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Remission of migraine after clipping of saccular intracranial aneurysms

Lebedeva ER, Busygina AV, Kolotvinov VS, Sakovich VP, Olesen J. Remission of migraine after clipping of saccular intracranial aneurysms.
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Background – Unruptured saccular intracranial aneurysm (SIA) is associated with an increased prevalence of migraine, but it is unclear whether this is altered by clipping of the aneurysm. The aim of our study was to determine whether remission rate of migraine and other recurrent headaches was greater in patients with SIA after clipping than in controls. *Methods* – We prospectively studied 87 SIA patients with migraine or other recurrent headaches. They were interviewed about headaches in the preceding year before and 1 year after clipping using a validated semi-structured neurologist conducted interview. The remission rates of migraine and tension-type headache (TTH) in these patients were compared to 92 patients from a headache center. Diagnoses were made according to the ICHD-2. *Results* – During 1 year preceding rupture 51 patients with SIA had migraine. During the year after clipping, this was reduced by 74.5% ($P < 0.0001$). At first encounter, 47 control patients had migraine during the preceding year, and during 1 year of treatment, it was 41, a reduction 12.8% ($P > 0.5$). The decrease of migraine in SIA patients was significantly higher than in controls: 74.5% vs 12.8% ($P < 0.001$). A history of TTH was given by 33 patients with SIA during the year preceding rupture and by 44 during 1 year after clipping ($P > 0.75$). Forty-one control patients had TTH, 27 after 1 year of treatment, a reduction 34.1% ($P < 0.05$). No factors except clipping of the aneurysm could explain the remission of migraine. *Conclusions* – Migraine prevalence in patients with SIA decreases significantly after clipping. Further comparative studies of migraine after coiling vs clipping in SIA patients are needed.

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Introduction

It was previously uncertain if unruptured saccular intracranial aneurysms (SIA) were associated with headache or migraine. Recently, we conducted a large prospective case–control study and found markedly increased prevalence of migraine, but *not* tension-type headache (TTH), in patients with unruptured SIA (1). The pathophysiological relationship remains elusive. Studies of headache prevalence after surgical treatment have provided conflicting results. Schwedt et al. (2) reported substantial reductions in headache frequency 6 months after treatment in the majority of patients who had headache before surgical treatment of unruptured SIA. In marked contrast, Baron et al. (3) found that stent-assisted coiling increased the prevalence of headache. The role of surgical treatment of SIA thus remains unclear.

Because of the increased prevalence of migraine in patients before rupture of SIA and no increase of the prevalence of TTH, our hypothesis was that clipping of the SIA would decrease the prevalence of migraine but not the prevalence of TTH. To test the hypothesis, we conducted a large, prospective, case-controlled study interviewing patients before and 1 year after clipping of SIA. The control group included headache patients from a headache clinic who received the

same semi-structured interview used for the SIA patients at first consultation and 1 year later.

Methods

As a basis for the present study, we previously performed a prospective case–control study which included 199 consecutive patients with SIA and 194 control subjects–blood donors at the regional blood transfusion center (1). Before operation, these patients were interviewed about a past history of recurrent headaches using a purpose built semi-structured face to face interview by a neurologist (E.R.L.). Diagnoses of headache were made according to the International Classification of Headache Disorders, second edition (ICHD-2) (4). The main result of this study was that the 1-year prevalence of migraine without aura (MO) was significantly higher before rupture of SIA (42.2%) than in controls (8.8%) and also significantly higher than in the general population of Russia (20.8%) (1, 5).

This study is a follow-up of these patients 1 year after operation using exactly the same semi-structured interview. It includes 87 patients with SIA who had recurrent headache during the year preceding rupture. Seventeen patients had multiple SIA. Patients with single aneurysms had the following location of aneurysms: internal carotid artery—20, anterior cerebral artery—anterior communicating artery—30, middle cerebral artery —14, posterior circulation—6. Clipping of SIA was performed using a low-invasive small craniotomy (35–40 mm) and a pterional keyhole approach.

To determine the 1-year remission rate of migraine in patients without SIA, the same investigator (E.R.L.) also interviewed 92 patients with headache from the Europe–Asia headache clinic twice with a 1-year interval. Thus, the 1-year remission rate in SIA patients was compared with the rate in patients from the headache center.

