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Toward a Further Elucidation: Role of Vertebral Artery Hypoplasia in Migraine with Aura

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Key Words
Vertebral artery · Flow volume · Duplex · Migraine with aura · Magnetic resonance angiogram · Hypoperfusion

Abstract
A higher frequency of hypoplasic vertebral artery (VA) in patients with migraine with aura than in normal controls has been documented. However, the role of a hypoplasic VA in a migraine attack remains unclear. The aim of our work was to measure the net VA flow volume and related spectral parameters in patients with migraine with aura and a hypoplasic VA. From January 2005 to October 2005 we reviewed the records of 250 migraine outpatients (108 men and 142 women; mean age = 30.8 ± 14.0 years, range = 25–55). Ninety-two patients with migraine with aura were selected. Among these patients, 26 had a hypoplasic VA that was delineated by cervical magnetic resonance angiography. We performed a case-control study that included these 26 migrainous patients. Duplex color-coded ultrasonography was utilized to calculate the spectral parameters during attacks and headache-free periods. The net VA flow volume did not decrease during attacks. A reduction in the resistance index of the hypoplasic VA was noted during attacks in subjects who had migraine with aura. Our observation of VA vasomotor alteration during migraine attacks extends the understanding of the role of a hypoplasic VA. Vasomotor regulation of the VA could be neurogenic in origin. We hypothesize that VA hypoplasia contributes to migraine through complex neurovascular pathways rather than through its low flow volume.

Background and Purpose

Congenital vertebral artery (VA) hypoplasia is an uncommon embryonic variation of the posterior circulation. The frequency of this congenital variation has been reported to range from 2 to 6% based on autopsy findings and angiograms [1–4]. Lovrencic et al. [5] reported a 4 times higher frequency of hypoplasic VA in patients with migraine with aura than in normal controls. It was postulated that the hypoplasic VA leads to hypoperfusion during the aura phase. However, there is evidence that argues against this hypothesis. Zwetsloot et al. [6] found no difference in blood flow velocities in the vertebrobasilar system during migraine attacks and headache-free periods. In migraineurs both with and without aura, no differences in spectral parameters were found between during attacks and pain-free periods. Currently, the sonographic diagnostic criteria for extracranial VA hypoplasia and its net VA flow volume value can be easily de-

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fined by duplex color-coded ultrasonography [2, 3, 7]. The normal range of net VA flow volume has been established and the consequent diagnostic criteria for vertebrobasilar insufficiency with net VA flow volume measurement has also been determined [1, 7].

It seems possible to answer the following question: does VA hypoplasia lead to a net VA flow reduction in migraine with aura? We performed a case-control study in migraine with aura patients who had a hypoplasic VA. We calculated the spectral parameters and net VA flow volume measurements during attacks and headache-free periods in migraine with aura subjects.

Table 1. Baseline characteristics

	Tested group migraineur with VAH	Control migraineur without VAH
Number of patients	26	26
Females/males	14/12	14/12
Mean age ± SD, years	33.2 ± 11.2	33.5 ± 11.6
Usual attack duration ± SD, h	37.2 ± 16.2	35.2 ± 17.5
Duration of attack until examination ± SD, h	8.6 ± 5.3	7.9 ± 6.8

VAH = Vertebral artery hypoplasia.

Subjects and Methods

We reviewed the records of 250 migraine outpatients based on the outpatient disease registration (108 men and 142 women; mean age = 30.8 ± 14.0 years, age range = 25–55; usual attack duration = 36.2 ± 15.8 h; duration of attack until examination = 9.6 ± 6.2 h) for the period of January 2005 to October 2005. These 250 patients were called back and the diagnosis of migraine with or without aura was reassessed by 2 board-certified neurologists (C.Y.M. and H.Y.C.) in accordance with the International Headache Society criteria [8]. Our inclusion criteria were (a) clinical diagnosis of migraine with aura and (b) diagnosis of extracranial VA hypoplasia based on the cervical MR angiogram if <2 mm in diameter. Exclusion criteria were psychiatric illness (n = 3), diabetes mellitus (n = 2), epilepsy (n = 2), hypertension (n = 6; diastolic pressure >95 mm Hg), cardiovascular disease (n = 3), ischemic cerebrovascular disease (n = 2) and abuse of narcotics or ergotamine (n = 5). Agreement on diagnosis was reached for 92 patients who had migraine with aura and 126 patients who had migraine without aura. Cerebral MRI and MR angiography (0.3-tesla, Airisii, Hitachi Medical Corporation) were performed only on the patients who had migraine with aura (n = 92) to detect existing VA hypoplasia. All these 92 cases had cerebral MRI and MR angiography studies only during the migraine-free period. The results of cerebral MRI and MR angiography were reviewed by a board-certified radiologist (Y.C.Y.). The diagnosis of extracranial VA hypoplasia was based on the cervical MR angiogram if the diameter was <2 mm [9]. Diagnosis of VA hypoplasia was established in 26 subjects. All of these subjects had right-sided hypoplasic VA. All 26 patients had visual aura (12 men and 14 women; mean age = 34.1 ± 10.2 years; table 1); in 1 patient (a 44-year-old female), this was accompanied by right hemiparesis. The control group was recruited from the remaining 66 subjects of migraine with aura but without a hypoplastic VA, which consisted of 26 age- and sex-matched subjects (12 men and 14 women) with a mean age of 33.5 ± 11.6 years (range = 25–45).

