Anterior	11 (64.7%)	11 (42.3%)	NS
Medial	5 (29.4%)	9 (34.6%)	
Posterior	0 (0.0%)	5 (19.2%)	
Anterolateral	1 (5.9%)	0 (0.0%)	
Posteromedial	0 (0.0%)	1 (3.8%)	

L, left; *R*, right; *OA*, ophthalmic artery; *ICA*, internal carotid artery; *NS*, not significant
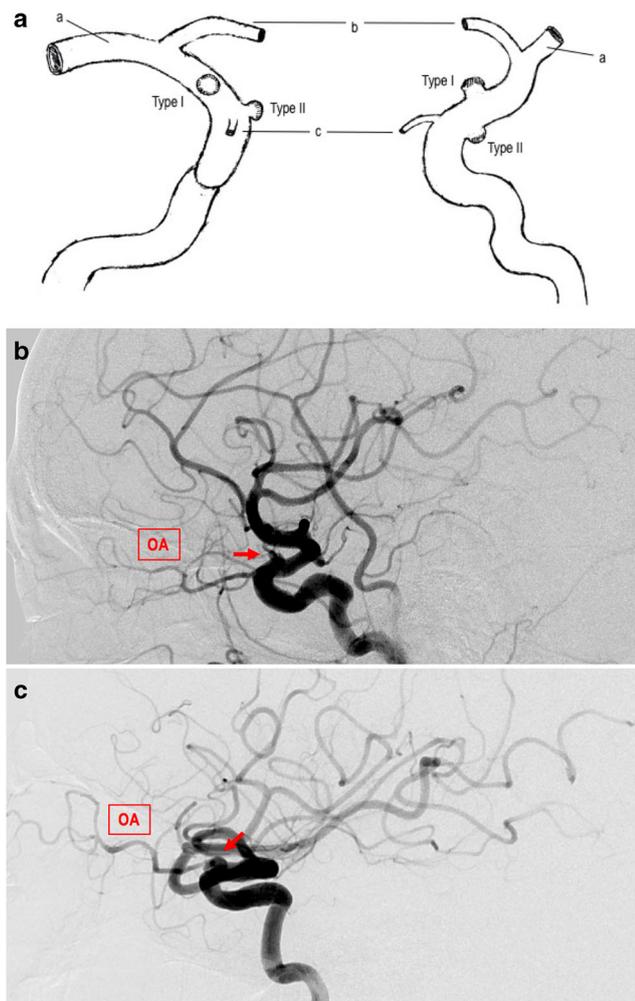
Fig. 4 Two types of relationships between the aneurysms and the ophthalmic artery (OA) branching site. **a** A schematic diagraph. Type I: the aneurysms located distal to the OA branching site; type II: the aneurysms located around the OA branching site. **b** Angiography showing a type I BBA (arrow). **c** Angiography showing a type II BBA (arrow). a Middle cerebral artery, MCA. b Anterior cerebral artery, ACA. c Ophthalmic artery, OA

Discussion

With a growing number of studies focusing on treatment strategies for blood blister-like aneurysms (BBAs), a variety of means including microsurgery and endovascular therapy had been put out to deal with these challenging lesions [1, 4, 16]. However, the identification of BBAs had been divergent according to different method (by surgical inspection or by radiography) adopted by different therapists [3, 11, 19]. Previous studies have suggested that small, wide-necked, supraclinoid ICA aneurysms might be blister-like or ordinary saccular, and these two types share very similar features [13]. Therefore, it is reasonable to postulate such inconsistency in diagnosis might lead to bias of studies and partial interpretation of systematic reviews by mistaken some non-blister

aneurysms for BBAs, especially in endovascular studies where surgical inspection was not available and hence leading to better results in endovascular series. Our study aimed to compare radiological characteristics between BBAs and non-blister aneurysms on ICA, find identifiable features, and propose a pre-surgical diagnostic method for BBAs.