Inclusion criteria of SIA patients were the presence of SIA, clipping of aneurysm and no other surgical treatment, presence of recurrent headaches before clipping of aneurysms, patient able to give characteristics of headaches before and after clipping of SIA, absence of other brain lesions on MRI that potentially could contribute to headache such as cavernous angioma, arteriovenous malformation, brain tumor, operation confirmed the presence of SIA and no other disorders of brain, the patient agreed to conduct additional examinations and follow up during the period of 1 year after initial examination.

Exclusion criteria of SIA patients were the presence of non-saccular aneurysm such as fusiform or dissecting aneurysm, presence of memory disturbances after SAH or surgery, serious disorders or death after clipping, patient cannot be interviewed 1 year after clipping or refused further examination and follow-up.

In the control material inclusion criteria were the presence of migraine or TTH, patient able to give characteristics of headaches before and after 1 year, patient agreement to conduct additional examinations and follow up during the period of 1 year after initial examination.

Exclusion criteria in the control material were development of memory disturbances during 1 year after treatment, development of serious disorders during 1 year after treatment, patient cannot be interviewed 1 year after treatment or refused further examination and follow-up.

At final assessment patients provided information regarding their headache characteristics, acute medication use and other complaints. Common analgesics and triptans were used for acute headache treatment during the follow-up period of patients with operated SIA, but no prophylactic drug therapy was prescribed. Clinic patients in the control material used acute and prophylactic drug therapy. Baseline clinical characteristics of SIA patients with headache and control patients are given in Table 1.

The Medical Ethics Committee of the Urals State Medical University approved this study. Written informed consent was obtained from all participants.

Statistical analysis

The remission rates in SIA patients and in controls for migraine and for TTH were tested using McNemar's test. Remission rates in SIA patients were compare to remission rates in controls using the chi-square test. Level of significance was set at $P < 0.05$.

Results

In total, we recruited 199 patients with SIA. 124 had a past history of migraine or other recurrent headaches (1-year prevalence 62.3%). However, 6 patients refused operation, 3 were excluded on the basis of the inclusion criteria, 28 were lost to follow-up. Therefore, we included 87 patients with SIA and a past history of recurrent headaches before rupture in this study. Ninety-two consecutive patients from the Europe–Asia headache center were the control group (Table 1).

Table 1 Clinical characteristics of saccular intracranial aneurysm (SIA) patients and controls at first interview

	SIA patients with headache (n = 87)			Clinical control patients with headache (n = 92)		
Characteristics	Migraine (n = 51)	TTH (n = 33)	All headache (n = 87)*	Migraine (n = 47)	TTH (n = 41)	All headache (n = 92)*
Mean age	45.8	46.9	46.1	39.0	42.6	40.4
Female	35 (68.6%)	15 (45.4%)	52 (59.8%)	32 (68.1%)	20 (48.8%)	54 (58.7%)
Arterial hypertension	40 (78.4%)	18 (54.5%)	60 (68.9%)	11 (23.4%)	10 (24.4%)	22 (23.9%)
Mean age at headache onset	26.2	35.9	30.2	18.3	28.1	23.1
Mean duration of headache	19.6	10.9	16.0	19.7	14.9	17.1
Headache frequency per month						
<1 time	15 (29.4%)	7 (21.2%)	22 (25.3%)	2 (4.2%)	1 (2.4%)	3 (3.3%)
1–4 times	19 (37.2%)	20 (60.6%)	39 (44.8%)	22 (46.8%)	14 (34.1%)	38 (41.3%)
5–10 times	11 (21.6%)	4 (12.1%)	18 (20.7%)	4 (8.5%)	8 (19.5%)	14 (15.0%)
11–15 times	1 (1.9%)	1 (3.0%)	2 (2.3%)	7 (14.9%)	13 (31.7%)	20 (21.5%)
>15 times	5 (9.8%)	1 (3.0%)	6 (6.9%)	12 (25.5%)	5 (12.2%)	17 (18.5%)
Severity of headache						
Moderate	9 (17.6%)	22 (66.6%)	32 (36.8%)	9 (19.1%)	21 (51.2%)	32 (34.8%)
Severe	16 (31.4%)	3 (9.1%)	20 (2.3%)	25 (53.2%)	8 (19.5%)	35 (38.0%)
Different	26 (50.9%)	8 (24.2%)	35 (40.2%)	13 (27.6%)	12 (29.3%)	25 (27.2%)
Unilaterality of headache	14 (27.4%)	2 (6.1%)	17 (19.5%)	23 (48.9%)	7 (17.1%)	32 (34.8%)
Unilaterality alternated with bilaterality	5 (9.8%)	2 (6.1%)	7 (8.0%)	14 (29.8%)	5 (12.2%)	19 (20.6%)
Bilaterality of headache	32 (62.7%)	29 (87.9%)	63 (72.4%)	10 (21.3%)	29 (70.7%)	41 (44.6%)

