Retrospective Study

Multidisciplinary Care of Unruptured Brain Arteriovenous Malformations to Improve Symptomatic Headache and the Onset, Progression, and Outcomes of Unruptured Brain Arteriovenous Malformations

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Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 01-30-2016
Revised manuscript received: 02-02-2016
Accepted for publication: 06-01-2016

Free full manuscript: www.painphysicianjournal.com

Background: Symptomatic headaches attributed to unruptured brain arteriovenous malformations (ubAVMs) are very common and affect patients' quality life, but multidisciplinary care of ubAVMs to improve symptomatic headache remains unclear.

Objective: The objective is to identify the features of symptomatic headaches, and to obtain headache outcomes following multidisciplinary care of ubAVMs, as well as provide background on the natural history of ubAVMs.

Study Design: The features of symptomatic headaches and headache outcomes were analyzed in a large cohort of cases after multidisciplinary care of ubAVMs. We have also provided information on the natural history of ubAVMs

Setting: This study was conducted at the Department of Neurosurgery of Zhujiang Hospital where 336 patients from 1998 to 2014 were reviewed by a multidiscipline team. Only 124 patients were eligible.

Methods: The demographics, clinical features, imaging features, and headache details of eligible patients were reviewed. An 11-point pain scale score was used to assess symptomatic headaches before, during, and after treatment. The headache outcomes, death or stroke, and adverse functional outcomes (modified Rankin Scale score ≥ 2, mRS ≥ 2) were assessed following multidisciplinary care of ubAVMs.

Results: Twenty-three (56.1%) of 41 patients had migraine-like headaches located in occipital lobe ($P < 0.001$), while forty (63.5%) of 63 patients had tension-type-like headaches located in frontotemporal lobe ($P < 0.001$). For patients with tension-type-like or all types of headache, headache improvement differed between the multidisciplinary group and medical group (87.8% vs. 31.8%, $P < 0.001$; 85.7% vs. 40.7%, $P < 0.001$). The risk of death or stroke did not differ between multidisciplinary group and medical group ($P = 0.393$), whereas the risk of adverse functional outcome (mRS ≥ 2) differed significantly by long-time follow-up (23.0% vs.10.0%, $P = 0.022$).

Limitations: This study provides the initial experience to support multidisciplinary care for ubAVMs to improve symptomatic headaches and patients' quality life, but based on the retrospective study with inherent limitations, larger samples and multi-center trials are needed on this interesting issue.

Conclusions: Occipital ubAVM is more likely to present with migraine-like headache, while frontotemporal ubAVM tends to present with tension-type-like headache. The effectiveness of multidisciplinary care for ubAVM to improve headache has been shown, but the natural history of ubAVM patients with headache remains unclear.

Key Words: Unruptured brain arteriovenous malformations, headache, headache improvement, natural history

Pain Physician 2017; 20:E127-E136

An unruptured arteriovenous malformation (ubAVM) accompanying symptomatic headache is very common, with wide range of values of 14% - 79% in these ubAVM patients (1-4). The mechanism underlying the occurrence of symptomatic headache in ubAVM patients remains unclear (4), and symptomatic headache affects patients' quality of life (5). Previous studies (6-9) reveal single or multimodal therapy for ubAVMs is used to relieve the symptomatic headache and improve patients' quality of life. Some studies (10,11), however, believe obliteration of an ubAVM cannot improve symptomatic headaches. Two 2 randomized trials (1,12) showed that ubAVM patients treated with interventional therapy conferred a high risk of stroke or death. Therefore, the benefits of treating symptomatic headaches from ubAVMs by single or multi-modality therapy remains unclear.

