Headache and Treatment of Unruptured Intracranial Aneurysms

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Background and Purpose: The relationship between unruptured intracranial aneurysms (UIAs) and chronic headache and the impact of aneurysm treatment on headache outcome are controversial. The aim of this study was to determine clinical features of a supposedly primary headache in patients with UIA. We also assessed changes in headache characteristics after UIA treatment. *Methods:* We examined clinical and imaging data of patients in whom a UIA was diagnosed during diagnostic workup of a suspected primary headache. Medical records were reviewed and personal telephone follow-ups were performed after UIA treatment to assess changes in the frequency and intensity of the headache. *Results:* Forty-two patients (76%) reported a substantial improvement in headache frequency and intensity after UIA treatment. Forty-five patients (81%) reported a decrease in headache frequency from a median of 8 days/month before treatment to 1 day/month after treatment (95% confidence interval [CI] 81-83, $P < .001$). The average intensity in an analog pain scale was 7.7 ± 1.6 before treatment and 5.6 ± 2.4 after treatment ($P < .001$). Higher headache frequency was associated with a greater odd of improvement after treatment (odds ratio 1.12, 95% CI 1.0-1.26, $P = .03$). No associations were found between the type of headache, type of treatment (endovascular versus surgical), number, size, or localization of the aneurysms and the response to treatment. *Conclusions:* The treatment of UIA had a robust beneficial effect on previous headache. Although a "placebo" effect of aneurysm treatment cannot be ruled out, these results suggest a potential association between UIA and certain chronic headaches usually considered to be primary. **Key Words:** Headache—intracranial aneurysm—therapeutics—endovascular therapy.

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Introduction

Unruptured intracranial aneurysms (UIAs) are common in the general population. Imaging and autopsy studies have shown a prevalence ranging from .4% to 6%.[1,2] Aneurysmal subarachnoid hemorrhage has an incidence of 6-8 cases per 100,000 person/year[3] and generally occurs in patients unaware of the presence of a UIA. Chronic primary headache is not usually considered a clinical manifestation of UIAs.[2]

Certain UIAs can become symptomatic due to enlargement and compression of the second and third cranial nerves. UIAs are clinically expressed as vision loss or oculomotor abnormalities, respectively. Signs of brainstem compression, as well as cerebral ischemia as a result of emboli originating in the aneurysm, can also occur.[4,5] However, most UIAs are diagnosed in patients undergoing imaging studies during workup for long-standing uncomplicated headache. Those UIAs are usually deemed incidental and presumed asymptomatic.

Despite the fact that the nature of the association, if any, between headache and UIA is not well established, several studies have mentioned the presence of headache in subjects with UIAs, in 18%-34% of cases.[6-8] Several types of headache including cluster headache, hemicrania continua, and migraine, are present in patients with UIAs. Symptoms occasionally improve after treatment of the aneurysm.[9-15] In prior reports, aneurysm treatment was followed by improvement in severity or frequency of headache in 59%-92% of patients, regardless of the type of treatment (endovascular or surgical).[16-19] However, these studies included patients in which the aneurism had been diagnosed in the workup of various conditions other than headache. Also, information about the characteristics of the headache that may indicate the presence of a UIA and its response to treatment is scarce.

The aims of the present study were to describe headache characteristics in patients diagnosed with a UIA during workup of an otherwise primary headache, to determine clinical features that should raise suspicion of a possible underlying UIA, to assess headache changes after UIA treatment, and to find potential predictors of favorable outcome.

Methods

In this single-center study, we identified patients undergoing endovascular or surgical treatment for UIA between 2002 and 2013, and selected those in which the UIA was diagnosed during the workup of a headache determined to be primary by International Classification of Headache Disorders, 3rd edition (ICHD-III), criteria.[20] All patients were followed up at the outpatient clinic or received phone calls for verification of outcome and vital status.

Although current guidelines do not strongly recommend treatment of UIAs, the decision to treat the aneurysms was finally based on the preference of the patient and the primary physician.

Patients meeting criteria for thunderclap headache according to ICHD-III[20] were excluded from the study because this could also be a manifestation of subarachnoid hemorrhage or could represent "sentinel headache" from early bleeding of the aneurysm.[21-23]

Medical records were reviewed and demographic characteristics and comorbidities were assessed. The characteristics of the previously referred headache, including type (in some cases more than 1 type of headache were reported), localization, frequency, intensity (using a numeric rating scale for pain),[24] and response to medication, were assessed. Headache types were classified according to the ICHD-III criteria.[20] Aneurysm characteristics (i.e., number, location, and size) and type of treatment (i.e., endovascular versus surgical) were also recorded.