*These headaches include also cluster and posttraumatic headaches.

Table 2 Number of patients with migraine, tension-type and other headache at first and second interview

Types of headaches	SIA patients before rupture (n = 87)	SIA patients 1 year after clipping (n = 87)	P	% change	Control patients at first interview (n = 92)	Control patients 1 year after treatment (n = 92)	P	% change
Migraine	51 (58.6%)	13 (14.9%)	<0.0001	74.5%	47 (51.1%)	41 (44.6%)	>0.50	12.8%
Tension-type headache (TTH)	33 (37.9%)	44 (50.6%)	>0.75	−33.3%	41 (44.5%)	27 (29.3%)	<0.01	34.1%
Other headaches (cluster headache and post-traumatic headache)	3 (3.4%)	2 (2.3%)	>0.50	33.3%	4 (4.3%)	1 (1.1%)	>0.10	75%

ICHD-II headache diagnoses included: migraine, TTH, cluster headache and post-traumatic headache (Table 2). Too few patients had cluster headache and post-traumatic headache to evaluate any changes. Prior to aneurysm clipping, 51 (58.6%) patients had a 1-year history of migraine, among them 48 patients with migraine without aura and three patients with migraine with aura. One year after clipping 13 (14.9%) had migraine. Thus, 38 patients had not had any attack of migraine after clipping (Table 2, Fig. 1). The remission rate was 74.5% ($P < 0.0001$, McNemar's test). Forty-seven (51.1%) control patients had migraine at first encounter, and 41 (44.6%) had migraine after 1 year of treatment. The remission rate was 12.8% ($P > 0.50$, McNemar's test). The percent remission of migraine in SIA patients was significantly higher than in controls 74.5% vs 12.8% ($P < 0.01$, chi-square test). Thirty-three (37.9%) patients with SIA had

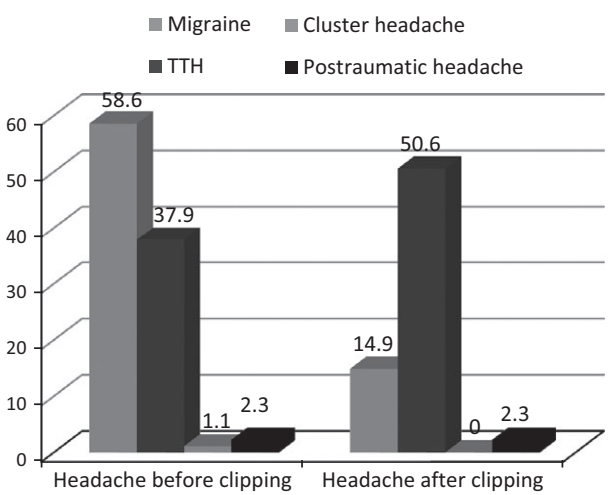

Figure 1. One-year prevalence of headache disorders before and after clipping of saccular intracranial aneurysms in percent of the number of included patients. All of them had a history of recurrent headaches in the year before clipping of the aneurysm.

