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Clinico-radiologic factors in paraclinoid aneurysms associated with aneurysm rupture: A CTA study

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A B S T R A C T

Background and purpose: Paraclinoid aneurysms are commonly noted as incidental findings by computed tomography angiography (CTA), and there exists disagreement in the literature as to which patient and aneurysm characteristics predict subsequent rupture. This question is of particular significance given the complex anatomy of the paraclinoid region and the associated risks of aneurysm treatment. The purpose of this study was to determine significant associated risk factors for paraclinoid aneurysm rupture.

Materials and methods: Medical records and CTA imaging from 179 patients with 205 paraclinoid aneurysms. Patient and aneurysm characteristics including aneurysm size, morphology, and multiplicity were gathered for analysis of rupture risk. Factors influencing the decision to treat or observe unruptured aneurysms were also evaluated. A Cox regression analysis was used, and results were corrected for multiple comparisons using the Bonferroni method.

Results: Aneurysm size, diameter:neck ratio, and multilobularity were significantly associated with increased rupture risk; however, only multilobularity remained significant after Bonferroni correction for multiple comparisons. Intervention for unruptured aneurysms was significantly more likely to occur among younger patients and multilobulated aneurysms, or those having a larger diameter, height, height:neck ratio, or diameter:neck ratio.

Conclusions: Multilobularity constitutes a significant associated risk factor for rupture among paraclinoid aneurysms. Younger age, larger size and multilobulated aneurysms are characteristics that favored treatment over observation in this cohort.

1. Introduction

Intracranial aneurysms involving the paraclinoid internal carotid artery are frequently seen on computed tomography angiography (CTA) studies, either as incidental findings, or occasionally found ruptured and a source of subarachnoid hemorrhage. In spite of this, the optimal strategy for management of unruptured paraclinoid aneurysms remains uncertain. Aneurysms in this location are a surgical challenge given the close proximity of osseous structures, cavernous sinus, and critical cranial nerves [1]. Favorable short-term results have previously been demonstrated using endovascular techniques in a number of trials and clinical scenarios [2–7], but it remains unclear which patients are likely to benefit most. Prior work on risk factors for paraclinoid aneurysm rupture has been limited by factors such as low rupture rates [8] and focus on hemodynamic parameters not used in routine clinical practice [9]. Additionally, these trials have occasionally generated conflicting results [9], further complicating a unified interpretation of the extant literature. In the present study, we sought to contribute to this ongoing discussion by retrospectively evaluating our database for associated risk factors of patients with paraclinoid aneurysms imaged with CTA. Separately, we analyzed unruptured aneurysms to identify factors that may influence active surgical or endovascular management over conservative follow-up in these patients.

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2. Methods

A review of medical records and diagnostic imaging from patients with paraclinoid aneurysms was performed, with a waiver of informed consent obtained from the institutional review board. To identify relevant cases for review, an in-house radiologic report search tool was used to identify all consecutive CTA studies of the intracranial vessels completed over a 3 year period. Because of the known variance in terminology relating to the anatomy of the intracranial internal carotid artery (ICA), the search was initially kept broad to capture all radiologic reports containing terms such as "paraclinoid," "supraclinoid," "clinoid," and "ophthalmic artery." This yielded a large volume of studies (Fig. 1), which was further parsed by direct review of the raw CTA imaging data to generate a cohort of exclusively paraclinoid aneurysms. For this study, a conservative definition of paraclinoid aneurysms was adopted to include all intracranial ICA aneurysms arising between the origins of the ophthalmic and posterior communicating arteries. In cases where the posterior communicating artery was not definitively visualized, aneurysms beyond the dorsum sella were not included. CTA imaging techniques used at our institution have been previously described [10], using multidetector CTA on either 16- or 64-detector row units scanning from the base of the C1 vertebral body to the vertex using an axial technique with 0.5 pitch, 1.25 mm collimation, 350 maximal mA, 120 kVp, 22 cm field of view and 65–85 mL of iodinated contrast material administered by power injector at 4–5 mL/s into an antecubital vein with either a fixed 25 s delay between the onset of contrast injection and the start of scanning or a semi-automatic contrast bolus triggering technique. Among patients with multiple CTA studies within the search database, only the initial CTA study was included for analysis.

