The Clinical Relevance of Vertebral Artery Hypoplasia

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Abstract

Congenital vertebral artery (VA) hypoplasia is an uncommon embryonic variation of posterior circulation. The frequency of this congenital variation was reported to be 2-6% from autopsy and angiograms. Is it a congenital risk factor of ischemic stroke? In this review, we gave an overview of the literature concerning vertebral artery hypoplasia. VA hypoplasia served as an independent factor of a reduction of the posterior circulation blood flow velocity. VA hypoplasia can play a negative role in cases of occlusion of a major brain vessel since it limits the potential of compensatory blood circulation. VA hypoplasia may also lead to regional hypoperfusion and complex neurovascular consequences which correspond to vestibular neuronitis and migraine pathogenesis.

Key words: Vertebral artery hypoplasia, fetal, posterior circulation, vestibular neuronitis, migraine

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INTRODUCTION

Vertebral artery hypoplasia (VAH) was described in the 19th century[(1)]. Congenital vertebral artery (VA) hypoplasia is an uncommon embryonic variation of posterior circulation[(1,2)]. The frequency of this congenital variation was reported to be 2-6% from autopsy and angiograms[(1-3)]. Is it a congenital risk factor of ischemic stroke? VAH with caliber discrepancies of more than 1:1.7 were observed in up to 10% of normal individuals[(3)]. There is no general agreement as to the definition of VAH. Operational definitions of VAH vary between diameters of less than 2 to less than 3 mm or an asymmetry ratio of equal or greater than 1:1.7[(3-6)]

Given the importance of these vascular variations, it is astonishing how little is known about their clinical relevance. In other words, is VAH a risk factor for strokes in the posterior cerebral circulation? Does a hypoplastic VA impair cerebral perfusion and manifest a hidden disease? It has been reported that, during extreme cervical injury, cerebral ischemia would occur in the territory of a hypoplastic vertebrobasilar system [(7)]. We wondered if this congenital variation played a role similar to spontaneous brainstem/cerebellum ischemic stroke. Recently, congenital VA hypoplasia could be easily defined by duplex color-coded ultrasonography[(2,5)]. The normal range of net VA flow volume has been established. And consequently diagnostic criteria of vertebrobasilar insufficiency with net VA flow volume <100 ml/min have also been determined[(4)]. In

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the early 1990s, a study that analyzed MR angiograms found symptomatic or asymptomatic pontine infarctions to be twice as frequent in patients with VAH as in patients with symmetric vertebral arteries[8]. The same group[9] found in an autopsy study VAH to be more frequent in cases with basilar artery occlusions than in cases with nonbrainstem infarctions.

Recently, VAH has been considered as risk factor of posterior circulation ischemia[2], and VAH has been associated with migraine with aura and vestibular neuronitis[6,10]. The aim of the current study was to evaluate whether VAH is a possible risk factor for posterior circulation stroke.

Association between Vertebral artery hypoplasia and Stroke

We examined 158 hemispheric ischemic strokes (108 men, 50 women, aged 53.5±13.8 years, range 30-95 years) and 33 brainstem/cerebellum ischemic strokes (22 men, 11 women, aged 55.8±14.0 years, range 25-83 years), which was confirmed by MRI[2]. The diagnosis of hypoplastic VA was established with MRA in 22 subjects. The incidence of a unilateral congenital hypoplastic VA was 11.51% (n = 22). Right-side preponderance was evident (R:L = 22: 0). As for the topographic distribution and TOAST classification of stroke with VA hypoplasia, an association of right-sided brainstem/cerebellar infarction with ipsilateral hypoplastic VA was found. The incidence of VA hypoplasia with brainstem/cerebellar ischemic stroke was 72.72% (n = 18) which was significantly higher than the 2.53% of hemispheric ischemic stroke patients (n = 4; p =0.022) and the 2.09% of the control group (n = 4; p =0.021). (Figure 1.)

In the net VA flow measurement of acute ischemic stroke subjects, victims with VA hypoplasia had a lower net VA flow volume (81.6±16.5 ml/min; hypoplastic VA: 20.3 8 12.8, contralateral VA: 60 8 11.6) than those without VA hypoplasia (123.2±13.5 ml/min; p = 0.032). VA hypoplasia had a corresponding lower net VA flow volume without topographic difference in hemispheric (84.5±12.6 ml/min, n = 4) and infratentorial ischemic stroke (83.4±10.2 ml/min; p = 0.12). Nevertheless, in the control group, the net VA flow volume measured in 4 subjects with VA hypoplasia (132.3±12.4 ml/min; 3 males and 1 female, ages 42.2±2.5 years) was comparable with the other controls (135.5±18.9 ml/min; p =0.0763).

