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Effect of Size and Location of Unruptured Intracranial Aneurysms on Self-Reported Headache

Juan M MARQUEZ-ROMERO[1,4], Dulce A ESPINOZA-LÓPEZ[2], Juan M CALLEJA-CASTILLO[3], Fernando ZERMEÑO-PÖHLS[2], Rogelio SALINAS-GUTIÉRREZ[4]

[1]Hospital General de Zona #2, IMSS, OOAD Aguascalientes
[2]Departamento de Neurología, Instituto Nacional de Neurología "Manuel Velasco Suárez", Mexico
[3]Centro Neurológico ABC, Mexico
[4]Centro de Ciencias Básicas, Universidad Autónoma de Aguascalientes, Mexico

Corresponding author: Juan M CALLEJA-CASTILLO ✉ juancalleja@me.com

ABSTRACT

AIM: To describe the relationship between aneurysm size and location with the prevalence of headache at diagnosis and three- and six-month follow-up in a sample of patients with UIA.

MATERIAL and METHODS: In this cohort study, patients were diagnosed with UIAs by digital subtraction angiography (DSA). Follow-up visits occurred three and six months after the diagnosis. Headache presence was registered, and headache was further classified by phenotypes. After DSA, the recorded variables were aneurysm number, morphology, location, and size (diameter [W], neck [N], and dome-neck distance [H]). The aspect ratio (H/N) and the dome/neck ratio (W/N) were calculated. The outcome of this study was the self-reported headache status at follow-up.

RESULTS: Data from 42 patients and 46 aneurysms were available; 81.0% of patients were women, with a mean age of 57.4±14.3 years. Headache was reported by 61.9% of the patients. The pain phenotype was tension-type in 38.1%, migraine in 11.9%, neuralgia in 2.4%, and unclassifiable in 9.5%. The median (min–max) measurements were W=5.05 (0.89–22.9); N=3.02 (0.52–17.9); H=5.08 (0.92–23.0); aspect ratio 1.59 (0.68–17.69) and W/N ratio 1.65 (0.62–16.92). Thirty-three patients (37 aneurysms) received treatment, 47.8% by surgical clipping and 32.6% by endovascular occlusion. In the treated patients, headaches had persisted in 14.3% until the first visit and in 9.5% until the second visit. There were no differences in any registered variables between patients with and without headaches at follow-up.

CONCLUSION: In this study, data was found that support that headaches in patients with UIAs improve after treatment and that such improvement is probably unrelated to the size and shape of the UIAs.

KEYWORDS: Intracranial aneurysm, Prevalence, Headache, Outcome

INTRODUCTION

The overall prevalence of incidental unruptured intracranial aneurysms (UIAs) ranges from 3.8% (95% CI 3.0% to 4.8%) to 8.3% (95% CI 7.1% to 9.7%), depending on which definitions are used, and is according to size and location (8). Up to one third of patients with UIAs will present with headaches (2,9). Although there are defined criteria for secondary headaches attributed to UIAs, (6) headaches have generally been considered unrelated to the presence of UIAs (2).

While the true nature of the relationship between UIAs and headaches is still being studied, a meta-analysis suggests that headache intensity significantly decreases after treatment (3). To further increase the knowledge regarding the course of

Juan M MARQUEZ-ROMERO : 0000-0002-5059-1174
Dulce A ESPINOZA-LÓPEZ : 0000-0001-8920-3901
Juan M CALLEJA-CASTILLO : 0000-0002-0423-9719
Fernando ZERMEÑO-PÖHLS : 0000-0002-1694-8395
Rogelio SALINAS-GUTIÉRREZ : 0000-0002-1669-4460

headaches in patients with UIAs, this study aimed to describe the relationship between aneurysm size and location and the prevalence of headaches at three-month follow-ups in a sample of patients with UIAs.

MATERIAL and METHODS

Participants

This cohort study included all consecutive patients diagnosed with UIAs at a third-level care facility. The inclusion criteria were as follows: 1) age 18 or older; 2) presence of one or more UIAs confirmed by digital subtraction angiography (DSA); and 3) signed an informed consent form. The exclusion criteria were as follows: 1) acute onset of headache; 2) progressive worsening; and 3) presence of systemic symptoms.

