Location specific rupture risk of intracranial aneurysms: case of ophthalmic aneurysms

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Abbreviations and acronyms

- DSA: Digital Subtraction Angiography
- RIA: Ruptured Intracranial Aneurysm
- UIA: Unruptured Intracranial Aneurysm

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Pr Frédéric Clarençon is consultant for Medtronic, Balt Extrusion, Penumbra, Microvention and Stryker; board member of Artedrone and has stock options with Intradys and Collavidence.

Dr Gaultier Marnat is a consultant for Stryker Neurovascular, Balt, Microvention Europe, Sim and Cure and has done paid lectures for Medtronic, Phenoc, Johnson & Johnson, Bracco.

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Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study received approval from the CERIM institutional review board (IRB): CRM-2201-220. The need for patient signed consent was waived by the IRB.

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Abstract

Background

Aneurysm location is a key element in predicting an intracranial aneurysm's rupture risk. A common impression suggests that pure ophthalmic aneurysms are under-represented in ruptured intracranial aneurysms (RIAs). The purpose of this study is to specifically evaluate the risk of rupture of ophthalmic aneurysms and to compare it to the other aneurysm locations.

Methods

This multicentre study compared the frequency of ophthalmic aneurysms in a prospective cohort of RIAs admitted in 13 neuroradiology centres between January 2021 and March 2021 with a retrospective cohort of patients having unruptured intracranial aneurysms (UIAs) who underwent cerebral angiography at the same neuroradiology centres during the same time period.

Results

Six hundred and four intracranial aneurysms were included in this study (355 UIAs and 249 RIAs; mean age 57 years, IQR [49; 65]; female 386/604 [64%]). Mean aneurysm size was 6.0 mm (5.3 mm for UIAs; 7.0 mm for RIAs, p-value < 0.0001). Aneurysm shape was irregular for 37% UIAs and 73% RIAs (p-value < 0.0001). Ophthalmic aneurysms frequency was 14.9% of UIAs (2nd most common aneurysm location) and 1.2% of RIAs (2nd least common aneurysm location); OR 0.07 (95% CI [0.02; 0.23], p-value < 0.0001).

Conclusions

Ophthalmic aneurysms seem to have a low risk of rupture compared to other intracranial aneurysm locations. This calls for a re-evaluation of the benefit-risk balance when considering preventive treatment for ophthalmic aneurysms.

Key points:

- What is already known on this topic: Internal carotid artery (ICA) aneurysms (including ophthalmic, carotid-cave, superior hypophyseal, anterior choroidal and ICA termination aneurysms) have a lower risk of rupture compared to other aneurysms. However, the specific relative rupture risk of ophthalmic aneurysms is not known.
- What this study adds: Ophthalmic aneurysms are under-represented among ruptured aneurysms compared to unruptured aneurysms, suggesting a relatively lower risk of rupture
- How this study might affect research, practice or policy: the benefit-risk balance should be carefully re-evaluated before deciding on the preventive treatment of unruptured ophthalmic aneurysms

INTRODUCTION

Intracranial aneurysms have an estimated prevalence of 3-8% in a population with a mean age of 50 years without major cardiovascular comorbidities[1, 2]. With the increased use of non-invasive brain vessel imaging in the last decades, incidental detection has become more and more frequent.

