

Magnetic resonance angiographic screening of aneurysms in migraine

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Abstract

Objective: The purpose of the present study was to screen the prevalence of aneurysms in migraineurs; to differentiate presenting features in migraineurs with and without aneurysm; and also to correlate the locations of aneurysm to the clinical features of migraine. **Methods:** A total of 4,416 subjects were interviewed and completed self-reported questionnaires on headache. Of these, 1,773 subjects diagnosed to have migraines based on the International Classification of Headache Disorders II (ICHD-II) criteria were screened for aneurysm by magnetic resonance angiography (MRA). When aneurysm was suspected, further investigation with trans femoral cerebral angiography (TFCA) or three dimensional computerized tomography (CT) angiography was performed. Based upon MRA findings, subjects were grouped into unruptured aneurysm migraine patients (UAMP) and no aneurysm migraine patients (NAMP). **Results:** The prevalence of aneurysm was 3.6% (63 of 1,773) with the mean age of 56.0 years, which were not different from those of general population. There was no difference in migraine subtypes between UAMP and NAMP. Aggravation of headache by estrogen replacement therapy during menopause ($p=.039$), history of migraine in young age ($p=.021$), diplopia ($p=.026$), and retroauricular pain ($p=.025$) were significantly associated with presence of aneurysm. Although aneurysms were detected more in anterior circulation, there was no correlation between aneurysm site and headache location. The average size of aneurysm was 3.5 ± 2.1 mm and none were ruptured. Interventional therapy of aneurysm did not alter the feature of migraine.

Conclusions: The incidence of aneurysm was not different in migraine patients as compared to the general population. Some features which significantly differentiate whether migraineurs have aneurysm or not warrant further study to have a predictive and localizing value.

INTRODUCTION

As brain neuroimaging technology advanced, morbidity from cerebral aneurysm to subarachnoid hemorrhage (SAH) has decreased. Patients with aneurysm are usually asymptomatic prior to enlargement to a certain size before rupture. Sudden severe headache can be the only symptom in SAH. Headache in unruptured cerebral aneurysms may be due to small hemorrhages in the cerebral vasculature, destruction of the aneurysmal sac, or by direct pressure to the adjacent pain-sensitive structures such as trigeminal nerve, or free edge of the tentorium.¹ These pains may resemble migraine or tension type headache.^{2,3} Without neuroimaging, early detection of aneurysm is difficult and misdiagnosis is not uncommon.^{4,5}

Migraine is a common neurological disorder

with the prevalence of 10-15% in general population. In the acute stage of migraine attack, it can present as SAH-like manifestation, which may lead to the physicians performing brain imaging or cerebrospinal fluid analysis. Unruptured aneurysm can be detected in patients with migraine. Although many co-morbid disorders such as epilepsy, essential tremor, stroke, white matter abnormalities, or mood disorders (depression, anxiety, mania, and panic attacks) have been reported to be associated with migraine⁶, the prevalence of cerebral aneurysm and its significance in migraine is unknown.

The risk factors for developing cerebral aneurysm are old age, female gender, smoking, hypertension, excessive use of alcohol, having one or more affected relatives with SAH, and autosomal dominant polycystic kidney disease.⁷ In the present study, we screened for aneurysms in

a group of migraineurs using magnetic resonance angiography (MRA). Our aims were to determine the prevalence of aneurysms in migraineurs; to differentiate presenting features in migraineurs with and without aneurysm; and to correlate the locations of aneurysm to the clinical features of migraine.

METHODS

Subjects

A total of 4,416 consecutive patients who visited the headache clinic at Seoul National University Hospital (SNUH) between March 2003 and June 2010 were reviewed. All subjects were interviewed and were asked to complete a self-report questionnaire. Among the patients diagnosed to have migraine, 1,173 underwent MRA. Patients were selected for MRA according to clinician's decision and patient's agreement. The diagnosis of migraine was based on the International Classification of Headache Disorders II (ICHD-II) criteria.⁸ Patients who met the criteria of migraine without aura, migraine with aura, probable migraine, and migraine with other primary headaches were included in this study. The patient enrollment protocol was approved by SNUH Institutional Review Board.