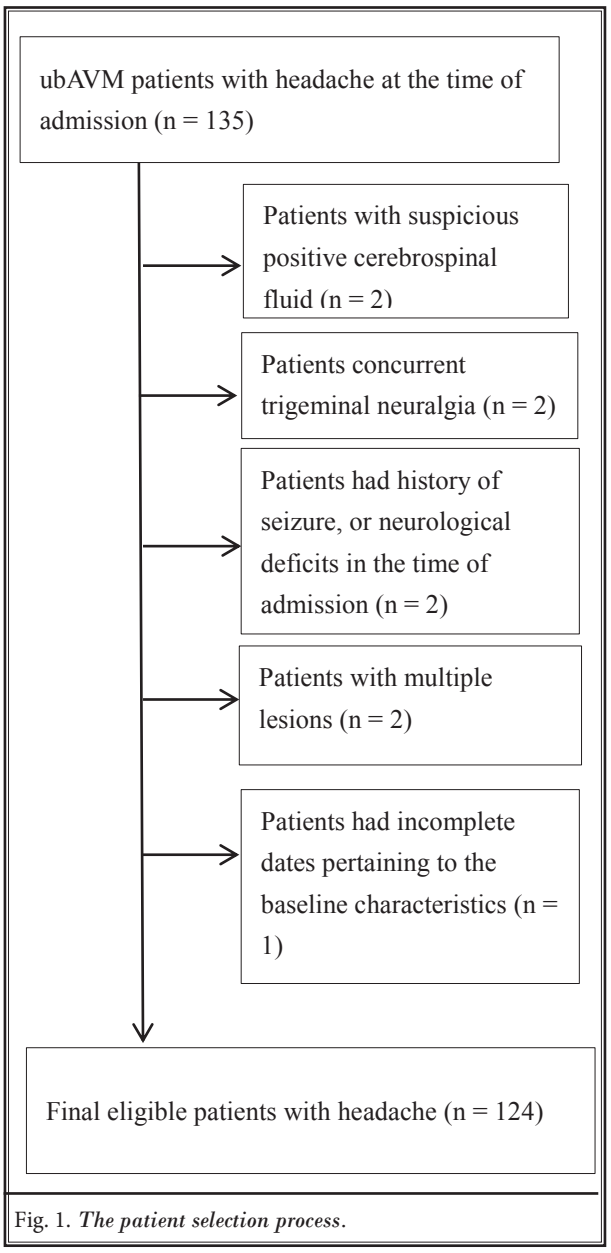

Fig. 1. *The patient selection process.*

Demographics, clinical features, imaging features, and headache details of included eligible patients from 1998 to 2014 were used to identify the features of symptomatic headache. An 11-point pain scale score (13-15) was used to assess symptomatic headache. Therefore, according to the potential hemorrhage risk factors (e.g., aneurysms, deep venous drainage, or drainage vein stenosis) ubAVMs patients have (16) and their 11-point pain scale score, patients were allocated to the multidisciplinary care group or medical treatment group. Finally, the headache outcomes were obtained, and the risk of death or stroke, and the risk of adverse functional outcomes (modified Rankin Scale score ≥ 2, mRS ≥ 2) for eligible patients treated by various therapies were explored through prospective long-time follow-up.

Methods

Patients

The study was approved by the Institutional Review Board of Zhujiang hospital. Of 336 patients who presented with headache from ubAVMs at the time of admission (age ≥ 18 years) from 1998 to 2014, 135 (40.2%) were excluded according to the following criteria: 1) patients with suspicious positive cerebrospinal fluid; 2) concurrent other brain lesions, possibly contributing to the headache, such as cerebral infarction, intracerebral hemorrhage, trigeminal neuralgia, cerebral venous sinus thrombosis, or brain tumors; 3) other comorbid diseases, such as hepatic encephalopathy, psychotic disorder; 4) patients with a history of seizure or neurological deficits at the time of admission; 5) patients with multiple ubAVM lesions; 6) patients had incomplete dates pertaining to baseline characteristics; and 7) patients had no follow-up dates. Finally, 124 (36.9%) patients were eligible. The flowchart shows the selection process for eligible patients (Fig. 1), and the baseline characteristics of ubAVMs in 124 eligible patients are summarized (Table 1).

Treatment Principles

A multidiscipline team consisting of neurosurgeons, neuroradiologists, and neurologists, by consen-

sus, determined patient management. The deciding factor for multidisciplinary care was based on the lesions and potential hemorrhage risk factors (16), no matter how mild the headache was. If there were no potential hemorrhage risk factors, multidisciplinary care for patients with serious headache was still used when medicine could not relieve the symptoms, by contrast, medical treatment was performed on patients with mild headache when this therapy had significant effect on the symptomatic headache.

With respect to the multidisciplinary care of ubAVMs, patients with small superficial lesions (< 3 cm) were prioritized for microsurgery, but for patients with small deep lesions (< 3 cm), radiosurgery was the first choice until the lesion completely obliterated. For patients whose ubAVM was characterized by single vein drainage, larger size, Spetzler-Martin Grade (S-M) of ≥ III, or focal angioarchitectural weakness, endovascular embolization was performed. If patients had residual ubAVM following embolization, further therapies combined with microsurgery or radiosurgery would be recommended in order to obliterate the residual lesions.

Consequently, of 124 eligible patients, 54 (43.5%) were treated by medical treatment, 70 (56.5%) underwent multidisciplinary treatment. For patients receiving multidisciplinary care, 21 cases were treated by radiosurgery alone, 12 were treated with endovascular embolization alone, 14 were treated with microsurgery alone, 27 were treated with endovascular embolization combined with radiosurgery, and 3 were treated with endovascular embolization combined with microsurgery.