During a one-year recruitment period at the institution, 204 patients received a diagnosis of an intracranial aneurysm; out of them, 42 patients had UIAs and were enrolled. Regardless of the initial cause of consultation and neuroimaging modality utilized to diagnose or suspect the presence of UIAs, all patients underwent a six-vessel DSA (internal and external carotids and vertebral arteries). After DSA, a case-by-case analysis by an internal committee comprised of vascular neurosurgeons and endovascular neurologists recommended the best treatment modality for each patient. After the committee´s review, it was recommended which patients required treatment, and consent was obtained for the therapeutic procedure. Reasons for not being treated included a recommendation by the committee or rejection of the treatment offer.

Irrespective of the treatment status or modality after the committee recommendation, all the patients were scheduled for follow-up visits at the outpatient clinic three and six months after the diagnosis.

Variables

At diagnosis, data registered included the dates for all evaluations, the patient demographics, and the characteristics of headache [including if the patient fulfilled the International Classification of Headache Disorders 3rd Edition (ICHD 3) criteria for 6.3.1, Headache attributed to an unruptured saccular aneurysm] (6) and the presence of vascular risk factors. Headache phenotypes were defined as follows: 1) migraine, a throbbing or pulsating hemicranial pain accompanied by hypersensitivity symptoms to light, sound, or smell and nausea or vomiting; 2) tension-type, a diffuse aching bilateral head pain without the characteristics of migraine or neuropathic pain; 3) neuralgia, an electric shock-like, shooting, stabbing or sharp paint that might be accompanied by autonomic symptoms (ptosis, lacrimation, rhinorrhea, facial swelling, conjunctival injection or pupil changes); and 4) unclassified, all other types of headaches distinct from those previously described, including those combining characteristics of two or more of the phenotypes. Headache was considered chronic if it occurred for 15 or more days/month for three or more months.

After DSA, we registered the number of aneurysms, their morphology, location (for carotid aneurysms; we used the Bouthillier classification) (1), and size (diameter [W], neck [N], and dome-neck distance [H]) in millimeters. We then calculated and registered the aspect ratio (H/N) and the dome/neck ratio (W/N). Whenever multiple aneurysms were identified, the measurements for each aneurysm were recorded. We registered the treatment modality and treatment-related morbidity for the patients who received treatment.

The outcome of this study was the self-reported headache status (no headache despite a previous headache, a previous persistent headache, and development of headache in a patient without a previous headache) at three and six months after the confirmation of UIAs by DSA.

Statistical Analysis

Categorical variables are expressed as frequencies and percentages, and comparisons were made with the chi-square test. Normality was tested using the Kolmogorov-Smirnov test. Continuous data are presented as the mean ± standard deviation/median (maximum and minimum values) according to the data distribution. Accordingly, the differences between groups were determined by employing the independent samples T Test/Mann-Whitney U. The predictive performance of the aneurysm measurements to discriminate patients with headaches was assessed with receiver-operating characteristic area under the curve analysis (ROC-AUC). We considered a value of $p \leq 0.05$ as significant. All analyses were performed utilizing SPSS version 22.0 (IBM, Armonk, NY, USA).

Protocol approval and informed consent

The Institutional Review Board of the National Institute of Neurology and Neurosurgery "MVS" reviewed and approved the study protocol and informed consent form (Reference DIC/043-44/12). All participants signed the approved informed consent form.

RESULTS

For basal characteristics, data from 42 patients were available; 34 were women (81.0%), with a mean age of 57.4 ± 14.3 years. The median time from diagnosis of UIA as confirmed by DSA was 43.5 days (0-287). Three patients missed both follow-up visits. Therefore, the analysis regarding outcomes was performed with data from 39 patients. Twenty-five patients (59.5%) exhibited at least one comorbidity; the most common was hypertension in 21 patients (50.0%), followed by diabetes mellitus in three patients (7.2%) and rheumatoid arthritis, extrapyramidal syndrome, and parotid cancer, each in one patient.