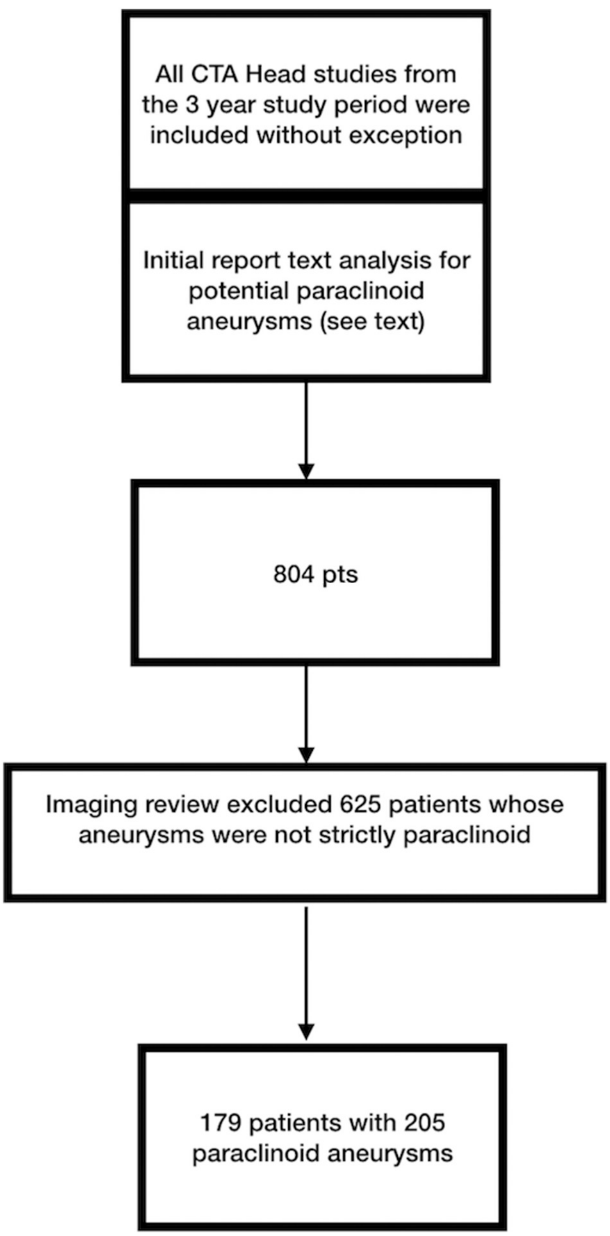

Fig. 1. Patient selection.

Radiological characteristics of these aneurysms and the presence of other intracranial aneurysms on CTA were recorded by three trained observers (MH, NM, JR). Subsequently, images of all aneurysms included on this study were meticulously reviewed and validated by the lead author to ensure consistency of measurements and conformity to the study protocol prior to incorporating the data into the master chart. Aneurysm factors assessed on initial head CTA included: lobulation (nonlobulated or multilobulated); neck diameter; maximum fundus diameter; height; fundus:neck and height:neck ratios; orientation (superior, medial, lateral, or inferior); position with respect to the optic strut (proximal or distal [11]); and multiplicity.

An extensive chart review was performed to obtain pertinent demographic information (age and sex), clinical risk factors (hypertension, smoking, diabetes mellitus, family history of aneurysm), follow-up duration, and rupture status (unruptured or ruptured). These chart review data were accurate as of January 2015 for follow-up duration and rupture status.

Follow-up duration was calculated as the time interval between the date of initial identification of a paraclinoid aneurysm by CTA and the date of rupture, if ruptured; the date of the last-known-well clinic visit, if unruptured; or the date of first intervention if surgical/endovascular treatment was performed for unruptured aneurysms.