Migraine questionnaire

The study questionnaire was given to the patients at the outpatient clinic. They were completed at the outpatient department (OPD), or returned by mail within 7 days after the visit. The questionnaire included demographic features and clinical characteristics of headache, such as headache quality, severity, site, frequency, age of onset, duration, associated symptoms, aggravating factors, and family history.⁹⁻¹⁵ Migraine Disability Assessment Score (MIDAS) was also determined.^{16,17}

Angiographic evaluation for aneurysms

MRA was performed by Siemens 1.5 Vision (Erlangen, Germany). Images were reconstructed to view 360 degree by rotating the image for intracranial cerebral vessels including anterior, middle, posterior cerebral arteries, circle of Willis, vertebrobasilar arteries and both carotid arteries. MRA images for evaluation were taken within one month following the initial visit. Image analysis was performed by one of the three board-qualified radiologists of the Department of Radiology at SNUH. When the aneurysms were suspected

by MRA alone, further investigation with three dimensional computerized tomography (CT) angiography or trans femoral cerebral angiography (TFCA) was performed.

Features of aneurysms and comparisons between migraineurs

The aneurysm size in mm (millimeter), number (single or multiple), shape (saccular or fusiform), and location were determined. The subjects were divided into those having unruptured aneurysms (UAMP; Unruptured Aneurysm in Migraine Patients) and migraineurs without aneurysm (NAMP: No detectable Aneurysm in Migraine Patients). The demographics and clinical features of the two groups were compared. This included the type, onset, site and duration of headache, associated symptoms, aggravating factors, other environmental factors and family history. The headache severity and frequency were based on the MIDAS score and headache diary. Monthly headache frequency was analyzed in UAMP group. Management for aneurysms and treatment outcomes were also reviewed.

Statistical analysis

Demographics with continuous variables between the two groups were compared using Student's t-test. The Chi-square test was used to make comparisons of ordinal variables. The Wilcoxon signed rank test was used to compare monthly headache frequency and MIDAS. Kruskal-Wallis test was used to clarify the difference between headache grades and covariates (sex, age, the number of aneurysms, aneurysm management, and headache type) in UAMP. All analyses were performed by SPSS for windows (version 19.0; SPSS, Chicago, IL), and statistical significance was considered at $P < .05$.

RESULTS

Prevalence of aneurysm

Of a total of 4,416 patients who visited our clinic, 1,773 patients with migraine were screened for aneurysm by MRA. Of these, 1,710 patients did not show any evidence of aneurysm. Among them, 8 patients were initially suspected to have aneurysms but were confirmed to have no aneurysm with further evaluation by TFCA (Figure 1). MRA screening revealed that 63 out of 1,773 (3.6%) patients had unruptured aneurysms (UAMP). Of the 63 patients, CT angiography was performed in 4 subjects and TFCA in 29 subjects.

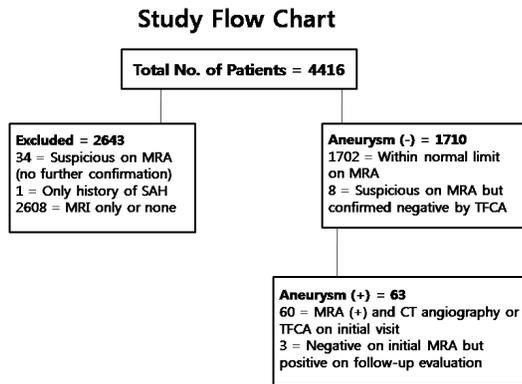


Figure 1. Study enrollment & classification
 R/O: rule out; S/P: status, post-operative; SAH: subarachnoid hemorrhage; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; TFCA: trans femoral cerebral angiography; CT= computerized tomography

One patient underwent clipping, although the aneurysm was not ruptured.

Sex, age distribution and migraine subtype

Table 1 shows the study patients' baseline characteristics.

Among the 63 UAMP, 55 were women (87.3%) and 8 were men (12.7%), the difference was statistically significant ($p= 0.005$). The mean age was 56.0 years (ranging from 24 to 77 years). Most patients were in their fifties (31.7%) and sixties (33.3%). However, this age distribution was not different from that of NAMP. Of the

headache subtypes, migraine without aura was the most common (57.1%), followed by probable migraine (19.0%) and migraine with aura (3.2%). The remaining 20.7% were patients with mixed features of migraine and other types of headache. In NAMP, migraine subtypes were similar to those in UAMP (migraine without aura; 40.9%, probable migraine; 20.9%, and migraine with aura; 3.9%).