Doppler examination was performed on the controls and on the 8 migraine with aura subjects during attacks and headache-free periods. The examinations were carried out by a technician, who was blind to the study protocol, in a semi-dark, quiet room. Attack-free registration was performed at least 3 days after an attack. The patient characteristics are shown in table 1. None of the migraine patients took acute antimigraine medication before undergoing duplex scanning or were taking a prophylactic medication at the time of the study. This study protocol was approved by the Institution Review Board of Keelung General Hospital and written informed consent was obtained from all patients and their relatives.

A 7.5-MHz linear transducer from a Philips SD 800 system was used. Before volume flow measurement was performed in the vertebral arteries, a routine examination of the carotid arteries was carried out. The patients rested in the supine position for about 15 min before the first data were obtained. Both sides of the patients were examined. The patient's head was turned slightly to the opposite side each time. The intertransverse (V2) segment of the VA was visualized by rotation of the probe posteriorly from the carotid plane. Duplex measurement of angle-corrected flow velocities was performed with the sample volume expanded over the entire vessel diameter. The peak systolic and end-diastolic velocities and time-averaged maximum velocity were recorded. Angle correction was done by 1° increments. The vessel diameter (d) was measured in a magnified B mode image for better accuracy at the site of the Doppler sample volume; adjustment of diameter measurement was done by 0.1-mm increments. All measurements were documented with a black-and-white video printer. All measurements were performed twice, and an average was determined. The flow volume was calculated according to the following equations: Q = time-averaged mean velocity × area with area (A) = $(d/2)^2 \times \pi$.

Data Analysis

A 2-sided p value <0.05 was considered to indicate statistical significance. SPSS soft software (version 10.0, SPSS Inc., Chicago, Ill., USA) was applied for statistical analyses. Paired t test was used in the 'migraine attack and migraine-free stage' comparison and Student's t test in the 'migraine with aura and control group' comparison.

Results

The incidence of VA hypoplasia in patients who had migraine with aura was 28.26%. There was no significant net VA flow volume reduction during the attack phase

Table 2. Spectral parameters measured during migraine attacks and headache-free periods

	Tested group (n = 26)		Control (n = 26)	
	headache-free	attack	headache-free	attack
Net VA flow volume, ml/min	128.7 ± 11.6	130.6 ± 12.1 (power: 0.51)	137.2 ± 11.8	135.2 ± 12.5 (power: 0.53)
Resistance index				
Left VA	0.65 ± 0.11	0.68 ± 0.13 (power: 0.49)	0.66 ± 0.12	0.65 ± 0.13 (power: 0.55)
Right VA	0.89 ± 0.12	0.79 ± 0.05[1] (p = 0.03)	0.65 ± 0.11	0.66 ± 0.14 (power: 0.53)
Diameter, mm				
Left VA	0.31 ± 0.09	0.30 ± 0.10 (power: 0.51)	0.29 ± 0.08	0.30 ± 0.06 (power: 0.50)
Right VA	0.19 ± 0.04	0.18 ± 0.06 (power: 0.53)	0.28 ± 0.07	0.29 ± 0.05 (power: 0.52)
Left VA				
PSV	59.8 ± 12.6	58.9 ± 13.9 (power: 0.53)	60.8 ± 15.6	61.2 ± 15. 4 (power: 0.55)
EDV	30.5 ± 8.7	32.7 ± 9.1 (power: 0.61)	31.7 ± 8.5	32.7 ± 8.9 (power: 0.51)
TAMV	43.6 ± 9.6	43.6 ± 9.6 (power: 0.52)	43.6 ± 9.6	42.9 ± 6.8 (power: 0.57)
Right VA				
PSV	27.8 ± 8.9	28.9 ± 9.1 (power: 0.51)	58.7 ± 12.8	57.9 ± 14.5 (power: 0.52)
EDV	9.6 ± 3.7	14.6 ± 5.7[1] (p: 0.032)	29.6 ± 8.8	28.6 ± 8.5 (power: 0.55)
TAMV	14.9 ± 5.8	18.7 ± 6.4[1] (p: 0.04)	46.5 ± 9.8	457 ± 85 (power: 0.55)