Characteristics of the headaches

At the time of the confirmation of the diagnosis, headache was declared by 26 patients (61.9%); only twelve patients (28.6%) fulfilled the criteria for headache attributed to an unruptured saccular aneurysm. The pain phenotype was tension-type in 38.1%, migraine in 11.9%, neuralgia in 2.4%, and unclassifiable in 9.5% of patients. Twenty-two patients (84.6%) fulfilled the criteria for chronic headache.

Characteristics of the UIAs

We identified 46 aneurysms in 42 patients; three carried multiple

aneurysms, one had three, and two had two aneurysms. Forty aneurysms were saccular, and six (14.3%) were fusiform. The aneurysms' locations were, in order of frequency, the internal carotid artery (20 aneurysms, 43.5%), the middle cerebral artery (12 aneurysms, 26.1%), the posterior communicating artery (nine aneurysms, 19.6%), the anterior communicating artery (four aneurysms, 8.7%) and the posterior inferior cerebellar artery (one aneurysm, 2.2%); 56.5% were on the left side. The carotid aneurysm locations were as follows: C4, three (15%); C5, five (25%); C6, eight (40%); and C7, four (20%). The median (min–max) measurements were W= 5.05 (0.89–22.9); N= 3.02 (0.52–17.9); H= 5.08 (0.92–23.0); aspect ratio 1.59 (0.68–17.69) and W/N ratio 1.65 (0.62–16.92). Table I shows the differences in the basal characteristics separated by the headache status at the time of the confirmation of the diagnosis.

Treatment and outcomes

Thirty-three patients (37 aneurysms) received treatment, 22 (47.8%) by surgical clipping and 15 (32.6%) by endovascular

Table I: Basal Characteristics of the Participants

	No Headache	Headache	p-value
Age, mean ± SD	59.3 ± 15.1	56.2 ± 13.9	0.49*
Female, n (%)	11 (32.4)	23 (67.6)	0.22**
Comorbidities, n (%)	16 (38.1)	26 (61.9)	
Hypertension, n (%)	9 (42.9)	12 (57.1)	
Diabetes Mellitus, n (%)	1 (33.3)	2 (66.7)	0.83**
Other, n (%)	1 (33.3)	2 (66.7)	
None, n (%)	5 (31.3)	11 (68.8)	
Number of aneurysms	1 (1 – 2)	1 (1 – 3)	0.84***
Aneurysms measurements			
Diameter, mm	8.10 (0.94 – 22.90)	4.49 (0.89 – 22.00)	0.42***
Neck, mm	3.57 (1.27 – 7.00)	3.00 (0.52 – 17.9)	0.41***
Dome-neck distance, mm	7.59 (1.02 – 20.06)	4.88 (0.92 – 23.00)	0.71***
Aspect ratio, mm	1.64 (0.68 – 3.97)	1.58 (0.72 – 17.69)	0.72***
Dome/neck ratio, mm	1.57 (0.62 – 5.59)	1.65 (0.75 – 16.92)	0.94***
Location			
Internal Carotid, n (%) C4 C5 C6 C7	9 (47.4) 2 (66.7) 2 (40.0) 2 (28.6) 3 (75.0)	10 (52.6) 1 (33.1) 3 (60.0) 5 (71.4) 1 (25.0)	
AcoA, n (%)	1 (50.0)	1 (50.0)	0.66*
Pcom, n (%)	2 (22.2)	7 (77.8)	
MCA, n (%)	4 (36.4)	7 (63.6)	
PICA, n (%)	0	1 (100.0)	
Treatment, n (%)	14 (42.4)	19 (57.6)	
Surgical, n (%)	8 (40.0)	12 (60.0)	
Endovascular, n (%)	6 (46.2)	7 (53.8)	0.51*
None, n (%)	2 (22.2)	7 (77.8)	