In this study, we reviewed data of 43 suspicious small, broad-based aneurysms arising from non-branching site of internal carotid artery that had been treated by microsurgery at our hospital. Based on intraoperative findings, 17 aneurysms were diagnosed as BBAs and 26 as non-blister aneurysms. Our findings showed that clinical characteristics were very similar between these two groups. No significant difference had been found regarding age range, gender, previous history of systolic hypertension, nor association with multiple aneurysms, making it very hard to distinguish BBAs from non-blister aneurysms by clinical materials only. BBAs had a slightly higher rate to spontaneous rupture and present with SAH (41.2 vs 15.4%); however, this finding was not statistically significant ($P = 0.058$). Consistent with previous studies [18, 21], in our series, BBAs presented a higher incidence of intraoperative rupture (17.6 vs 0.0%, $P = 0.026$); unfortunately, this feature could not contribute to pre-surgical diagnosis of BBAs (see Table 1).

Location of aneurysms was described in three aspects: side, location on the ICA wall, and their relationship with the ophthalmic artery branching site, but none was significantly different between the two groups, indicating diagnose by location might be inaccurate. In our series, the majority of blister-like aneurysms located on the anterior (64.7%) and medial wall (33.3%) of ICA (including one on the posteromedial wall), in accordance with previous literature (see Fig. 4). However, the distribution of non-blister aneurysms was almost the same to that of BBAs (anterior: 42.3%; medial: 34.6%; $P = 0.126$), except that five non-blister aneurysms protruded from posterior wall where no BBAs were found in this series ($P = 0.054$), suggesting aneurysms located at posterior wall of ICA might less likely be blister-like. Notably, though typical definition of blister-like aneurysms stated that they located at the "non-branching site" of ICA [13, 18], we did find in this series that three (17.6%) blister-like aneurysms located around or near the bifurcation of ophthalmic artery (see Table 2). Though the percentage was rather small, it is still worth noticing that the location of BBAs might be variational and small aneurysms near the OA bifurcation should also be kept vigilant of before surgery.

Morphologically, blister-like aneurysms are usually hemispherical or conical; hence, a dome/neck ratio less than 1 on radiography had been incorporated as an important term in the identifications of BBAs in previous literature [14, 20, 24]. Our findings showed that average dome/neck ratio of BBAs was significantly lower than that of non-blister aneurysms (0.62 ± 0.15 versus 0.76 ± 0.17, $P = 0.009$); however, their ranges were somehow overlapped. More importantly, dome/neck