Classification and Assessment of Headache

According to the International Classification of Headache Disorders, 3rd Edition, criterion (ICHD-III) (17), headaches were classified as migraine-like (with or without aura), tension-type-like (episodic or chronic), and others. The hemispheric side of the headache to the side of the ubAVM was divided into ipsilateral, contralateral, and both. Symptoms accompanying headache attacks were classified into photophobia, phonophobia, nausea or vomiting, and others. The baseline characteristics of symptomatic headaches in 124 patients with ubAVMs are summarized (Table 2).

An 11-point pain scale score (13-15) was used to assess the initial presentation through consultation for each patient. This assessment protocol would be per-

Table 1. *Baseline characteristics of ubAVMs in 124 patients with headache.*

Characteristics	No.	Percent (%)
Age (years)	34.4 ± 11.4	-
Female/male ratio	50 : 74	40.3 : 59.7
Right side of ubAVMs	82	66.1
Mean diameter of ubAVMs (cm)	5.1 ± 2.1	-
< 3 cm	37	29.8
3-6 cm	69	55.6
> 6 cm	18	6.9
Eloquent regions	68	54.8
Deep venous drainage	51	41.1
Drainage vein ectasia	27	21.8
Drainage vein stenosis	15	12.1
Fistula	10	8.1
Concurrent aneurysm	14	11.3
Flow-related	5	4.0
Intranidal	6	4.8
Unrelated	3	2.5
Spetzler-Martin Grade		
I	14	11.3
II	21	16.9
III	46	37.1
IV	36	29.0
V	7	5.7
Location of ubAVMs		
Frontal	20	16.2
Temporal	38	30.6
Parietal	13	10.6
Occipital	29	23.4
Multilobar	6	4.8
Basal ganglia	5	4.0
Cerebellar	5	4.0
Intraventricular	2	1.6
Corpus callosum	2	1.6
Brain stem	4	3.2
Concomitant presentation	19	15.3
Seizure	11	8.9
Neurological deficits	3	2.4
Visual deficits	4	3.2
Others	1	0.8

Note. ubAVMs: unruptured arteriovenous malformations.

Table 2. *The characteristics of headache in 124 patients with ubAVMs.*

Characteristics	No.	Percent (%)
Mean preoperative headache score	5.5 ± 2.6	-
Type of headache		
Migraine-like (with or without aura)	41	33.1
Tension-type-like (episodic or chronic)	63	50.8
Unclassified others	20	16.1
Hemispheric side of migraine-like headache to ubAVMs		
Ipsilateral	32	78.0
Contralateral	3	7.3
Both	6	14.7
Hemispheric side of tension-type-like headache to ubAVMs		
Ipsilateral	23	36.5
Contralateral	16	25.4
Both	24	38.1
Associated symptoms with headache	17	13.7
Photophobia	6	4.8
Phonophobia	4	3.2
Nausea or vomit	5	4.1
Others	2	1.6

Note. ubAVMs: unruptured arteriovenous malformations.

formed within 3 months following multidisciplinary care. For patients receiving medical treatment, the headache assessment protocol was performed every 3 months until the last visit, and for patients receiving multi-staged embolization, the same headache assessment protocol would be performed 8 - 12 weeks after the next therapy repeatedly until lesion extirpation. If patients were treated by radiosurgery, headache assessment was implemented every 6 months until complete pain relief was achieved.

The 11-point pain scale score ranged from 0 to 10, with 0 being defined as "freedom of headache" and 10 being defined as "hard to bear headache or the most terrible pain." The headache outcome after all treatment was classified as 1) improvement (including complete relief that hardly felt the pain, or partial relief, a 50% decrease from the initial 11-point pain scale score), 2) headache worsening or new onset (increased over 50% from the initial 11-point pain scale score), and 3) unchanged.

Follow-up and Indices of Clinical Outcome

Follow-up was performed on every eligible patient from the time of diagnosis to the last visit by either telephone or questionnaire. The primary outcome is death or stroke, which is defined as the first occurrence of composite events comprising death due to any cause or nonfatal symptomatic stroke (any new focus neurological deficits, seizure, or new headache) that is associated with hemorrhage or infraction, while the secondary outcome is adverse functional outcomes, which is defined as the modified Rankin scale score of 2 or higher (mRS ≥ 2) which is obtained by the last visit (1).The final result after multidisciplinary care of ubAVMs is complete obliteration. Radiological outcomes for patients receiving medical management were detected by computed tomography (CT), magnetic resonance imaging (MRI), or digital subtraction angiography (DSA) when new symptoms like seizure, focus neurological deficits, or headache occurred, or hemorrhage occurrence were suspected. For patients treated by radiosurgery, MRI or magnetic resonance angiography (MRA) was used to detect ubAVM size every 6 months until the lesion was completely obliterated, except when new symptoms occurred. If patients were treated by microsurgery, DSA would be immediately performed after the procedure to identify whether patients had a residual lesion. When patients underwent multi-staged embolization, the residual size was evaluated with every procedure until the lesion extirpation.