Headache frequency, age of onset (first attack)

UAMP had a mean monthly headache frequency of 17.0 ± 11.0 times per month based on headache diary. The mean age of onset was 42.9 years. However, 85.7% of them reported that their first migraine attack was more than 10 years ago. Based on self-report questionnaire, 41.3% reported that their headache frequency was more than two times a week. The mean duration of headache was 38.1 hours.

Disability due to migraine

The MIDAS questions showed that 28.0% of UAMP reported difficulties in daily life at home, school, or social life. Close to a quarter of patients could not go to school or the office (27.0 %), or were only able to work with less than half of their previous efficiency (19.0 %). Close to a third of patients could not perform any housework (32.0 %), could complete only about half of household chores (38.0 %), or could not participate in social life or leisure (27.0 %). When compared to NAMP, the differences were not statistically significant.

Table 1: Study patients' baseline characteristics

Characteristics	UAMP (n=63)	NAMP (n=1710)	P-Value
Sex (%)			.005
Woman	55 (87.3)	1218 (71.2)	
Man	8 (12.7)	492 (28.8)	
Age (%)			NS
10-19	0	26 (1.5)	
20-29	3 (4.8)	95 (5.6)	
30-39	2 (3.2)	155 (9.1)	
40-49	12 (19)	346 (20.2)	
50-59	20 (31.7)	511 (29.9)	
60-69	21 (33.3)	397 (23.2)	
70-79	5 (7.9)	163 (9.5)	
80-89	0	17 (1.0)	
Headache frequency -mean (SD)	16 (± 11)	17 (± 11)	NS
Headache severity - mean (%)	Moderate (46)	Moderate (49)	NS

UAMP, unruptured aneurysm migraine patients; NAMP, no aneurysm migraine patients

Table 2: Comparison in location of pain, associated symptoms, and aggravating factors between unruptured aneurysm migraine patients (UAMP) and no aneurysm migraine patients (NAMP)

Category of question	UAMP (n=63)	NAMP (n=1710)	P-Value	Category of question	UAMP (n=63)	NAMP (n=1710)	P-Value
Pain location %(n)							
Left	24 (14)	700 (17)	NS	Aggravating factor %(n) Physical stress (work, examination) Anxiety Menstruation Anti-hypertensive Taking any other specific medication Estrogen replacement Menopause Improved during pregnancy Allergy	14 (11)	416 (11)	NS
Right	27 (15)	596 (14)	NS		40 (31)	1064 (29)	NS
Both	26 (15)	684 (16)	NS		4 (3)	123 (3)	NS
Forehead	20 (11)	463 (11)	NS		3 (2)	28 (1)	NS
Temple	18 (10)	421 (10)	NS		2 (2)	23 (1)	NS
Vertex	15 (9)	317 (8)	NS		3 (2)	25 (7)	.039
Retro-auricular	21 (12)	367 (9)	.025		5 (4)	110 (3)	NS
Neck (posterior part)	26 (15)	653 (16)	NS		1 (8)	7 (2)	NS
Post-herpetic pain	5 (8)	60 (4)	.056		1 (8)	34 (1)	NS
Alcohol					8 (6)	282 (8)	NS
Associated symptoms %(n)							
Flashes of light	3 (5)	67 (4)	NS	Ache after exercise	3 (2)	96 (3)	NS
Double vision	4 (7)	36 (2)	.026	Head trauma	2 (2)	107 (3)	NS
Blurring of vision	3 (5)	56 (3)	NS	Headache usually in the morning	9 (7)	244 (7)	NS
Spinning sensation	3 (5)	47 (3)	NS	Headache usually in the afternoon	10 (8)	351 (10)	NS
Shimmering vision	3 (5)	77 (5)	NS	Seasonal variation of headache	5 (4)	202 (6)	NS
Imbalance	1 (2)	46 (3)	NS	Heat	11 (8)	239 (7)	NS
Odd sense of one's body	3 (5)	34 (2)	NS	Genetic and Environmental factor %(n)			
Frequency of urination	1 (2)	58 (4)	NS	History of migraine in youth	26 (25)	478 (17)	.021
Frequent loose bowels	1 (2)	7 (4)	NS	Family history (maternal)	10 (10)	362 (13)	NS
Feeling of generalized body weakness	4 (7)	74 (4)	NS	Motion sickness	12 (12)	447 (16)	NS
Nervous [touchy]	2 (3)	118 (7)	NS	Chocolate	7 (7)	144 (5)	NS
Dizziness	3 (5)	122 (7)	NS	Ramen	4 (4)	150 (5)	NS
Depressive mood	3 (5)	98 (6)	NS	Yogurt	12 (12)	239 (8)	NS
More sleepy than usual	4 (7)	60 (4)	NS	Kimchi	24 (23)	683 (24)	NS
Did not stop yawning	2 (3)	75 (5)	NS	Other fermented food	4 (4)	173 (6)	NS