Fig. 5 Comparison of radiological measurements of BBAs and non-blister aneurysms. **a** Average dome/neck ratio of BBAs was significantly smaller than that of non-blister aneurysms (0.62 ± 0.15 vs 0.76 ± 0.17, $P = 0.009$). **b** Average degree of apex angle was not significantly different between the groups ($63.33 \pm 19.61°$ vs $68.40 \pm 14.46°$, $P = 0.341$). **c** Average degree of proximal angle was not significantly different between the groups ($83.45 \pm 24.41°$ vs $87.22 \pm 18.15°$, $P = 0.571$). **d** Average degree of distal angle in BBAs was significantly smaller than that in non-blister aneurysms ($71.69 \pm 18.41°$ vs $95.57 \pm 25.73°$, $P = 0.002$)
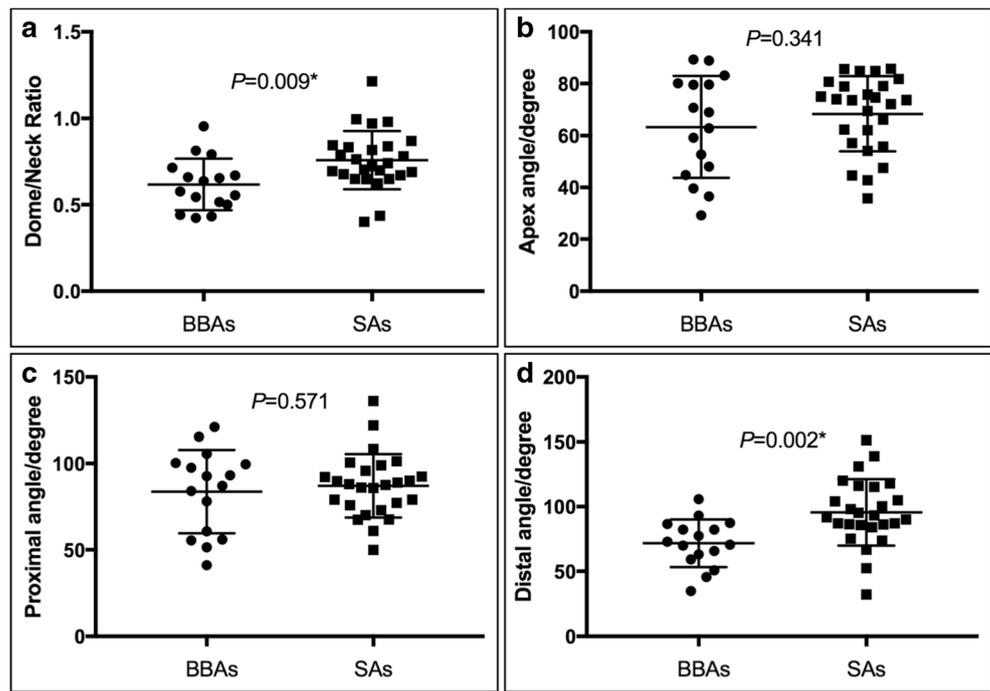
ratio of non-blister aneurysms had a wide range from 0.40 to 1.21 (see Fig. 5a); therefore, it is reasonable to postulate that diagnosing BBAs mainly by dome/neck ratio < 1 might lead to nonnegligible bias in studies. To investigate more morphological features which could probably be incorporating in the diagnosis, we further compared the degree of apex angle, proximal angle, and distal angle (measurements seen as in Fig. 2) between the two groups. Interestingly, mean distal angle of BBAs was significantly smaller than that of non-blister aneurysms ($P = 0.002$, Fig. 5d), which might be a newly found morphological characteristic of BBAs.

To generate a pre-surgical diagnostic method for BBAs, we performed a discriminant analysis with dome/neck ratio and degree of distal angle included as predictive factors. A linear function with an overall accurate classification rate of 76.2% was yielded (sensibility 81.3%; specificity 73.1%). To our best knowledge, this was a first study that provided a discriminant function for the differentiation between BBAs and non-blister aneurysms based on measurements acquired from radiological angiography. This function could be useful in increasing the accuracy of diagnosis based on sole radiological angiography. With lots of ongoing studies aiming to find the optimal treatment for BBAs, a unified diagnostic standard seemed important, especially for future meta-analysis and systematic reviews with larger sample size. More importantly, pre-surgical diagnosis of BBAs might affect the following treating strategies at bedside practice. Our study provided not only the current function but also new insights into the pre-surgical discriminance of BBAs from non-blister aneurysms. However, it also has to be noticed that in this study, predictive factors were identified from the same data that yielded the sensibility and specificity; therefore, the proposed parameters in the given function are yet not validated by an independent cohort. Future studies are definitely needed to enrich material and validate parameters for this model.