Personal or telephone interviews were conducted after endovascular or surgical treatment by neurologists using a standardized questionnaire. The questionnaire included questions about headache characteristics before and after aneurysm treatment, including the number of days with headache, analog pain scale rating, response to symptomatic treatment, and subjective impression of improvement, worsening, or no change after treatment. Headache was classified according to the ICHD-III criteria.[20] Also, as endovascular treatment does not result in aneurysm size change, whereas surgery produces a reduction in the size of the lesion, we compared outcomes in both groups.

Anxiety, in general,[25] and in patients with UIA diagnosis in particular, may influence symptoms and the effect of treatment.[26] We investigated changes in headache characteristics in the period between aneurysm diagnosis and treatment (type of headache, frequency, intensity, and response to symptomatic treatment) to assess potential changes in headache due to the psychological impact of harboring a UIA. Additionally, 29 migrainous patients without UIAs, previously studied with magnetic resonance angiography, were randomly selected from our clinic database, and served as controls. We investigated whether migraine in patients with UIA had clinical or demographic features distinct from those who had migraine but no UIA.

Approval from the Ethics Standards Committee was obtained to conduct the present study.

Statistics

We assessed differences between groups using the Fisher exact test, χ^2 test, or analysis of variance according to variable type. A Poisson regression model with mixed effects for individuals, adjusted by age, gender, and type of headache, was used to compare pre- and post-treatment headache episodes. Logistic and ordinal mixed effects models were used to assess changes in headache intensity and subjective improvement. Factors associated with headache improvement were studied in univariable and

multivariable analyses. All variables with a *P* value of .20 or less in the univariable analyses were included in the multivariable regression model. Variables were then added in a backward stepwise procedure. A *P* value of less than .05 was considered significant. All statistical analyses were performed using STATA version 12 (Statacorp, Texas, USA).

Results

Sixty-four out of 190 patients who underwent treatment for UIAs during this period had been diagnosed during workup for long-standing headache. Eight subjects were lost to follow-up, and clinical and imaging data were available for 56 subjects who were included in the study. The patients' demographics and clinical features are shown in Table 1.

We classified aneurisms according to their size: small (0-4.9 mm), medium (5.0-9.9 mm), large (10.0-24.9 mm), and giant (larger than 25 mm).

No stroke, death, or other events were reported as complications of aneurism treatment procedures.

Fifty-two percent of patients with UIA had migraine without aura, 12% had migraine with aura, 29% had tension-type headache, and 7% had trigeminal neuralgia.

Forty-two patients (76%) reported subjective substantial improvement of headache after treatment, 12 patients (22%) reported no significant changes, and 1 subject (2%) reported worsening of headache (Fig 1). Forty-five patients (81%) reported a decrease in headache frequency from a median of 8 days/month (range 1-30) before treatment to 1 day/month (range 0-20) after treatment (95% confidence interval [CI] 81-83, $P < .001$). The mean intensity in the pain analog scale (0-10) also decreased from 8 (range 2-10) to 6 (range 1-10) ($P < .001$) with an odds for pain improvement after treatment of 4.9 (95% CI 2.4-9.9, $P < .001$) (Fig 2).

We assessed potential changes in headache due to the psychological impact of harboring a UIA and the effect of UIA on treatment. Most patients (91%) did not report changes in their headache frequency or intensity after UIA diagnosis, with only 4% reporting headache worsening and 5% reporting some degree of improvement.

We did not find differences in outcome between patients taking or not taking aspirin after aneurism treatment ($P = .26$).

Potential predictors of a favorable outcome after UIA treatment were investigated using a logistic multivariable model built with a backward stepwise procedure. We compared age, gender, headache type, number of aneurysms and size, headache frequency, headache severity and type of treatment received (endovascular versus clipping) in the group with improvement versus the group without improvement. Only higher headache frequency was associated with a greater odd of improvement after treatment (odds ratio 1.12, 95% CI 1.0-1.26, $P = .03$).