Values are means ± SD. PSV = Peak systolic velocity; EDV = end-diastolic velocity; TAMV = time-average mean velocity.
[1] Test group: migraine without a hypoplastic VA; control: migraine with a hypoplastic VA.

compared with the headache-free period (table 2). The net VA flow volume in the migraine with aura group was comparable to that in the control group. Given that there was right-sided hypoplasic VA in our migraine with aura group, finding a smaller caliber right VA with a higher resistance index (RI) in this group than in the control group was unremarkable. The exception was that the RI of the right VA decreased significantly during the attacks of migraine with aura. Meanwhile, the RI of the left VA remained stationary. All subjects with migraine had concurrent right-sided hypoplasic VA. One subject developed a prolonged visual aura which lasted for 32 h. The Doppler studies in this patient were performed at 6, 10, and 20 h after aura onset. The net VA flow volumes were 121.6 ± 8.8, 128.8 ± 9.2 and 125.6 ±7.1 ml/min, respectively, which were comparable to the value during her headache-free period (124.8 ± 6.8 ml/min; fig. 1).

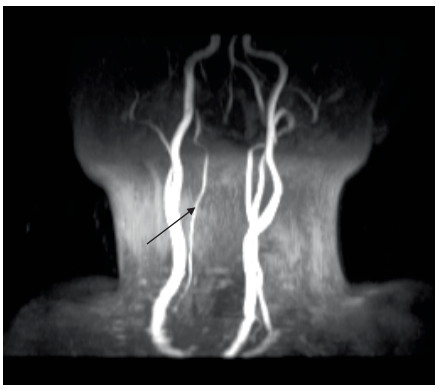

Fig. 1. The net VA flow volume measured in a woman who had migraine with prolonged aura was 128.8 ml/min. The corresponding cervical MR angiogram confirmed the diagnosis of right-sided VA hypoplasia (arrow).

Discussion

The incidence of VA hypoplasia in patients who had migraine with aura (28.26%) was 14 times higher than that of the normal controls in our previous study (2.09%), which involved the same hospital outpatients [4]. Our result supports the observation of Lovrencic et al. [5] but argues against their proposed hypothesis. The net VA flow volume measured during the attack phase was satisfactory [1]. It can therefore be argued that the role of VA hypoplasia in migraine may not involve hypoperfusion during the attack phase. The result is basically a negative one, while the meaning of RI remains unclear in the presence of VA hypoplasia.

A significant RI reduction in the hypoplasic VA was evident during the attacks of migraine with aura. The

phenomenon did not occur in the control group of migraine patients without VA hypoplasia. Thus, the results obtained may be attributed to the VA hypoplasia itself rather than migraine pathogenesis. Despite alteration of the RI, the net VA flow volume was stationary. This may be attributable to the extremely small caliber of the vessel and the low baseline flow velocity of a hypoplasic VA. The net hemodynamic influence, therefore, may be limited [2].

It is not as straightforward because some bias would exist. There are limitations with regard to duplex study. Inadequate insonation angle correction and diameter measurement with inappropriate gain have been well recognized. In our study, we recruited only 1 sonographic operator in order to eliminate interexaminer bias. Nevertheless, with regard to these limitations of duplex study, the net VA flow volume measurement may not truly reflect the corresponding cerebral flow [9, 10]. Further studies, comparing duplex Doppler with isotope studies, may determine the hemodynamic role of hypoplasic VA with regard to cerebral blood flow in the whole cranial hemisphere [11].

A second explanation is that a hypoplasic VA may not contribute to migraine attack through its net VA flow volume reduction. In our work, reduction of the RI was evident during the aura phase and during attacks of migraine with aura. Vasomotor regulation of the VA may be neurogenic in origin. Vasomotor regulation of the VA is innervated by the cervical perivascular sympathetic plexus [12, 13]. The cervical sympathetic trunk directly contributes to the trigeminovascular pain-producing mechanism of migraine [14]. Our observation of VA vasomotor alteration during migraine attacks further extends the knowledge about the role of the hypoplasic VA. Based on the above facts, we hypothesize that VA hypoplasia might contribute to migraine through complex neurovascular pathways of the trigeminovascular pain-producing mechanism rather than through its corresponding low flow volume.

Finally, the sample size of our study was relatively small (n = 250). Given the low frequency of VA hypoplasia, this bias could have been enhanced. Besides, a possible alteration of VA diameter on attack/free stage would exist [15]. In the current study, cervical MR angiography was done only during the migraine-free period for assumed intolerable for migraineurs on attack stage. A large-scale study with double MR angiographic confirmation of VA hypoplasia upon attack and migraine-free periods is necessary to verify the reproducibility of our findings. Despite these limitations, we believe that the association of a hypoplasic VA and migraine is a real association, which deserves greater attention.

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