Recent literature had classified BBAs into four types based on morphology, as previously described in the Methods

Table 3 Results of discriminant analysis

	Predicted membership		
	Blister-like aneurysms	Non-blister aneurysms	Total
Blister-like aneurysms	13 (81.3%)	3 (18.8%)	16
Non-blister aneurysms	7 (26.9%)	19 (73.1%)	26
Total	20	22	42

Canonical correlation = 0.489; eigenvalue = 0.314; Wilks λ = 0.761; chi square = 10.651; degrees of freedom = 2

Table 4 Comparison of characteristics between subtypes of BBAs

	Blister-type I ($n = 6$)	Blister-type II ($n = 9$)	Blister-type III ($n = 2$)
Female	6 (100.0%)	5 (55.6%)	2 (100.0%)
Age (year)	50.7 ± 9.6	53.1 ± 12.4	61.0 ± 2.8
Side (right)	1 (16.7%)	6 (66.7%)	2 (100.0%)
History of hypertension	4 (66.7%)	5 (55.6%)	2 (100.0%)
Rupture	2 (33.3%)	5 (55.6%)	0 (0.0%)
Hunt-Hess grading			
I	2 (33.3%)	2 (22.2%)	
II	0 (0.0%)	3 (33.3%)	
Intraoperative rupture	1 (16.7%)	2 (22.2%)	0 (0.0%)
Postoperative ischemia	0 (0.0%)	3 (33.3%)*	0 (0.0%)
mRS ≥ 2 at discharge	0 (0.0%)	2 (22.2%)	0 (0.0%)
Multiple aneurysms	2 (33.3%)	4 (44.5%)	1 (50.0%)
Bilateral OA aneurysms	0 (0.0%)	1 (11.1%)	0 (0.0%)
Unilateral multiple OA aneurysms	2 (33.3%)	1 (11.1%)	0 (0.0%)
Dome/neck ratio	0.55 ± 0.12	0.63 ± 0.13	0.73 ± 0.31
Apex angle	69.38 ± 12.90	61.60 ± 24.40	55.95 ± 4.60
Proximal angle	69.38 ± 24.16	85.87 ± 22.99	108.0 ± 10.46
Distal angle	61.40 ± 15.37	78.56 ± 18.16	66.50 ± 22.20

mRS, Modified Rankin Scale; *OA*, ophthalmic artery

*$P < 0.05$

section. To further investigate detailed information of BBAs among different subtypes, in this study, we also classified BBAs into these subtypes accordingly and compared characteristics between the groups. In our series, the majority of BBAs were type II (52.6%), followed by type I (35.3%) and III (11.8%), correlating with distribution of types in previous literature [2]. No type IV BBAs were found in the current series, probably due to the rarity of this type. This might account for the lower incidence of rupture and more favorable outcome in our series comparing to previous literature [6, 14, 23], as had been reported in recent study that type IV BBAs turned to be more unstable and have more disastrous outcome than other types of BBAs [10]. Our results showed that comparing to type I BBAs, more postoperative ischemic events occurred in type II BBAs (33.3 versus 0.0%, $P = 0.028$), apart from which no other significant difference was found between these two groups (Table 4). Our finding indicated that type II BBAs might be more difficult to treat comparing to type I BBAs, supposedly due to that more portion of ICA wall was involved in type II than type I. Therefore, extra attention is required while treating type II BBA with direct clipping technique in order not to stenose the lumen of parent artery.

There were a few limitations to the current study. First, our sample size was not abundant enough because of the rarity of blister-like aneurysms, which might lead to compromised statistical efficacy. Second, due to the retrospective nature of this study, the factors investigated were restricted and potential bias might not be excluded. We strongly hope future studies with larger sample size would provide more data of blister-like

aneurysms and their non-blister counterparts to enrich this model, further standardizing the pre-surgical diagnose of BBAs.

Conclusions

BBAs and non-blister aneurysms shared similar characteristics, including age range, female domination, association of multiple aneurysms, and location on ICA. Dome/neck ratio of BBAs was lower than that of non-blister aneurysms, but dome/neck ratio < 1 did not guarantee an accurate diagnosis of BBA. A discriminant function incorporating dome/neck ratio and degree of distal angle as factors was provided, yielding a greater predictive accuracy for pre-surgical screening of BBAs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the institutional review board of Beijing Tiantan Hospital, Capital Medical University.

Informed consent All patients included in this study had consent with their information being used for clinical investigation anonymously.

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