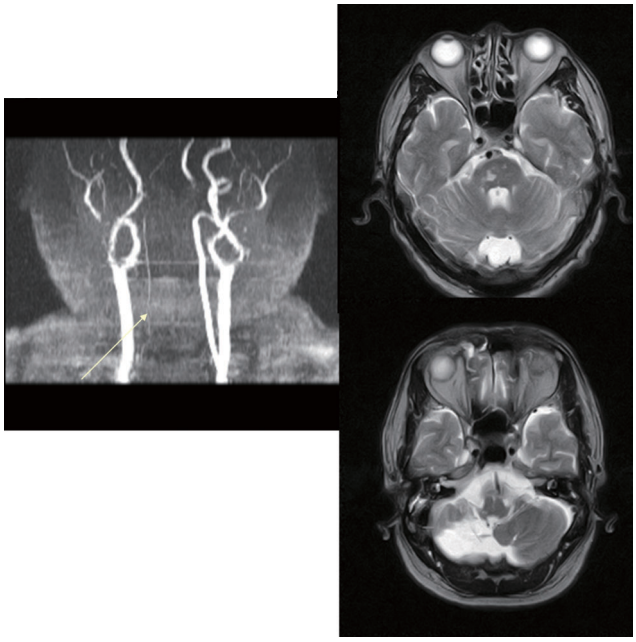

Figure 1. A 65 years old had a 5 years hypertension history developed acute onset of vertigo and ataxic gait with lateropulsion to right side. The corresponding brain MRI (T2WI) disclosed right cerebellar infarction with size>1.5cm and ipsilateral pontine infarct; which fulfilled the TOAST subtype criteria of large-artery artherosclerosis. The net VA flow volume was 78ml/min. Cervical magnetic resonance angiogram disclosed small caliber of right sided VA with caliber<2mm which correlated with diagnosis of VA hypoplasia (arrow).

Based on the results of our small-scaled study, we postulate a likely pathophysiology of stroke related to VA hypoplasia: (a) etiological preponderance of the TOAST infarction subtype 'large-artery atherosclerosis', (b) topographic preponderance of brainstem/cerebellar compared to hemispheric infarction, (c) ipsilateral side preponderance of VA hypoplasia and brainstem/cerebellar infarction, (d) VA hypoplasia having a corresponding lower net VA flow volume without topographic difference of the infarction site. Our study supported the hypothesis of Oder et al.[11] that the congenital VA varia-

tions would contribute to symptomatic vertebrobasilar occlusive disease.

Association between Vertebral artery hypoplasia and Migraine

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[10]. 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 compared with the headache-free period. 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). (Table 1.)

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[2]. Our result supports the observation of Lovrencic et al.[12] but argues against their proposed hypothesis. The net VA flow volume measured during the attack phase was satisfactory[13]. 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.

One 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[14,15]. The cervical sympathetic trunk directly contributes to the trigeminovascular pain-producing mechanism of migraine[16]. 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.

Vertebral artery hypoplasia and Vestibular evoked myogenic potential study (VEMP)

Among the 52 sides of the 26 subjects of experimental group, except for 1 side that showed no response, VEMP tests disclosed delayed responses in 22 subjects, including unilateral delay in 20 and bilateral delay in 2 subjects[17]. The remaining 3 subjects (11.53%) showed

Table 1. The net VA flow volume and RI during and outside migraine attacks

	Without aura (N=18)		With aura (N=8)		Control (N=26)
	free	attack	free	attack	
Net VA flow volume (ml/min)	132.8±12.4	130.6±11.3(P:0.19)	128.7±11.6	130.6±12.1(P:0.13)	137.2±11.8
RI of VA					
Left	0.67±0.12	0.70±0.11(P:0.22)	0.65±0.11	0.68±0.13(P:0.17)	0.66±0.12
Right	0.85±0.11	0.83±0.13(P:0.18)	0.89±0.12	0.79±0.05* (P:0.03)	0.65±0.11

normal vestibular evoked myogenic potentials bilaterally. In contrast, in the control group, VEMP testing disclosed delayed response in three subjects (11.53%), including unilateral delay in two and bilateral delay in one subjects.