Table 1. *Patients' clinical and demographic characteristics*

Characteristics	Patients with all types of headache (n = 56)
Age (years, SD)	51.8 ± 14
Gender (F : M)	45:11
Headache type, n (%)	
Migraine without aura	29 (51.8)
Migraine with aura	7 (12.5)
Tension type	16 (28.6)
Trigeminal neuralgia	4 (7.1)
Comorbidities, n (%)	
Dyslipidemia	16 (29)
Hypertension	17 (30)
CHD	4 (7)
CVD	5 (9)
Smoking	39 (70)
Number of aneurysms, n (%)	
1	40 (71)
2	9 (16)
More than 2	7 (13)
Aneurysm type, n (%)	
Saccular	50 (90)
Fusiform	2 (4)
Other	4 (6)
Aneurysm size, n (%)	
Small	39 (49)
Medium	28 (35)
Large	10 (12)
Giant	3 (4)
Aneurysm localization, n (%)	
Carotid	22 (26)
MCA	24 (28)
PCA	1 (1)
ACA	3 (3)
Acom	8 (9)
Pcom	4 (5)
ICA-Ophthalmic S.	16 (19)
Ophthalmic	1 (1)
Basilar	1 (1)
Vertebral	1 (1)
Choroidal	2 (2)
Hypophyseal	3 (3)
Type of intervention, n (%)	
Coiling	16 (29)
Stenting	9 (16)
Coil–stent	22 (39)
Clipping	9 (16)
Treatment after intervention, n (%)	
None	18 (32)
ASA	6 (11)
Clopidogrel	2 (4)
ASA + clopidogrel	30 (54)

Abbreviations: ACA, anterior cerebral artery; Acom, anterior communicating artery; ASA, aspirin; CHD, congestive heart disease; CVD, cardiovascular disease; F, female; ICA-Ophthalmic S., internal carotid artery–ophthalmic segment; M, male; MCA, middle cerebral artery; PCA, posterior cerebral artery; Pcom, posterior communicating artery; SD, standard deviation.

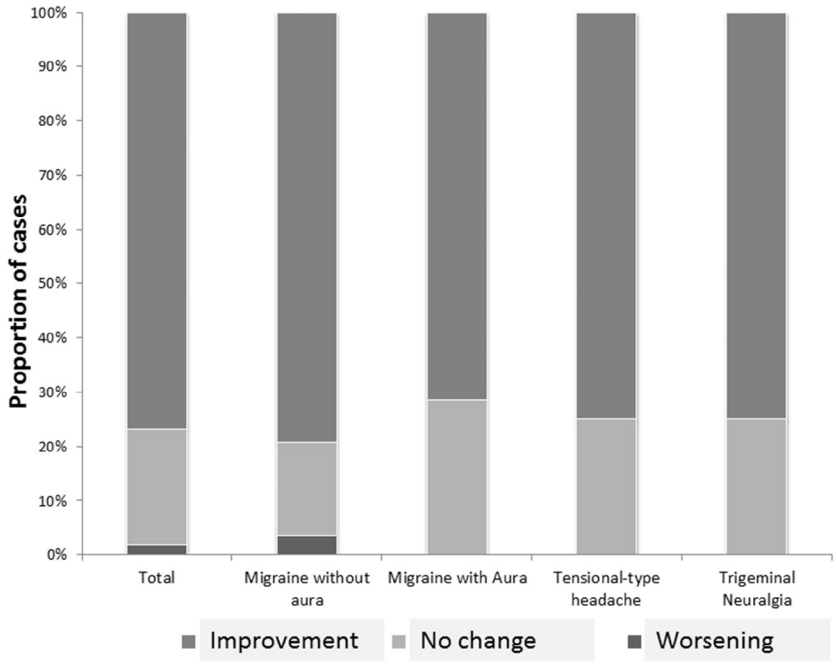

Figure 1. *Outcomes after treatment. Percentage of patients referring to improvement, worsening, or no change according to different headache types.*

Migraine patients harboring a UIA tended to be older than those without UIA (51 versus 42 years old, $P = .05$).

The onset of migraine occurred later in life in the UIA group (34 versus 25 years old, $P = .02$). There were no significant differences between prior headache intensity and frequency and the likelihood of harboring a UIA.

Nine (16%) patients underwent treatment with stent placement, 22 (39%) had treatment with stent and coils, 16 (29%) had treatment with coil placement alone, and 9 (16%) underwent surgical clipping. The type of treatment received (i.e., endovascular versus clipping) did not influence the outcome of the headache.