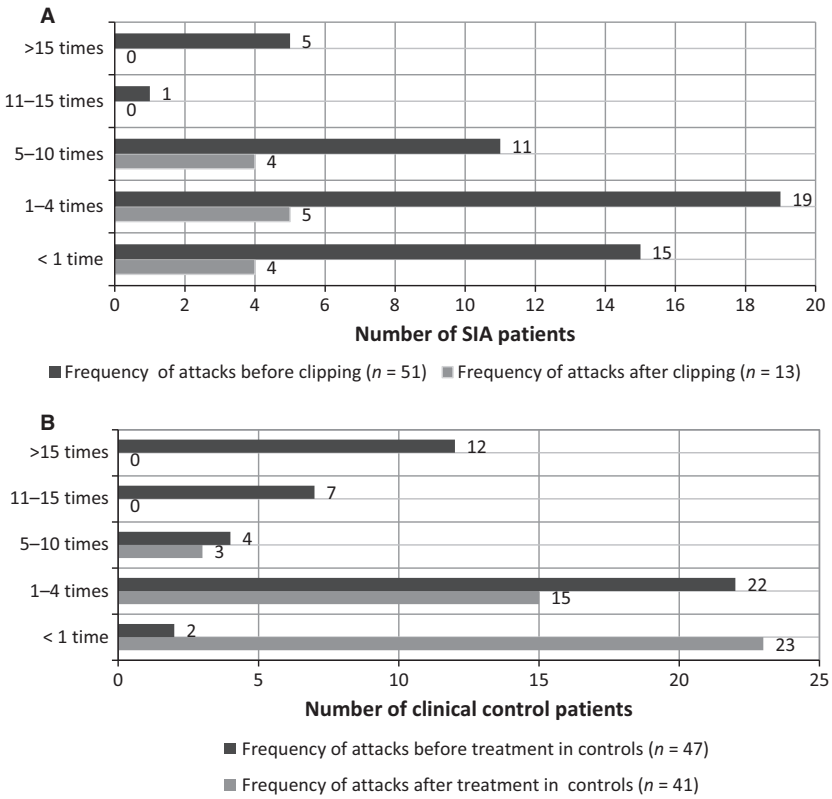

Figure 2. Frequency of attacks of migraine was recorded in intervals as indicated on the ordinate. (A) Before and after clipping of saccular intracranial aneurysm (SIA) (B) controls before and after treatment. Note the marked reduction in migraine frequency in both groups. Only in SIA patients was there also a marked and highly significant remission of migraine.

TTH before rupture. One year after clipping 44 (50.6%) patients had TTH. The increase was 33.3% ($P > 0.75$, McNemar's test). Forty-one (44.5%) control patients had TTH at first encounter and 27 (29.3%) had TTH after 1 year of treatment. The reduction was 34.1% ($P < 0.01$, McNemar's test). The change in TTH in controls was significantly different from the change in SIA patients ($P < 0.05$). The frequency of migraine attacks per month decreased after clipping of SIA in 13 patients who did not have complete remission and became <5 per month in most cases (69.2%) even if prophylactic therapy was not prescribed (Fig. 2A). Those who had arterial hypertension used antihypertensive drugs after surgery (56.3%) and almost half of them (48.9%) used angiotensin-converting enzyme (ACE) inhibitors, which may have a migraine prophylactic effect (Table 3). There was, however, no difference in migraine relief between patients who received antihypertensive treatment and those who did not (Table 4). Control patients were prescribed prophylactic therapy for migraine in 95.7% of cases and in 25% more than one successive prophylactic drug as part of careful clinical management. A reduction in monthly headache frequency was seen in 65.8% of patients (Fig. 2B) but, as stated above, few had total remission.

Table 3 Migraine characteristics in patients with saccular intracranial aneurysm (SIA) relieved and not relieved by clipping

Headache characteristics	Patients relieved of migraine after clipping ($n = 38$)	Patients not relieved of migraine after clipping ($n = 13$)	P
Frequency of attacks			
<1 time per month	12 (31.6%)	3 (23.1%)	0.564
1–4 times per month	14 (36.8%)	5 (38.4%)	0.92
5–10 times per month	7 (18.4%)	4 (30.8%)	0.35
Severity of pain			
Moderate	8 (21.0%)	1 (7.7%)	0.28
Severe	13 (34.2%)	3 (23.1%)	0.45
Variable	17 (44.7%)	9 (69.2%)	0.13
Unilaterality of pain	12 (31.6%)	2 (15.4%)	0.26
Headache on the same side as aneurysm	9 (23.7%)	1 (7.7%)	0.21
Acute medication use			
<15 times per month	33 (86.8%)	12 (92.3%)	0.59
≥15 times per month	5 (13.2%)	1 (7.7%)	0.59
Prophylactic medication use	0	0	