All values median (min-max) unless otherwise specified. ***SD:*** *Standard Deviation.* ***AcoA:*** *Anterior Communicating Artery.* ***Pcom:*** *Posterior Communicating Artery.* ***MCA:*** *Middle Cerebral Artery.* ***PICA:*** *Posterior Inferior Cerebellar Artery. * Independent samples T-Test. ** Chi-square test. ***Independent samples Mann-Whitney U Test.*

Table II: Receiver-Operating Characteristic Area Under the Curve Analysis for the Measurements and Composite Indexes of the Aneurysms

	Three months			Six months		
	AUC	**95% CI**	**p**	**AUC**	**95% CI**	**p-value**
Neck	0.523	0.306 – 0.741	0.86	0.533	0.359 – 0.707	0.83
Dome-Neck distance	0.549	0.290 – 0.808	0.71	0.332	0.158 – 0.506	0.28
Diameter	0.551	0.322 – 0.780	0.69	0.368	0.196 – 0.541	0.39
Aspect ratio	0.491	0.206 – 0.776	0.94	0.283	0.040 – 0.526	0.16
Dome/neck ratio	0.546	0.277 – 0.815	0.72	0.355	0.107 – 0.603	0.35

AUC: *Area under the curve,* ***CI:*** *Confidence interval.*

occlusion. Nine aneurysms from seven patients were left untreated; in all but one patient, the decision not to treat was medically advised. For the 33 patients who received treatment, the median time from DSA to treatment was 28 days (0-274). Complications occurred in three patients (6.5%): one in the surgical group and two in the endovascular group. One patient recovered completely in the immediate postoperative period, and one patient from each treatment modality had a permanent deficit that remained (both patients had mild aphasia).

At three months, 37 patients (85.7%) attended their follow-up visit. The median time to follow-up was 91 days (60–92). Six patients (14.3%) had persistent headaches. The pain phenotype at this visit was tension-type in three patients (50.0%) and migraine in three patients (50.0%). At six months, 34 patients (81.0%) attended their follow-up visit, and the median time to follow-up was 182 days (129–184). Four patients (9.5%) had persistent headaches. The pain phenotype at six months was tension-type in three patients (75.0%) and migraine in one patient (25.0%). There were no differences in the registered variables between patients with and without headaches at three or six months of follow-up. Additionally, at follow-up, no patients were diagnosed with new headaches. Table II shows the results of the ROC-AUC analysis. The overall discriminatory capacity of the aneurysm measurements and its composite measures (aspect and W/N ratios) for identifying the persistence of headache was near 50% at three months but was lower (≈30%) at six months.

DISCUSSION

In this cohort of patients with UIA-related headaches, the basal characteristics of the population correspond with those of other series, namely, the female preponderance among participants and a mean age between 50 and 60 years (2,4,9,11,12). The prevalence of headache (61.9%) is also similar to previous studies that report a prevalence up to 72% (10). When the ICHD 3 criteria for secondary headache attributed to UIAs were utilized, the prevalence decreased to 28.6%. In most previous reports, the headache diagnosis was not based on the ICHD 3 (2,11), but in the study by Schwedt et al., 10.3% of the participants fulfilled such criteria (13). In the series by Raps et al., 51.4% of the UIAs that presented as chronic symptoms corresponded to headache, which was attributed to mass effect (the mean aneurysm diameter was 22 mm compared to 5 mm in the present study) (12). Additionally, in the series by Deruty et al., 54.5% of the UIAs labeled as questionably symptomatic were associated with headaches, although the authors did not report the diameter of the aneurysms (4). Both prevalences are similar to the prevalence obtained in the participants of this study.

Regarding headache phenotype, tension-type was the most frequent, followed by migraine, which is similar to results described in Asian (9), and North American populations (13) but different from the results of the meta-analysis (3). Interestingly, in this study, the prevalence of migraine was 11.9%, more than half of that reported in a study from the Netherlands (24.4%) (14). This discrepancy could be explained because, in the Dutch study, migraine history was assessed via a telephone interview, which causes a susceptibility to recall bias. In contrast, in our study, the headache phenotype was registered at the diagnosis of the UIA.