Two separate Cox regression analyses were performed. In the first, hazards for the outcome of aneurysm rupture (initial or on follow-up) were determined; these were used to identify factors that may predispose to rupture. For the second analysis, instead of rupture, we used the outcome of definitive surgical or endovascular treatment instead provided an insight into multidisciplinary treatment decision making (at our institution). In this second analysis, "hazards" for surgical/endovascular treatment of unruptured aneurysms were determined; these were used to identify factors that may inform the decision to treat versus conservatively manage aneurysms. For both these analyses, a random patient effect was included in the Cox model to account for multiple observations in some patients.

In a study with multiple variates, it becomes necessary to avoid the pitfall of multiple comparisons potentially falsely elevating the chance of a Type I error (i.e. wrongly rejecting a null hypothesis). A popular method is the Bonferroni correction, which uses a stricter p-value threshold by dividing the original p-value by the number of comparisons to obtain a Bonferroni-corrected p-value. In our case, we set a p-value of < 0.05 for statistical significance (without correction) and a Bonferroni-corrected p-value of < 0.0033(i.e. 0.05/15, given 15 independent variables studied). Using Bonferroni correction does markedly reduce the chance of a Type I error, with a trade-off in that Type II error (rejecting a null hypothesis that in reality should have been accepted) may be increased. We reported results using both uncorrected and Bonferroni-corrected p-values. Statistical significance was set at an overall $\alpha = 0.05$ without correction, and at $\alpha = 0.0033$ following application of the Bonferroni correction for multiple comparisons.

3. Results

A total of 205 paraclinoid aneurysms in 179 patients (149 female, 30 male, age range 59.0 ± 15.5 years) were identified. Twelve patients had aneurysms that ruptured; of these, 10 had ruptured at initial

Table 1
Hazard ratios for rupture.

Predictor	P-value*	Hazard ratio	95% lower confidence limit for hazard ratio	95% upper confidence limit for hazard ratio
Age	0.1080	1.035	0.993	1.079
Diabetes mellitus	0.7743	0.801	0.175	3.660
Family history	0.9942	0.000	0.000	
Hypertension	0.4191	1.714	0.464	6.334
Smoking	0.7636	0.838	0.266	2.642
Sex (male)	0.3914	1.771	0.479	6.543
Maximum diameter	*0.0207*	1.067	1.010	1.127
Maximum diameter:neck ratio	*0.0280*	1.407	1.038	1.908
Height	*0.0491*	1.062	1.000	1.128
Multiplicity	0.5508	0.694	0.209	2.305
Multilobulated	***0.0025***	5.790	1.852	18.105
Neck	0.5166	1.146	0.760	1.728
Height:neck ratio	0.1693	1.287	0.898	1.846
Side (laterality)	0.2645	0.505	0.152	1.677
Distal to optic strut	0.7723	1.262	0.261	6.111

* $p < 0.05$ is italicized, Bonferroni p-value < 0.0033 is bolded and italicized.

presentation and 2 at follow-up. Mean follow-up duration was 2.3 ± 2.3 years, with a median follow-up duration of 0.9 years.

The results of the Cox regression analysis for rupture are shown in Table 1, with aneurysm diameter, multilobulated morphology, and diameter:neck ratio identified as significant positive hazards A separately performed sub-analysis (not included in Table 1) did not show aneurysm orientation (superior/medial/lateral/inferior) to be a significant hazard.

Table 2 shows hazard ratios for the treatment of unruptured aneurysms for these same parameters, as an indicator of factors that may influence clinical decision making in managing unruptured aneurysms. Age was seen as a negative predictor for treatment, with older patients significantly less likely to be treated. Aneurysms that were multilobulated, or having a larger diameter, height, height:neck ratio, or diameter:neck ratio were also more likely to be treated. Diabetics and males were significantly less likely to be treated; however, these were not statistically significant when corrected for multiple comparisons.

Table 2
Hazard ratios for treatment of unruptured aneurysms (aneurysm clipped or coiled).