Deciding preventive treatment of asymptomatic unruptured intracranial aneurysms (UIA) is challenging. It relies on assessing the projected balance between the expected benefit (lowering the risk of neurological impairment or death by rupture and subarachnoid haemorrhage, associated with a 44% mortality rate in Europe) and the risks of treatment-related complications [3]. To improve the estimation of the rupture risk of untreated aneurysms, scoring systems incorporating clinical and imaging criteria have been proposed [4–6]. Aneurysm location is one of the main risk factors predictive of rupture[7]. Ophthalmic aneurysms, superior hypophyseal aneurysms, carotid cave aneurysms, internal carotid artery termination aneurysms, anterior choroidal artery aneurysms and sometimes posterior communicating artery aneurysms are often grouped under the “internal carotid artery aneurysms” label [4–7]. However, a widespread clinical impression suggests that ophthalmic aneurysms (i.e.: aneurysms close to the ophthalmic artery, or with the ophthalmic artery arising from their neck) are under-represented among ruptured intracranial aneurysms (RIAs) compared to UIAs. In parallel, ophthalmic aneurysms are more often treated with flow diversion or stent-assisted coiling because of anatomical considerations (especially wide neck) and a better long-term occlusion rate [8]. Despite discrepancies in the literature, stent-assisted coiling and flow diversion seem to have

higher complication rates compared to coiling: 4-8% versus 1-4%, respectively [9–12]. Taken together, these two facts call for an appraisal of the specific risk of rupture of carotid ophthalmic aneurysms.

The purpose of this study was to compare the frequency of ophthalmic aneurysms in patients with aneurysmal subarachnoid haemorrhage and patients with UIAs, in order to estimate the relative rupture risk of ophthalmic aneurysms.

MATERIAL AND METHODS

This was a multicentre, observational study performed according to the STROBE guidelines [13]. A national institutional review board (IRB) approved the study protocol (IRB approval # CRM-2201-220). This work adheres to the World Medical Association Declaration of Helsinki.

Study population: ruptured intracranial aneurysms

Prospective selection of patients with aneurysmal subarachnoid haemorrhage from January 2021 to March 2021 has previously been reported [14]. Academic centres having contributed to the original study were invited to participate. Thirteen centres (12 French and 1 Swiss) participated in the present study.

Study population: unruptured intracranial aneurysms

Patients having undergone a cerebral digital subtraction angiography (DSA) performed in all participating centres from January 2021 to March 2021 were screened. Clinical charts and DSAs of all eligible patients were reviewed including age, sex, origin (Finnish, Japanese or other), hypertension, history of subarachnoid haemorrhage, multiple aneurysms and smoking, and aneurysm characteristics, including irregular shape, size and location. Ophthalmic aneurysms were defined as aneurysms with the ophthalmic artery arising from the neck or in the immediate vicinity of the aneurysm, and whose dome pointed superior in agreement with Rhoton's 3rd rule of aneurysms (illustrated in **Supplemental Fig. 1**) [15]. Superior hypophyseal aneurysms and carotid cave aneurysms were grouped together, as well as posterior inferior cerebellar artery aneurysms and V4 segment of the vertebral

artery aneurysms. Inclusion criteria in the UIA subgroup were (a) baseline exploration of an intracranial aneurysm by DSA performed between January 2021 and March 2021; (b) patients aged 18 or more. Exclusion criteria were (a) clinical charts unavailable; (b) imaging data unavailable; (c) dissecting aneurysms and (d) intracavernous aneurysms.

Statistical analysis

Categorical variables were compared using the χ^2 test. Continuous variables with a normal distribution were compared among groups using the Student's t-test. Continuous variables without a normal distribution were compared among groups using the Mann—Whitney U test. Odds-ratios for aneurysm rupture were calculated for each aneurysm location, as is recommended for case-control studies [16]. A multivariable logistic regression was applied to identify confounding factors, using age, sex, history of subarachnoid haemorrhage, hypertension, smoking, multiple aneurysms, aneurysm size, irregular aneurysm shape, and aneurysm location as explicative variables. Statistical analysis was performed using MedCalc® Statistical Software version 20.218 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023).

RESULTS

Patients' demographics

From January 2021 to March 2021, a total of 604 intracranial aneurysms (355 unruptured and 249 ruptured) were included in this study (Fig. 1). Median age was 57 years (IQR [49;65]), with a female predominance: 386/604 (64%). Irregular shape was observed for 131/355 (36.9%) unruptured aneurysms and 183/249 (72.3%) ruptured aneurysms ($p<0.0001$). Detailed characteristics are reported in **Supplemental Table 1**. No Finnish or Japanese patients were included.