Table 3 Management of the aneurysms by site of aneurysm and age

Site, age	Observation (n=17)	Endovascular coiling (n=18)	Surgical clipping (n=4)	Surgical trapping (n=1)
Anterior, %(n)	76(13)	100(18)	100(4)	0
> 50 years	38(5)	33(6)	0	0
50- 60 years	15(2)	50(9)	25(1)	0
60- 70 years	30(4)	11(2)	75(3)	0
< 70 years	15(2)	5(1)	0	0
Posterior, %(n)	23(4)	0	0	100(1)
> 50 years	25(1)	0	0	0
50- 60 years	25(1)	0	0	100(1)
60- 70 years	50(2)	0	0	0
< 70 years	0	0	0	0

Vascular risk factors, location and aggravation of pain, associated symptom

As for vascular risk factors, i.e., alcohol consumption, smoking and hypertension, there was no significant difference between the UAMP and NAMP groups. Of the UAMP group, smokers were 37.5% in men and none in women. Habitual alcohol drinking, (defined as drinking alcohol out of habit, not solely for enjoyment) was 12.5% in men and 3.6% in women. Half (50%) of men and 47.2% of women did not drink any alcohol. Hypertension was reported in 37.5% of men and 38.1% of women.

There were several difference between UAMP and NAMP in the character of pain, associated symptoms and aggravating factor of headache (Table 2). Patients with UAMP have more pain at the retro-auricular area ($p=.025$), associated symptom of diplopia ($p=.026$), aggravation of headache by estrogen replacement therapy during

menopause ($p= 0.039$), and history of migraine in young age ($p= .021$).

Features of aneurysms and correlation with headache site

In the UAMP group, 54 patients (86%) had single aneurysm while multiple aneurysms were seen in 14% of patients (5 patients had 2, and 4 patients had 3 aneurysm). The aneurysms located in the anterior circulation were most frequently in the age group of fifties (38%), while aneurysms in the posterior circulation were most frequently in the sixties (50%). The average size of aneurysms was 3.5 ± 2.1 mm. Large majority (95%) were saccular and 5% were fusiform. The aneurysm site was 85% in the anterior circulation and 13% in the posterior circulation.

For patients with unruptured aneurysm, there was no correlation between the headache frequency, severity and number with the locations

Table 4: Correlation between aneurysm site and migraine site

Aneurysm site	Migraine site, %(n)							
	Right	Left	Both	Forehead	Temple	Retro auricular	Back of Neck	Vertex
Anterior (n=54)	41(22)	51(28)	35(19)	29(16)	31(17)	22(12)	42(23)	12(7)
ICA + P-com (n=33)	48(16)	57(19)	33(11)	30(10)	24(8)	18(6)	36(12)	15(5)
MCA (n=12)	33(4)	50(6)	41(5)	25(3)	41(5)	33(4)	50(6)	0
A-com (n=6)	33(2)	33(2)	33(2)	33(2)	50(3)	16(1)	50(3)	33(2)
Posterior (n=7)	28(2)	42(3)	57(4)	42(3)	14(1)	28(2)	71(5)	14(1)

ICA, internal carotid artery; P-com, posterior communicating artery; MCA, middle cerebral artery; A-com, anterior communicating artery

and shape of the aneurysm. There was also no correlation between the site of aneurysms and site of the migraine headache (Table 4).