Table 4 Possible risk factors that might influence the prevalence of migraine after clipping

Possible risk factors	Patients relieved of migraine after clipping (n = 38)	Patients not relieved of migraine after clipping (n = 13)	P
Mean age	47.6	40.4	
Male	13 (34.2%)	3 (23.1%)	0.46
Mean age of beginning of headache	28.6	21.0	
Smoking	16 (42.1%)	5 (38.5%)	0.82
Arterial hypertension	31 (81.6%)	9 (69.2%)	0.35
Using of ACE-inhibitors or angiotensin II receptor blockers or β-blockers antihypertensive drugs	14 (36.8%)	9 (69.2%)	0.05
Large SIA (11–25 mm)	1 (2.6%)	0	0.56
Giant SIA (>25 mm)	1 (2.6%)	2 (15.4)	0.09
Normal size SIA (5–10 mm)	33 (86.8%)	11 (84.6%)	0.84
Small SIA (<5 mm)	3 (7.8%)	0	0.30
Localization of SIA			
ACoA-ACA	17 (44.7%)	2 (15.4%)	0.06
MCA	11 (28.9%)	2 (15.4%)	0.34
ICA	9 (23.7%)	7 (53.8%)	0.05
Posterior circulation (vertebral, basilar, PICA)	1 (2.6%)	2 (15.4%)	0.09
Right sided aneurysm	23 (60.5%)	3 (23.1%)	0.02*
Ruptured SIA	35 (92.1%)	11 (84.6%)	0.44
Clinical symptoms of SIA			
SAH	25 (65.8%)	7 (53.8%)	0.44
SAH + intracerebral heamatoma	9 (23.7%)	4 (30.8%)	0.61
Single heamorrhage	26 (68.4%)	11 (84.6%)	0.26
Recurrent heamorrhage	9 (23.7%)	2 (15.4%)	0.53
Period of operation			
Acute period	5 (13.1%)	3 (23.1%)	0.40
After 1 month	33 (86.8%)	10 (76.9%)	0.40

ACE, angiotensin-converting enzyme; SIA, saccular intracranial aneurysm.
*statistically significant.

We also analyzed factors other than clipping which could influent the remission of migraine. We did not find any significant differences in migraine characteristics before clipping in patients with migraine relieved and not relieved by clipping (Table 3). Mean age at migraine onset in patients not relieved after clipping was less than in those who were relieved. The presence of cerebral infarct after SAH was associated with continued migraine after clipping while right sided aneurysm was associated with a significantly higher remission rate (Table 4). None of these findings were, however, significant after correction for multiple comparisons.

Discussion

The main result of this study was a considerable and statistically significant remission of migraine in patients with SIA after clipping of the aneurysm. The remission was significantly greater than in a comparable group of headache patients treated in a headache clinic. It was not possible to attribute the remission to any previous migraine characteristics or to any specific features of the aneurysm.

To our knowledge, this is the first prospective case–control analysis of remission rates of migraine and other headaches in patients diagnosed according to ICHD-2 after clipping of SIA.