Aneurysm location frequency

The frequency for every aneurysm location is shown in **Fig. 2** and reported in **Table 1** for all aneurysms (**Fig. 2A**), UIAs (**Fig. 2B**) and RIAs (**Fig. 2C**). Odds-ratios for aneurysm rupture is given for each aneurysm location (**Fig. 2D** and **Table 1)**. Ophthalmic aneurysms represented 9.3% (56/604) of intracranial aneurysms, 14.9% (53/355) of UIAs (second most common) and 1.2% (3/249) of RIAs (second least common, tied with anterior choroidal artery aneurysms). Initially, 4 ruptured ophthalmic aneurysms and 57 unruptured ophthalmic aneurysms were reported. Two of these aneurysms were consensually reclassified as a carotid cave aneurysm upon review during manuscript preparation (one ruptured illustrated in **Supplemental Fig. 2** and one unruptured**)**. Ophthalmic aneurysms were incidentally discovered 12.4 times more frequently than they were detected during haemorrhage. The unadjusted odds-ratio was 0.07 (95% confidence interval [0.02; 0.23], p value < 0.0001).

Adjusted odds-ratio in the multivariable logistic regression for aneurysm rupture for ophthalmic aneurysms was 0.12 (95% confidence interval [0.03; 0.43], p-value = 0.001).

Aneurysm size

Mean size was 6.0 mm for intracranial aneurysms, 5.3 mm for UIAs, and 7.0 mm for RIAs (**Fig. 3A and 3B**), $p < 0.0001$. Mean size of unruptured ophthalmic aneurysms was 5.4 mm (6^{th} highest out of 11 locations), and mean size of ruptured ophthalmic aneurysms was 12.7 mm (highest among all locations). Median size of ruptured ophthalmic aneurysms was 12.0 mm, while median size of ruptured non-ophthalmic aneurysms was 6.0 mm, p-value = 0.11. Ratio between mean size of ruptured aneurysm and mean size of unruptured aneurysm (Fig. 3C) was 2.4 for ophthalmic aneurysms (3^{rd} highest). Only anterior choroidal artery and posterior cerebral artery aneurysms, representing respectively 2.5% and 0.8% of intracranial aneurysms, were found to have a higher ratio.

DISCUSSION

Our study compared the proportions of each aneurysm location in a prospective cohort of ruptured intracranial aneurysms and a retrospective population of unruptured intracranial aneurysms. Ophthalmic aneurysms were under-represented in the RIA population by more than an order of magnitude. Furthermore, ruptured ophthalmic aneurysms seemed to have a higher mean size compared to other ruptured aneurysms in our study population, while the mean size of unruptured ophthalmic aneurysms is average compared to other unruptured intracranial aneurysms. Although no statistically significative difference was observed regarding the second point, this warrants further study with a larger population, as we only had 3 ruptured ophthalmic aneurysms in our study population. As previously described in the scientific literature, we found that anterior communicating artery aneurysms (and to a lesser extent posterior circulation aneurysms and posterior communicating artery aneurysms) were over-represented in the RIA population, suggesting a higher relative rupture risk compared to other intracranial aneurysms.

Estimating the rupture risk of an UIA is a key element of the decision-making process when considering preventive treatment. Our results are in accordance with existing literature, as internal carotid artery aneurysms have been described as having a lower risk of rupture compared to other intracranial aneurysms[4–7, 17, 18]. To our knowledge, no previous study has estimated the relative risk of rupture for different internal carotid artery aneurysm subgroups and specifically the carotid ophthalmic aneurysm location. Under-representation of carotid cave / superior hypophyseal aneurysms in our ruptured intracranial aneurysm population was not an expected