Statistical Analysis

Frequencies and percentages were calculated for categorical variables. Means and standard deviations (SD) were calculated for continuous variables. Categorical data were analyzed using Fisher's exact test or chi-squared test, as appropriate. Continuous variable analysis was performed using Student's t-test or Wilcoxon rank sum test. Log-Rank was used to analyze the difference between multidisciplinary care and medical treatment in death or stroke and adverse functional outcome (mRS ≥ 2) through follow-up prospectively. A probability value lower than 0.05 was statistically significant. The Statistical Package for the Social Sciences version 13 (SPSS, Chicago, IL, USA) was used in statistical analysis.

Results

The Distribution of ubAVMs to Anatomical Location for Patients with Migraine-like or Tension-type-like Headache

For 41 patients presenting with migraine-like headache, there were 23 (56.1%) with ubAVMs located in the occipital lobe ($P < 0.001$, OR = 16.40, 95% CI 5.83 - 46.15) (Fig. 2A). For 63 patients presenting with tension-type-like headache, there were 40 (63.5%) with ubAVMs located in the frontotemporal lobe ($P < 0.001$, OR = 4.16, 95% CI 1.96 - 8.82) (Fig. 2B).

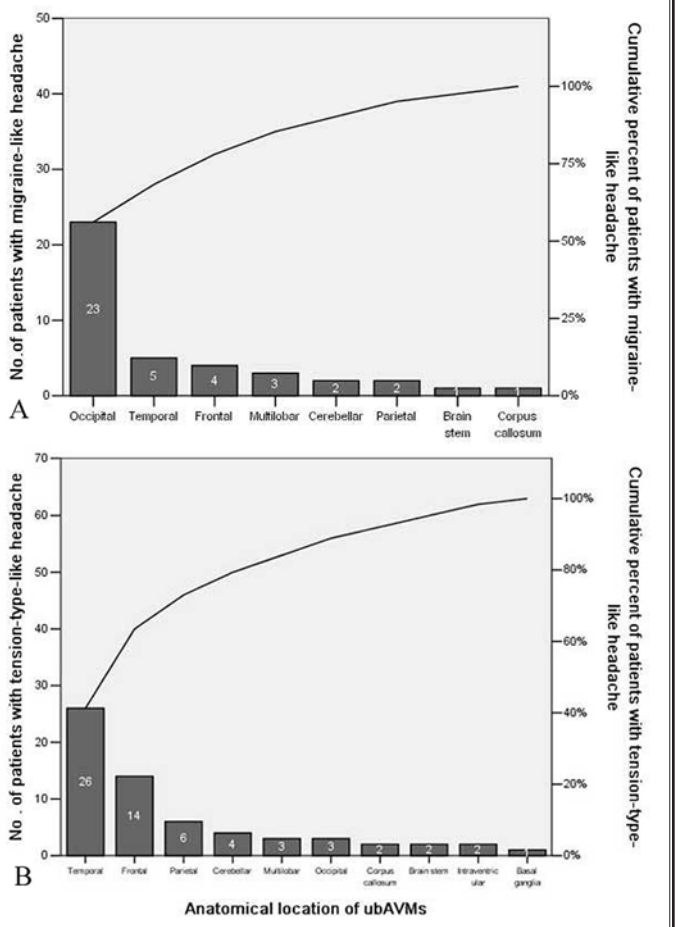

Fig. 2. *The distribution of ubAVMs to anatomical location for patients with migraine-like (A) or tension-type-like headache (B).*

The Headache Outcomes of Migraine-like Headache, Tension-type-like Headache, or All Types of Headache Following Multidisciplinary Care or Medical Treatment

The mean preoperative 11-point pain scale score of the multidisciplinary care group was higher than that of the medical treatment group for migraine-like headache ($P < 0.001$), tension-type-like headache group ($P < 0.001$), and all types of headache group ($P < 0.001$). the mean preoperative 11-point pain scale score was higher than the mean postoperative 11-point pain scale score following multidisciplinary care for migraine-like headache ($P = 0.007$), tension-type-like headache ($P < 0.001$), and all types of headache ($P < 0.001$), while the mean preoperative 11-point pain scale score was higher than the mean postoperative 11-point pain scale score following medical treatment in tension-type-like headache ($P = 0.013$) and all types of headache ($P = 0.004$).