Predictor	P-value*	Hazard ratio	95% lower confidence limit for hazard ratio	95% upper confidence limit for hazard ratio
Age	***0.0001***	0.961	0.942	0.981
Diabetes mellitus	*0.0084*	0.291	0.117	0.729
Family history	0.0636	1.719	0.970	3.049
Hypertension	0.2581	0.745	0.447	1.241
Smoking history	0.9117	1.030	0.607	1.748
Sex (male)	*0.0200*	0.252	0.079	0.805
Maximum diameter	< ***0.0001***	1.113	1.075	1.151
Maximum diameter:neck ratio	< ***0.0001***	1.779	1.445	2.190
Height	< ***0.0001***	1.114	1.076	1.154
Multiplicity	0.7181	1.098	0.660	1.826
Multilobulated	***0.0028***	2.562	1.384	4.745
Neck	< ***0.0001***	1.513	1.258	1.819
Height:neck ratio	< ***0.0001***	1.530	1.276	1.834
Side (laterality)	0.5059	0.843	0.509	1.395
Distal to optic strut	0.7529	0.901	0.471	1.724

* $p < 0.05$ is italicized, Bonferroni p-value < 0.0033 is bolded and italicized.

Table 3
Distribution of multilobulated and nonlobulated aneurysms in the ruptured and unruptured groups.

	Ruptured	Unruptured	Total
Nonlobulated	6	166	172
Multilobulated	6	27	33
Total	12	193	205

Fishers exact test: $p = 0.0051$.

Given the most significant hazard for rupture was multilobulated aneurysm morphology, this was separately analyzed in a 2 × 2 contingency table (Table 3). Fifty percent of ruptured aneurysms were multilobulated, as opposed to 14% of unruptured aneurysms (Fig. 2).

4. Discussion

In the present investigation, we found paraclinoid aneurysm multilobularity, fundus size (maximum aneurysm diameter), and diameter:neck ratio to be significant hazards for rupture. Multilobularity was the most significant differentiator, constituting 50% of ruptured aneurysms versus 14% of unruptured aneurysms, a finding consistent with previous studies in paraclinoid aneurysms [9,25], as well as intracranial aneurysms in general [10]. Moreover, only multilobularity remained a significant hazard following correction for multiple comparisons. Of note, we did not find aneurysm orientation to be a significant hazard, in contrast to a prior study by Oh et al. [12] that found superiorly-oriented aneurysms more prone to rupture. Also, increased aneurysm size constituted an increased risk of rupture, in contrast to Liu's finding that smaller aneurysms showed higher rupture rates [9]. Increased aneurysm size and diameter:neck ratio as risk factors for rupture are also consistent with Oh's findings based on catheter angiography [12].

All the significant hazards we found in our study did appear to be part of the current clinical decision-making at our institution, based on Table 3. The significantly greater chance of younger patients being treated is consistent with the general practice of more aggressive management in younger patients. It is not completely clear why diabetics and males were less likely to be treated; the former may potentially have factored into the overall risk of postsurgical morbidity/mortality, and the latter finding may be related to a smaller subgroup of patients being analyzed, and/or confounding by patient preference. However, when applying a multiple comparisons correction, the latter observations on diabetics and males no longer reached statistical significance.

Paraclinoid aneurysms present a surgical challenge given their close relationship to the anatomically-complex skull base, cavernous sinus, and critical cranial nerves. They also constitute a unique subgroup of aneurysms given their marked female preponderance [13–15] and an apparent lower influence on prevalence by atherosclerotic risk factors [16]. Endovascular options are increasingly available, including coil embolization—either stent-assisted or balloon-assisted, and pipeline devices. Individualized decisions for each patient, usually involving a multi-disciplinary team of neurosurgeons and interventional neuroradiologists, determine follow-up, surgery, or endovascular treatment of unruptured aneurysms [1,13,17–20]. There are morbidities and risks associated with treatment, and relative ethical and logistical difficulties in conducting large prospective randomized control trials when relatively few of these aneurysms rupture. Thus, a retrospective review of patient databases to sift out characteristics that may indicate a propensity to subsequent rupture—and thereby influence management decisions—remains useful. Numerous trials have sought to characterize risk factors for unfavorable outcomes among patients with unruptured aneurysms, most notably the landmark International Study of Unruptured Intracranial Aneurysms trial [21], which provided the most robust, long-term data to date. Nevertheless, while this and other trials helped delineate a broad set of guidelines for aneurysm management,