result, and also deserves to be explored, as unruptured carotid cave aneurysms make up roughly 10% of unruptured intracranial aneurysms. As mentioned in the introduction section, ophthalmic aneurysms are routinely treated by stent-assisted coiling and flow diverter stents, with better long-term occlusion rate than regular coiling [8]. However, despite some divergent data in the literature, stent-assisted coiling and flow-diverter stenting may have a higher than average complication rate, estimated at 4-8% [9–12]. Further studies with a prospective cohort are necessary to confirm that unruptured ophthalmic aneurysms have a low rupture risk, and that they may rupture at higher size compared to other aneurysm locations. Further studies with larger cohorts would enable in-depth analysis of ruptured ophthalmic aneurysms, as only 3 were present in our study. If the results are reproduced, serious reappraisal of carotid ophthalmic unruptured aneurysm preventive exclusion treatment is required. To put it plainly, if, on the one hand, stent-assisted coiling or flow diversion of an ophthalmic aneurysm presents twice as much serious adverse events as standard coiling and, on the other hand, ophthalmic aneurysms have a reduced rupture risk by an order of magnitude, then complication rates of ophthalmic aneurysm stent-based treatments need to be divided by 20 to match the benefit-risk ratio of say, an MCA aneurysm coiling. And this does not even take into account the discrepancy in rupture sizes between ophthalmic and non-ophthalmic aneurysms.

These results do not affect the decision-making process for large and giant aneurysms with compressive symptoms, for which treatment is indicated. However, these are an uncommon subgroup of ophthalmic aneurysms. Compressive aneurysms of the internal carotid artery in the literature tend to have a much higher diameter than asymptomatic aneurysms, over 15 mm[19, 20]. Meanwhile, the mean

size of unruptured ophthalmic aneurysms in our study population was 5.4 mm. No unruptured ophthalmic aneurysm in our study had a diameter over 15 mm, and only 4/53 (8%) had a diameter between 10 mm and 15 mm.

Our study suffers from several limitations. (i) It is a comparison of 2 populations (UIA and RIA), not a direct evaluation of the risk of rupture through a longitudinal follow-up study of a prospective cohort over time, falling short of the gold standard to evaluate risk of rupture statistics. (ii) The UIA populations is comprised only of aneurysms explored by DSA, while not all UIA undergo DSA. We expect that aneurysms that were not explored by angiography, and thus not included in our study, to have been evaluated as having a low risk of rupture based on non-invasive imaging and clinician preconceptions. Therefore, patients with unruptured ophthalmic aneurysms that did not undergo angiography are expected to be overrepresented compared to other locations, especially locations outside “internal carotid artery” aneurysms. If anything, the bias is expected to artificially increase the odds-ratio for ophthalmic aneurysm rupture provided in this study. Nevertheless, this limitation does impact our data. (iii) Counter to expectation, patients in the RIAs subgroup were found to be less prone to have blood hypertension as compared to patients in the UIA subgroup. Patient history data comes from patient interview, either during hospital stay or outpatient consultation. Patients with a RIAs are seen in an emergency setting, often comatose, with medical history often difficult to collect, whereas patients with an unruptured intracranial aneurysm are usually seen as outpatients in a consultation setting, making medical history collection easier and more thorough. Bias in data collection

could therefore potentially explain the surprising lower frequency of arterial hypertension in the RIA group. However, this does not impact results regarding aneurysm location. (iv) Carotid cave aneurysms are sometimes misclassified as ophthalmic aneurysms. However only one ruptured carotid cave aneurysm was observed in our study population (which was initially misclassified as an ophthalmic aneurysm). While it was not the purpose of the study, our results suggest that carotid cave / superior hypophyseal aneurysms also have a very low relative risk of rupture compared to other aneurysm locations (with the exception of ophthalmic aneurysms). Therefore, misclassifications between these 2 subgroups, if they have persisted, would not have a significative impact on the results.