The rate of headache improvement was higher for patients receiving multidisciplinary care than for patients receiving medical treatment (all types of headache, $P < 0.001$; tension-type-like headache, $P < 0.001$). But for patients with migraine-like headache, headache improvement did not differ between the multidisciplinary group and medical group (69.2% vs. 39.3%, $P = 0.074$) (Table 3).

The Outcomes of Patient Concomitant Presentation Following Multidisciplinary Care or Medical Treatment

Of 19 patients presenting with concomitant issues (in-

Table 3. *The headache outcomes of various types of headache following multidisciplinary care or medical treatment in 124 patients with ubAVMs.*

Headache outcomes	All types of headache		Migraine-like headache		Tension-type-like headache	
	Multidisciplinary care (n = 70)	Medical treatment (n = 54)	Multidisciplinary care (n = 13)	Medical treatment (n = 28)	Multidisciplinary care (n = 41)	Medical treatment (n = 22)
Mean preoperative 11-point pain scale score *	7.3 ± 1.7	3.1 ± 1.5	7.2 ± 1.8	3.0 ± 1.2	7.1 ± 1.7	2.9 ± 1.4
Mean postoperative 11-point pain scale score	1.7 ± 2.9 §	2.3 ± 2.1 §	3.2 ± 3.4 §	2.4 ± 2.0	1.6 ± 2.7 §	1.8 ± 1.3 §
Headache improvement (%)	60 (85.7) ¶	22 (40.8)	9 (69.2)	11 (39.3)	36 (87.8) ¶	7 (31.8)
Headache complete relief (%)	44 (62.9)	13 (24.1)	5 (38.5)	5 (17.9)	26 (63.4)	5 (22.7)
Headache partial relief (%)	16 (22.8)	9 (16.7)	4 (30.7)	6 (21.4)	10 (24.4)	2 (9.1)
Headache worsening or new onset (%)	4 (5.7)	6 (11.1)	1 (7.7)	4 (14.3)	2 (4.9)	1 (4.5)
Unchanged (%)	6 (8.6)	26 (48.1)	3 (23.1)	13 (46.4)	3 (7.3)	14 (63.7)

*Note. * The mean preoperative 11-point pain scale score of multidisciplinary care compared to that of medical treatment in types of headache ($P < 0.001$), migraine-like headache ($P < 0.001$), or tension-type-like headache ($P < 0.001$), respectively; § The mean postoperative 11-point pain scale score was significant than mean preoperative 11-point pain scale score following multidisciplinary care or medical treatment; ¶ The rate of headache improvement was higher for patients receiving multidisciplinary care than for patients receiving medical treatment ($P < 0.001$).*
ubAVMs: unruptured arteriovenous malformations.

cluding 11 cases with seizures, 3 with neurological deficits, and 4 with visual deficits), 12 cases (63.2%) were treated by multidisciplinary care and 7 cases were treated by medical treatment. After treatment, in 7 (63.6%) of 11 patients seizures improved in frequency, duration, and symptoms, in 2 (66.7%) of 3 patients neurological deficits were completely relieved, but in only one (25%) of 4 patients visual deficits improved.

The Complications of Patients who Underwent Multidisciplinary Care or Medical Management

Fifty-nine patients (84.3%) achieved complete elimination of ubAVMs following multidisciplinary care. Of 14 patients receiving microsurgery, one presented with subdural fluid accumulation following surgery and the fluid volume increased after 8 months, leading to left limb paralysis; one had hemorrhagic exudation within the surgical localization 3 days after surgery, leading to immediate removal of the hemorrhage because of cerebral hernia, right limb paralysis remained; intracranial infection was confirmed in another patient through lumbar puncture after a week, hydrocephalus occurred after the intracranial infection had been cured for two years; and the last showed a massive cerebral infarction one week after surgery possibly due to cerebral artery injury.

Five of the 12 patients receiving endovascular embolization alone had management-associated complications , one was left with aphasia because of glue reflux; one was left with upper limb paralysis due to normal feeding artery embolization; another showed hemianopia at the second procedure; one presented with hemorrhage due to residual nidus rupture 6 years later; and the last showed immediate hemorrhage when the first procedure was finished.

There were 21 patients receiving radiosurgery alone, one of whom died of radiation pneumonitis one month after radiosurgery, another experienced hemorrhagic events 8 years after treatment, and one showed homonymous hemianopia 2 weeks after radiosurgery.