Previous studies have also failed to demonstrate differences in the persistence or improvement of headaches concerning the aneurysm's location or size after aneurysm treatment, regardless of the treatment modality (2). In this regard, the present study adds to the current knowledge by analyzing aneurysm size and composite indices of shapes as a continuous variable and obtaining the same result as studies where the aneurysm size has been analyzed by categories (for example, small, medium, large, very large and giant) (2). Notably, the role of size and composite indices of UIAs was not studied in the meta-analysis by Dandurand et al. (3). This is important because the only headache-inducing mechanism in patients with UIAs that has been previously described is the mass effect in aneurysms with a diameter larger than 10 mm (7), and 20 mm (12). In a prospective study that showed improvement in the frequency of headaches after treatment of UIAs, the mean aneurysm size was similar to our findings and was unrelated to the persistence of headaches after treatment (13). Unfortunately, aneurysm size was reported as a single value possibly corresponding to diameter, and the location was dichotomized into anterior and posterior circulation. On the other hand, the authors examined the role of anxiety with

a standardized questionnaire and found it to be higher in patients with persistent headaches.

In another study, 77% of the patients recruited reported some improvement of their symptoms following endovascular treatment of UIAs (5). However, headache was assessed with the 11-point pain scale, which is only validated for migraine pain, and it is unclear whether all the patients included presented migraine or if distinct headache phenotypes were graded using the same scale. Additionally, the aneurism size was dichotomized into ≥ 10 mm and < 10 mm, with a higher proportion of smaller aneurysms (58.3 vs. 41.7%). Finally, the clinical outcome of some patients was evaluated by a telephone interview.

The findings of this and previous studies indirectly support the hypothesis that the improvement in the patient's headache after treatment of a UIA is probably due to the relief of the psychological stressor of carrying the UIA (3), and is unrelated to the removal of the aneurysm. Given that both surgical (14), and endovascular (10,11) treatment of UIAs have excellent outcomes and low morbidity and mortality, an improvement in headache is expected after discharge. Nevertheless, in the study by Ji et al., headache ipsilateral to the aneurysm location and size >10 mm were predictors for headache relief after endovascular treatment of UIAs; their findings support the role of the mass effect in headache pathogenesis (7). The issue remains unresolved for patients with UIAs <10 mm (3).

Similar to our results, in a study of 146 patients with UIAs, Toma et al. reported that the size of aneurysms, the status of the aneurysm (treated vs. untreated), and the method of treatment (surgical vs. endovascular) did not significantly differ between the groups, but they did find differences in the frequency of headache by the location of the UIA (15). There was a high incidence of headaches in patients with aneurysms of the ophthalmic segment of the internal carotid artery and the M1 segment of the middle cerebral artery.

This study is the first to report the outcome of headaches in a cohort of Latin American patients with UIAs. Its prospective design and detail in describing the different measurements and indices of the shape of the aneurysms constitute its main strengths. Nevertheless, it also has limitations. First, the sample was recruited from a major referral center, which can lead to selection bias. Second, not all the patients received treatment. Third, the outcome (headache persistence) was dichotomized, and the severity was not evaluated. Therefore, as previous investigators have stated (3,7), there is a strong need to develop a large, multicenter study with standardized inclusion criteria and outcome measures.

CONCLUSION

This study found that headache is highly prevalent in patients with UIAs, with the most common phenotype being the tension type. Additionally, the characteristics of the aneurysms, such as size, location, side, and composite indices of shape, do not appear to contribute to discrimination between patients who will have persistent headaches after treatment. The results reinforce two ideas: one, that headaches related to UIAs improve after treatment, and two, such improvement is probably unrelated to the size and shape of the UIAs.

AUTHORSHIP CONTRIBUTION

Study conception and design: JMMR, DAEL, JMCC
Data collection: DAEL, JMCC, FZP
Analysis and interpretation of results: JMMR, JMCC, RSG
Draft manuscript preparation: JMMR
Critical revision of the article: JMMR, DAEL, JMCC, FZP, RSG
All authors (JMMR, DAEL, JMCC, FZP, RSG) reviewed the results and approved the final version of the manuscript.

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