Schwedt et al. (2) compared headache prevalence prior to surgical treatment (coiling 86%) of unruptured intracranial aneurysms and 6 months after in 44 patients. ICHD-II headache diagnoses included: 11 episodic TTH, eight chronic TTH, eight episodic migraine, six chronic migraine, two occipital neuralgia, one post-traumatic headache and one primary stabbing headache. Headache frequency was reduced in 68% of patients, while 9% of patients had new or worsened headaches following aneurysm treatment. Presence of pretreatment migraine, more severe pretreatment headaches, higher pretreatment trait anxiety and stent-assisted aneurysm coiling were associated with a lack of headache improvement. Qureshi et al. (6) retrospectively studied headache characteristics in 47 patients who underwent endovascular treatment of an unruptured SIA. Thirty-two reported headaches prior to treatment (68.1%), 19 of whom reported improvement in severity of headaches after coiling. Two patients had worsening severity of headaches and five patients without pretreatment headaches reported onset of new headaches following aneurysm treatment. Specific headache diagnoses or remission rates were not reported. Kong et al. (7) retrospectively analyzed 81 patients who had undergone surgical clipping (n = 40) or endovascular treatment (n = 41) of unruptured SIA over a 5-year period. Forty-nine (60.5%) had chronic headaches prior to aneurysm treatment. Following treatment, 44 of 49 had headache improvement, four had no change, and one patient had headache worsening. Neither remission rates nor specific diagnoses were presented. Rocha-Filho et al. (8) prospectively studied headache characteristics during 6 months after craniotomy performed for treatment of cerebral aneurysms with or without rupture in 79 patients. Headaches increased significantly immediately after surgery but improved over several months thereafter.

Some other studies focused on headache immediately after coiling (3, 9, 10). Baron et al. (3) found post-procedure headache in 72% of patients. Takigawa et al. reported onset of headaches just after treatment in 46.6% of patients

after coiling. Hwang et al. (10) described headache (VAS score, 4.5–2.02) at 7.9 (range, 0–72) h after coiling in 55.6% of patients. They resolved within an average of 73.0 (range, 3–312) h.

None of the studies in the literature were prospective using repeated direct interview. Furthermore, none of the studies classified headaches according to ICHD-2, and the findings varied between studies. Collectively, these studies did, however, support our recent finding of an increased prevalence of migraine before rupture of SIA and our present findings of a decreased prevalence after clipping of the aneurysm.

Present findings: strengths and limitations

Our study was prospective, case controlled and had a very large sample size for this kind of study. It classified headaches according to ICHD-2 using the gold standard of headache diagnosis, a neurologist conducted standardized interview performed by the same author (E.R.L.). For these reasons, it is likely to have yielded reliable results. A very marked remission of migraine after clipping of SIA was demonstrated. It might have been ideal to use patients from the general population or patients with migraine who underwent another kind of surgery as a control group, but this was not possible. Instead, we used patients treated in a headache center to determine the 1-year remission rate in non-SIA patients. Patients from the headache center had more severe headache than would be expected in patients from the general population but they got expert prophylactic treatment. Their frequency of attacks decreased but not complete remissions.

Saccular intracranial aneurysm patients have an increased prevalence of arterial hypertension, but this explained only a small proportion of the increased migraine prevalence prior to rupture. The institution of antihypertensive treatment after clipping did not have a significant effect. Any confounding effect of antihypertensive treatment was more than compensated by optimal prophylactic treatment in the control group. Interestingly, TTH increased (not significantly) in SIA patients 1 year after clipping the aneurysm in marked contrast to the decrease of migraine. This could perhaps be due to unmasking as patients with migraine tend to underreport concomitant presence of TTH. Increased stress due to sequelae of the subarachnoid bleeding and worry about renewed bleeding are other possible explanations. However, we cannot exclude that some TTH-like headaches were caused by the operation, that is, post-procedural headache. In controls TTH prevalence decreased significantly, probably due to the expert treatment provided. Another possible limitation of our study could be recall bias because patients did not keep a headache diary. We considered it impossible to get compliance for diary recordings over 1 year. It was, however, our impression that patients very well knew and appreciated the disappearance of their migraine.

Our study showed that the prevalence of migraine is markedly reduced after clipping of SIA. The previous literature suggests that coiling of aneurysms does not necessarily have the same effect. Clipping of aneurysms may therefore with our present knowledge be preferred to coiling in patients with severe migraine. Further comparative studies of the effect on migraine of coiling vs clipping in SIA patients are, however, needed for any definite recommendations.

The reason for the decreased prevalence of migraine after clipping of SIA is uncertain. There were no distinguishing features between headache characteristics in those patients who remitted and those who did not. Likewise, there were no distinguishing features with regard to the aneurysm. One might speculate that input from the perivascular nerves around the aneurysm could be responsible for the increased prevalence before clipping, and this input would of course be abolished by clipping the aneurysm.

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Conflict of interest

No conflict of interest.

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