Of 24 patients receiving endovascular embolization in combination with radiosurgery, 2 experienced hemorrhagic events, one of whom was in coma, the other died of pneumonitis; 3 had cerebral infraction located in the basal ganglia and parietal lobe, leaving limb paralysis. There were no complications in the 3 patients receiving endovascular embolization combined with microsurgery.

Hemorrhagic events occurred in 7 of 54 patients receiving medical management, one of whom died of cerebral hernia secondary to hemorrhage; 3 patients suffered cerebral infraction located in the right basal ganglia, frontal lobe, and the left cerebella; one died of

liver cancer unrelated to ubAVMs, and 2 patients presented with seizures.

The Natural History of ubAVMs Patients Receiving Multidisciplinary Care or Medical Management

Death or stroke occurred in 17 (24.3%) of the 70 patients receiving multidisciplinary care (mean 9.44 years follow-up), while death or stroke occurred in 11 (20.3%) of the 54 patients receiving medical treatment (mean 10.16 years follow-up). The risk of death or stroke did not differ between the multidisciplinary group and medical group (P = 0.393) (Fig. 3A). Based on hemorrhagic events, 4 cases treated by medical treatment were allocated to the multidisciplinary group, therefore the risk of adverse functional outcomes (mRS ≥ 2) was higher for patients in the multidisciplinary group (17 of 74, 23.0%) vs. patients in the medical treatment group (5 of 50, 10.0%) (P = 0.022) (Fig. 3B).

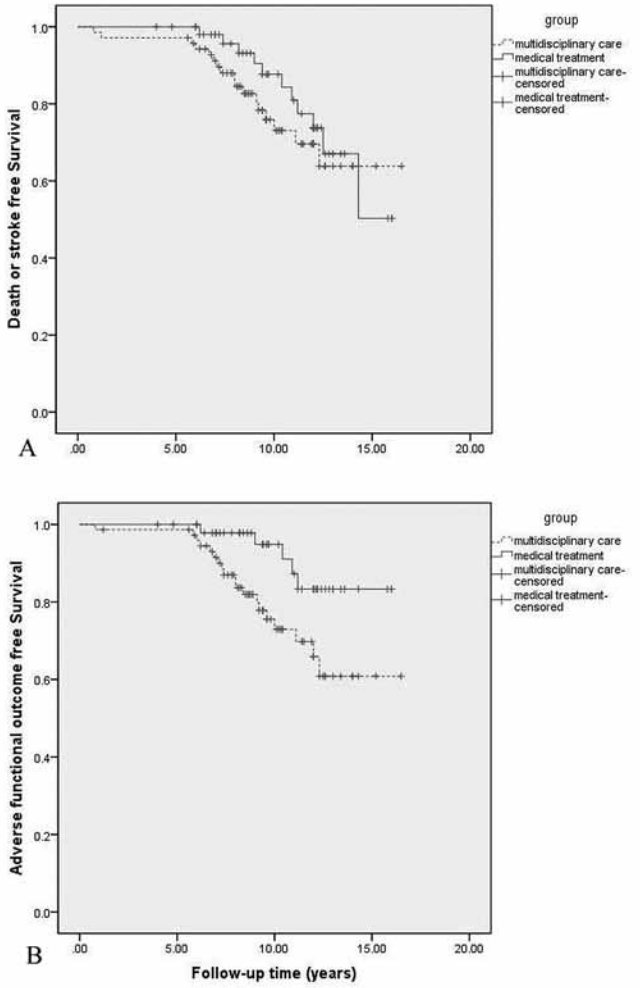

Fig. 3. *The natural history (including death or stroke and adverse functional outcomes) of ubAVM: A) the risk of death or stroke did not differ between the multidisciplinary group (17 of 70, 24.3%) and medical group (11 of 54, 20.3%) (P = 0.393); B) the risk of adverse functional outcomes (mRS ≥ 2) was higher for patients in the multidisciplinary group (17 of 74, 23.0%) vs. patients receiving medical treatment (5 of 50, 10.0%) (P = 0.022).*

Discussion

As symptomatic headaches attributed to ubAVMs are very common (1,2,18), they extremely affect patients' quality of life (5). In the ICDH-3 (17) the criteria for headaches attributed to bAVMs are outlined, nevertheless, the mechanism remains speculative and unclear (4). Previous authors (7,9,19) believed that obliteration of ubAVMs through radiosurgery, microsurgery, or multimodal treatment may relieve symptomatic headaches and improve patients' quality of life, but based on the insufficient number of cases, these studies included discrepancies on headache improvement. As a result, we conducted this study with a large cohort of patients with headaches.