In summary, our study suggested that ophthalmic aneurysms have a very low risk of rupture, and that ophthalmic aneurysms reach a higher-than-average size before they rupture. Operators should take this into account to critically re-evaluate the indication of preventive exclusion treatment of unruptured ophthalmic aneurysms, especially if treatment options with potentially higher complications rates, such as stent-assisted coiling or flow-diversion, are considered.

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Figure 1 – Flowchart of patient selection.

Figure 2 – Frequency of different locations for all intracranial aneurysms (A), unruptured intracranial aneurysms (B) and ruptured intracranial aneurysms (C). (D) Forest plot of odds-ratios for aneurysm rupture, comparing aneurysm locations.

AChoA: Anterior choroidal artery; MCA : middle cerebral artery; ICA: internal carotid artery; ACA: anterior cerebral artery; Pcom: posterior communicating artery; V4: fourth segment of the vertebral artery; PICA: posterior inferior cerebellar artery; PCA: posterior cerebral artery; Acom: anterior communicating artery.

Figure 3 – Mean size of unruptured intracranial aneurysms (A) and ruptured intracranial aneurysms (B) by location. (C) Mean size ratios between ruptured intracranial aneurysms and unruptured intracranial aneurysms by location.

AChoA: Anterior choroidal artery; MCA : middle cerebral artery; ICA: internal carotid artery; ACA: anterior cerebral artery; Pcom: posterior communicating artery; V4: fourth segment of the vertebral artery; PICA: posterior inferior cerebellar artery; PCA: posterior cerebral artery; Acom: anterior communicating artery.

Aneurysm location	Total (n=604)	UIA (n=355)	RIA (n=249)	Unadjusted odds-ratio [95%CI]	Adjusted odds-ratio [95%CI]	p-value for unadjusted OR
Superior Hypophyseal - Carotid Cave	37 (6.1%)	36 (10.1%)	1 (0.4%)	0.04 [0.005; 0.26]	0.08 [0.01 ; 0.69]	**0.001***
Ophthalmic	56 (9.3%)	53 (14.9%)	3 (1.2%)	0.07 [0.02; 0.23]	0.12 [0.03 ; 0.43]	**< 0.0001***
AChoA	15 (2.5%)	12 (3.4%)	3 (1.2%)	0.35 [0.10; 1.25]	0.66 [0.15 ; 2.96]	0.11
Basilar artery	33 (5.5%)	24 (6.8%)	9 (3.6%)	0.52 [0.24; 1.13]	0.65 [0.25 ; 1.72]	0.10
MCA	170 (28.1%)	117 (33.0%)	53 (21.3%)	0.55 [0.38; 0.80]	reference	**0.002***
ICA termination	19 (3.1%)	13 (3.7%)	6 (2.4%)	0.65 [0.24; 1.73]	1.08 [0.35 ; 3.33]	0.39
ACA	45 (7.5%)	28 (7.9%)	17 (6.8%)	0.86 [0.46; 1.60]	1.92 [0.89 ; 4.13]	0.63
Pcom	62 (10.3%)	27 (7.6%)	35 (14.1%)	1.99 [1.17; 3.38]	3.10 [1.59 ; 6.06]	**0.01***
V4 - PICA	20 (3.3%)	7 (2.0%)	13 (5.2%)	2.74 [1.08; 6.97]	3.16 [1.03 ; 9.71]	**0.03***
PCA	5 (0.8%)	1 (0.3%)	4 (1.6%)	5.78 [0.64; 52.03]	6.28 [0.63 ; 62.75]	0.12
Acom	142 (23.5%)	37 (10.4%)	105 (42.2%)	6.27 [4.10; 9.57]	6.51 [3.66 ; 11.59]	**< 0.0001***

Table 1 – Frequency of every aneurysm location for each group, and odds-ratios for aneurysm rupture based on aneurysm locations.

UIA: unruptured intracranial aneurysm; RIA: ruptured intracranial aneurysm; 95%CI: 95% confidence interval.

* p-value < 0.05.