Discussion

Our data add to previous reports of an association between treatment of UIAs and improvement of certain types of headache usually considered to be primary in origin. We report a robust beneficial effect of treatment of UIA on prior referred headache. The frequency of headaches decreased after treatment in 81% of the patients, and self-reported headache intensity improvement was present in 76% of the patients. Higher frequency of headaches was the only factor associated with greater odds of improvement after treatment. Aneurysm size and the

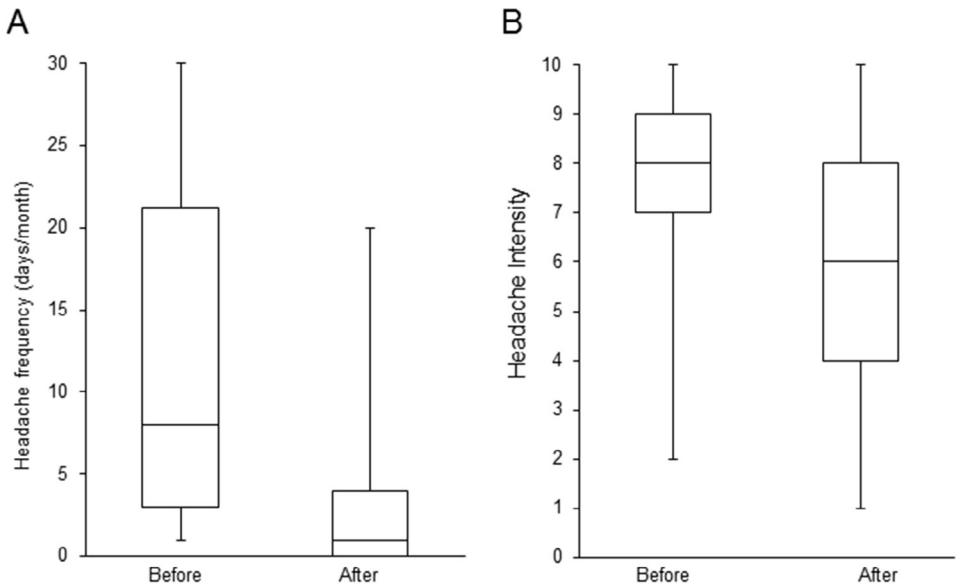

Figure 2. *Headache frequency (A) and intensity (B) before and after unruptured intracranial aneurysm intervention* ($P < .001$).

type of treatment received (i.e., endovascular versus surgical) did not influence headache outcome, suggesting that both baseline size and size reduction of the aneurysm are not strong factors influencing symptoms and outcomes.

Our study enrolled only patients meeting ICSH-III criteria for primary chronic headaches,[20] in which headache workup led to the diagnosis of the UIA. Previous studies reporting this association included patients in which UIAs had been diagnosed during the workup for several conditions.[16-19] Although patients with suspected primary headache do not have a formal recommendation for imaging studies, the current widespread availability of imaging and the preferences of patients and doctors make their performance very common in daily practice.[27]

Migraine without aura was the most frequent type of headache in this group of patients with UIAs. Migraine had a later age of onset in patients with aneurysms compared to patients without aneurysms. However, screening for UIAs in patients meeting criteria for primary headache is currently not recommended based on UIAs' low prevalence, low risk of rupture, and a yet unproven association with certain chronic headaches.[1,6,28,29]

The mechanisms underlying headache improvement after UIA treatment are not clear. It could be hypothesized that sensory nerves innervating intracranial arteries could be activated by structural changes affecting the vessel wall and aberrant blood flow in aneurysm sites.[19,30-32] Moreover, bleeding within the vascular wall may be also responsible for pain.[8] A placebo effect has also been proposed as a factor contributing to improvement[19] and cannot be completely ruled out in this group. The methodology used in this report for the evaluation of the effect of UIA treatment is routinely used to evaluate headache response to drugs and other treatment strategies. We found an improvement in the number of days of migraine in 81% of the patients. In previous studies, placebo use has shown such response in only 9.2% of migrainous patients.[33] Therefore, it is unlikely that the response to UIA treatment can be solely explained by a placebo effect in our population.

In conclusion, migraine without aura is frequent in patients with UIA. Patients suffering from migraine with onset later in life appear to be at higher risk of harboring a UIA. We found a substantial association between aneurism treatment and improvement of headache frequency and intensity. Higher frequency of headache episodes was associated with greater odds of improvement. Future research may help elucidate the mechanisms responsible for these findings.

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