Of 124 eligible patients in this study, 41 cases (33.1%) presented with migraine-like headache. The headaches were ipsilateral to the ubAVMs in 32 (78.0%) of 41 patients with migraine-like headache. De Lange initially reported migraine-like headache associated with bAVMs in 1927 (20) and early studies sought to explore the relationship between bAVMs and migraine-like headache (18,21). With regard to clinical manifestation, the symptomatic headache associated with bAVMs is hard to distinguish from migraine alone (22). Previous studies (9,19,23,24) demonstrated the strong association of symptomatic headache and occipital bAVMs, and these bAVMs patients with migraine-like headache showed a clear predominance to the occipital location, which is in line with our results (P < 0.001, Fig.2A). Galletti et al (23) reported the initial symptom of bAVMs was migraine-like headache in 9 women, and the cephalic pain in all eligible cases was ipsilateral to the lesion.

Ellis et al (4) reviewed previous publications pertaining to the association of bAVMs and migraine-like headache and reported that the hemispheric side of bAVMs was strongly correlated with the side of the headache. Therefore, occipital ubAVMs are more likely to present migraine-like headache, and the cephalic pain is ipsilateral to the lesion.

However, the pathophysiology of migraine-like headache attributed to bAVMs remains unclear. Three hypotheses (4), such as intracranial pressure (ICP), steal phenomenon, and cortical spreading depression (CSD), have been proposed. But these viewpoints could not explain all phenomena clearly, the pathophysiology of migraine-like headache associated with bAVMs remains to be fully resolved.

According to the ICDH-3 criteria (17), one type of headache associated with ubAVMs mimics the characteristics of tension-type headaches as our study described, called tension-type-like headache in order to distinguish them from tension-type headache alone. Sixty-three (50.8%) patients presented with tension-type-like headache in this study. The side of the lesion ipsilateral to the cranium of the headache did not show clear predominance, in accordance with Monteiro et al (n = 16, 31.4%) (25) and the ARUBA trial (n = 59, 47.6%) (1). Although the mechanism of this headache type is unclear, we still find that frontal or temporal ubAVMs (n = 40, 63.5%) are more likely to present tension-type-like headache ($P < 0.001$, Fig. 2B).

Due to the unclear mechanism of symptomatic headache associated with ubAVMs, obliteration of ubAVMs through single or multimodal treatment is the paramount way to relive pain and improve patients' quality of life (6,7,9-11,19). Meanwhile, the usefulness of pharmacotherapy in treating headache associated with bAVMs was not documented by a previous study (22). Kurita et al (19) believed radiosurgery for occipital bAVMs is useful for headache relief, and Dehdashti et al (9) reported favorable headache relief outcomes after multidisciplinary care for occipital bAVMs. Obliteration of ubAVMs is possible through single or multimodal treatments, thereby eliminating headache pain and improving patients' quality of life.

Because headache is hard to measure by some special instruments, an 11-point pain scale score (13-15) was used to measure headache in our study. Based on the potential hemorrhage risks for ubAVMs (e.g., aneurysm, deep venous drainage, drainage vein stenosis) and toleration of pain, the cases were allocated to multidisciplinary care or medical treatment. As a result, we found patients with high initial 11-point pain scale scores > 3 tended to receive multidisciplinary care ($P < 0.05$). For patients with an initial 11-point pain scale score ≤ 3, medical treatment also significantly improved the headache ($P < 0.05$), except for those of patients with migraine-like headache ($P = 0.174$), but the rate of headache development of patients treated by medical treatment in our study is obviously smaller than multimodal therapy of headache attributed to occipital bAVMs by Dehdashti et al (9) (40.7% vs. 84.0%). As one could infer, medical treatment for patients with lower initial 11-point pain scale scores (≤ 3) is not optimal to improve the associated headache. Because patients presenting with migraine-like headache did not differ in pre- or postoperative 11-point pain scale scores using medical treatment, the probability is that ubAVMs as a "trigger" leads to migraine-like headache attacks (4,23) and elimination of this "trigger" ubAVM may resolve the migraine-like headache. We also found that multidisciplinary care of ubAVMs to improve migraine-like headache (initial 11-point pain scale score > 3) is effective ($P < 0.001$), but the rate of headache improvement does not statistically differ between multidisciplinary care and medical treatment ($P = 0.074$).

Monteiro et al (25) showed similar results in 24 (47.0%) of 51 patients with intracranial vascular malformations (IVM) presenting with migrainous type headache who submitted to surgery or embolization had no significant changes in headache improvement. Therefore the authors speculated that IVM was not a trigger alone, yet the particular location of the lesion may increase susceptibility to migraine attack. Haas (26,27) believed migraine attacks may persist after total extirpation of bAVMs, and suggested that the neighboring brain was the generative site. The causal relationship between migraine-like headache and ubAVMs is blurred, hitherto there is not enough evidence to conclude multidisciplinary care of ubAVMs relieve migraine-like headache.