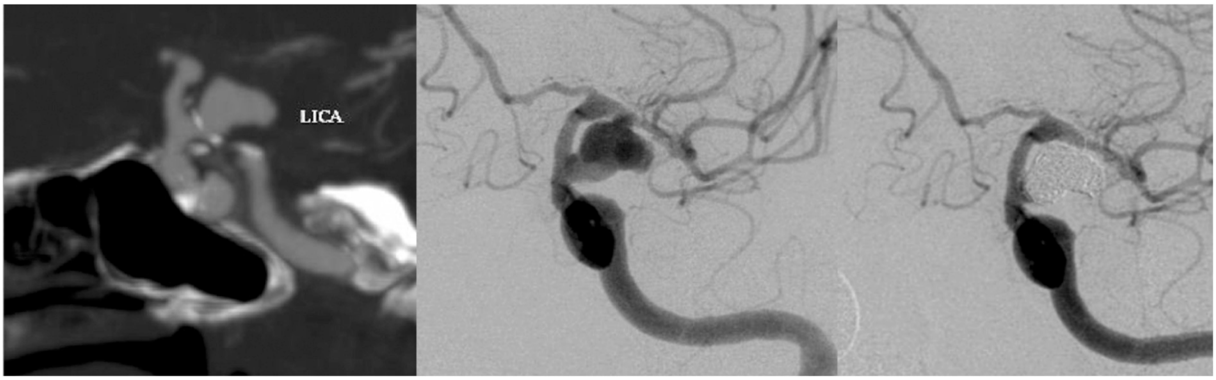

Fig. 2. A multilobulated left ICA aneurysm presenting with rupture. Shown are a reconstructed CTA MIP image (left) showing the aneurysm, a catheter angiogram redemonstrating the multilobulated aneurysm (middle), and a post-coiling angiogram (right).

details pertaining specifically to unruptured aneurysms within the paraclinoid distribution of the intracranial internal carotid artery are currently lacking. This study may support surgeons and interventionists in the decision making of patients with paraclinoid aneurysms as the detection of unruptured aneurysms have grown significantly in the era of modern imaging of the central nervous system.

A CTA is often the initial study in these patients. Higher CT resolution and multi-planar and 3D reformatting make this technique even more useful to assess lesions morphologically and their relation to surrounding anatomy. While there has been some variation in terminology and definition of aneurysms as paraclinoid, we included only aneurysms between the easily-identified ophthalmic artery and posterior communicating artery (al-Rodhan's Group 1a and 1b aneurysms [22]), or if the latter wasn't visible, the dorsum sella was considered the posterior limit of inclusion. Except in 10–11% of cases where the ophthalmic artery is extradural [23–25], most aneurysms thus defined would be categorized as intradural in location. In any case, precise identification on CTA or on angiography of the distal dural ring marking the border between the extradural and intradural ICA is challenging at best and is a determination best made at surgery [16].

Our study has a few limitations, including its retrospective nature, low number of aneurysm ruptures and a possible referral bias with the likelihood of more complex cases referred to our tertiary care center. Also, the scope of our study limited to the initial CTA imaging did not provide data on follow-up aneurysmal growth, which is likely a significant factor that influences active intervention. Larger pools of retrospective data from multiple centers and over larger time periods—in conjunction with prospective trials of unruptured aneurysm follow-up—would address some of these limitations.

5. Conclusion

Multilobulated paraclinoid aneurysms are significantly associated to rupture when compared to multiple clinical and radiological factors. In this cohort of patients with unruptured paraclinoid aneurysms, we identified a significant trend of treatment of younger patients, with larger and multilobulated aneurysm.

Multilobulated paraclinoid aneurysms may be more prone to rupture, constituting a statistically significant hazard even when corrected for multiple comparisons. Current management decisions at our institution, while remaining highly individualized, appear to show that treatment of unruptured aneurysms over follow-up is favored in younger patients and in larger, multilobulated aneurysms.

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