Management of aneurysm

As for management of the aneurysm (Table 3), 17 patients were observed only without intervention, while 18 patients received endovascular coiling. Four patients were treated with surgical clipping and one patient with fusiform aneurysm in the vertebral artery underwent trapping. The characteristics of the migraine feature did not change after the intervention treatment of the aneurysm

Observation and prognosis

All subjects with aneurysm had followed-up for at least one year. The follow-up was every three months in 2 patients, every six months to one year in 10 patients and every two or three years in 5 patients. Patient in the surgical group had follow up every three months in 4 patients, every six month to one year in 5 patients. Eleven patients (65%) without surgical management and 3 patients (14%) with intervention were currently still under regular follow up. The mean duration of follow-up was 3 years. During the follow-up period, one patient received re-embolization, but none of the aneurysms had ruptured.

DISCUSSION

The purpose of this study was to screen aneurysms in migraineurs, and then to compare the presenting features between migraineurs with or without aneurysm. We found that the prevalence of aneurysm in migraine was not different from that of general population. We also found some significant difference in the characteristics of migraines among patients with aneurysms.

Patients with subarachnoid hemorrhage may have headache once a week to several months prior to the aneurysm rupture. These so called "sentinel headaches" occur in 30-60% of patients due to leakage of blood from the unruptured aneurysm.¹⁹⁻²¹ These were most frequently misdiagnosed as migraine.^{2,3} We determined the prevalence of aneurysms in patients who had already been diagnosed as migraine. In this study, the prevalence of aneurysm was 3.6% which is within the range of the known global prevalence of aneurysm (1-5%). This prevalence is also not different from the previous report of the Korean population.²² Regarding the age distribution, there

were no difference between UAMP and NAMP. The age distributions were also similar to other studies on aneurysm.^{18,23} These results suggest that migraine in these patients with aneurysm was not associated with the development of aneurysm.

In previous studies, development of aneurysm is thought to be associated with consumption of oral contraceptive pill.²³ Other study has shown association between early menopause and aneurysm development. It has been proposed that early loss of estrogen in woman may promotes the development of aneurysm.²⁴ In our study, we found aggravation of headache by estrogen replacement therapy during the menopause to be more frequent in the UAMP group. This suggests that development of aneurysm related headache may have an association with female hormonal status.

SAH may cause impaired vision, eye movement disorders and diplopia.² In this study, the patients with unruptured aneurysm who complained of diplopia had the aneurysms at anterior communicating artery (5 mm), left distal internal carotid artery (2-3 mm), paraclinoid artery (2-3 mm) and right internal carotid artery. It was uncertain how these aneurysms can cause diplopia, although it is well-known that oculomotor nerve can be compressed by posterior communicating artery aneurysm. The diplopia may thus not be directly related to the aneurysm.

On the site of headache and the site of aneurysm, we found that the unilateral headache was not associated with aneurysm on the same side. The only significant association in the site of headache and unruptured aneurysm was pain in the "retro-auricular area" (Table 2). We thus conclude that the site of headache did not correlate with the location of the aneurysms.

We also found a "history of migraine in young age" to be significantly associated with the presence of unruptured aneurysm. However, only 2 out of 266 (0.7%) migraineurs in their twenties and 3 out of 506 patients (0.6%) at thirties were found to have aneurysm, which indicated that the prevalence of aneurysm in 20s and 30s was lower than that in the older age group. How a "history of migraine in young age" is associated with increased unruptured aneurysm is thus unclear.

For the outcome following the treatment of unruptured aneurysm, it has been reported that morbidity was 8.4% for clipping and 6.3% for coiling in the 30-day post-procedure period.²⁵ In this study, all the patients were in good condition during the follow-up period. However, migraine features did not alter following intervention,

suggesting that aneurysm itself does not affect the pathophysiology of migraine.

In summary, this study examined the relationship of migraine with aneurysm in a Korean population. The prevalence and age-distribution of aneurysm in migraine patients was similar to that of the general population. All aneurysms were found to be unruptured with small size and intervention did not change the manifestation of migraine. Characteristics such as 'pain location in the retro-auricular area', 'diplopia', 'aggravation of headache by estrogen replacement therapy during menopause' and 'a history of migraine in young age' were more frequent in migraineurs with unruptured aneurysm. However, to validate whether these factors are predictive and have localizing value, further prospective studies are needed.

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