By contrast, multidisciplinary care of ubAVMs to improve tension-type-like headache (87.8% headache improvement, $P < 0.001$) or all types of headache (85.7% headache improvement, $P < 0.001$) is effective. Wolpert et al (6) reported that 12 (63.0%) of 19 patients had decreased headaches over 2 years following embolization. Lunsford et al (28) reported that in 104 (46%) patients presenting with headache ahead of radiosurgery, outcomes were obtained in only 73 patients due to adequate follow-up and 56 patients (75%) showed headache improvement. The headache improvement strong-

ly correlated with reduction in bAVM size on serial MRI. Dehdashti et al (9) reported that after multidisciplinary care of 42 (31.1%) occipital bAVMs patients with headache, 34 (84.0%) patients showed improvement, which is consistent with our outcomes after multidisciplinary care. Therefore, multidisciplinary care of ubAVMs can resolve symptomatic headaches and improve patients' quality of life. But the mechanism of multidisciplinary care of ubAVMs to improve headache is unclear.

For the natural history of 124 ubAVM patients with symptomatic headaches in our study, the risk of death or stroke did not differ between the multidisciplinary care group and medical treatment group ($P = 0.393$, Fig. 3A), but the risk of adverse functional outcome (MRS ≥ 2) was higher for the multidisciplinary care group vs. for medical treatment group ($P = 0.022$, Fig. 3B).

The ARUBA trial (1) reported the death or stroke events were greater for patients receiving interventional therapy (35 of 110, 30.7%) vs. patients receiving medical management (11 of 109, 10.1%) ($P < 0{\cdot}0001$) at 36 months. The hazard of clinical impairment (mRS ≥ 2) was greater for the interventional therapy group (17 of 44, 38.6%) in comparison with the medical management group (6 of 43, 14.0%). But based on the trial design and short follow-up time, the results led to debate (29). Al-Shahi et al (12) conducted a prospective trial that interventional therapy of ubAVMs conferred a high risk of stroke or death, but a 66% obliteration rate and a poor outcome given that 90% of the treated ubAVMs were of low grade may overestimate treatment-associated with high risk of stroke or death (30).

However, Bervini et al (31) analyzed the risks from surgery to 427 patients with a ubAVM, and reported surgery for Spetzler-Ponce Class A (32) ubAVMs provided more benefits than conservative management. Potts et al (33) reported 78% of ruptured or unruptured ubAVM patients with Spetzler-Martin Grade I, II showed favorable outcomes (mRS score 0 or 1) after surgical treatment. Pollock et al (34) reported radiosurgery for ubAVMs with low-volume could decrease the risk of death or stroke, compared to the natural history of ubAVMs.

Therefore, although the multidisciplinary care of ubAVMs in our study conferred a higher risk of adverse functional outcomes (mRS ≥ 2), based on retrospective research sharing inherent limitations, the results of the natural history of ubAVMs in our study is not enough to conclude whether there are benefits from multidisciplinary care or medical treatment of ubAVMs in death or stroke and improvement of adverse functional outcome (mRS ≥ 2). The natural history of ubAVM patients remains unclear (9,23), larger sample and multi-center trials are needed to provide more information on the natural history of ubAVM patients with headache. But multidisciplinary care of ubAVMs definitely improves headaches according to our results of 85.7% of headache improvement.

This study shares the limitations of all retrospective studies. As the department is a tertiary referral center, the bias is referral patients that of selection on bad condition. Generally, various diseases could accompany with symptomatic headache presentation, such as brain trauma, seizure, psychotic disorder. Although we attempt to reduce the bias by excluding factors associated with headache as much as possible, some underlying factors still have possibility to affect the final results. In addition, the measurement protocol of 11-point pain scale score was used to assess the degrees of headache according to subjective judgement of patients, therefore different sensitiveness to headaches, and willpower may exaggerate or underestimate the value of 11-point pain scale score to headache, which further leads to affect final results. The paramount defaults is single center and limitation of number of sample, it is possible to debilitate the consequences.

Conclusion

Occipital ubAVM is more likely to present with migraine-like headache, while frontotemporal ubAVM is more likely to show tension-type headache. Multidisciplinary care of ubAVM to attenuate headache and to improve patient's quality of life is effective, but the natural history of ubAVM patients with headache is unclear. Multi-center trials with larger sample sizes are needed to provide more information on the interesting issue.

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