In other words, 88.47% of the subjects with VAH demonstrated abnormal VEMPs either unilaterally or bilaterally. This was significantly higher than the percentage of abnormal VEMPs in the subjects without VAH (p=0.019). Mean latencies of p13 and n23 were significantly longer in the right ear of the subjects with VAH than those in the left ear and those in the subjects without a VAH. Given the exclusive right-sided hypoplasic VA in our group of subjects with VAH, the majority (69.23%, N=18) had a concurrent ipsilateral delayed response or absence of VEMP. (Figure 2.)

The prolongation of mean latency of p13 and n23 imply a demyelination process of the vestibulospinal tract[18]. Segmental demyelination is probably secondary to ischemic axonal dystrophy[19]. VAH may lead to repetitive hypoperfusion injury to corresponding brainstem regions[20]. Although one may infer a brain stem lesion from a delayed VEMP, absence of VEMP would indicate interruption of the sacculo-collic reflex, not necessarily a brain stem lesion. Nevertheless, we postulate that a delayed response or absence of ipsilateral VEMP can be attributed to "hypoperfusion" of the hypoplastic VA.

Association between Vertebral artery hypoplasia and Vestibular Neuronitis

From January 2006 to October 2007, we consecutively recruited 70 unilateral VN patients who participated in a double-blind randomised placebo controlled trial on the therapeutic effect of valaciclovir on VN in a tertiary referral medical center[6].

The diagnosis of VAH (V4) was based on the MRA if <0.22 cm in diameter, a diameter AI >40% and exclusion of segmental artherosclerotic stenosis of the VA5 6 (AI=left minus right VA diameter/left plus right VA diameter).

There were 29 VAH (right/left: 23/6) in VN subjects (42.0%) which was statistically higher than in the controls (12%, N=6, right/left: 5/1) (p=0.009). After controlling for the medical risk factors, the RR of VAH in VN subjects compared with controls was elevated (RR=2.2; 95% CI 1.8 to 2.8). There was right VN predominance (right/left: 54/23) in our patients. Among 29 patients with VAH, 65.5% (N=19) had an ipsilateral VN lesion.

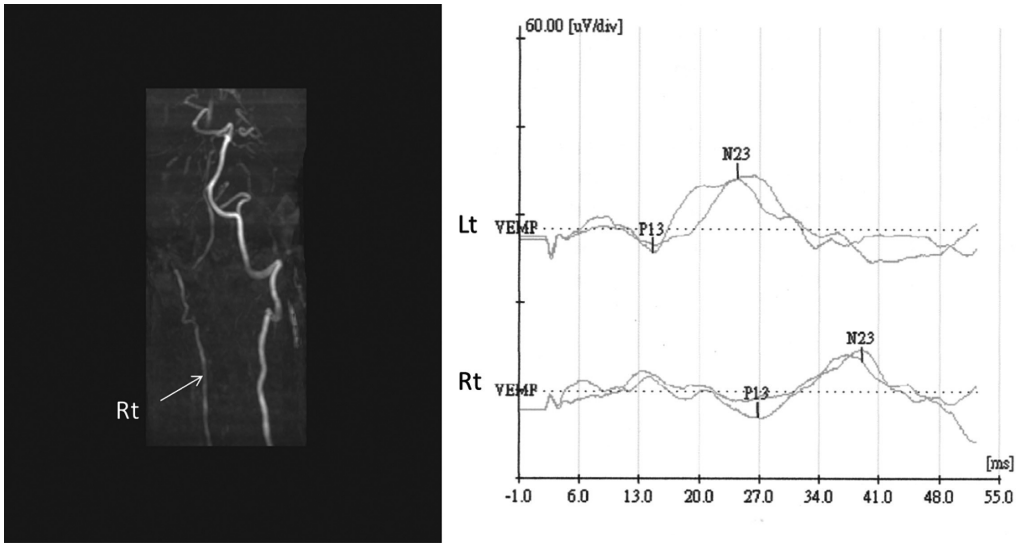

Figure 2. The n magnetic resonance angiogram in a woman who had migraine suggested the diagnosis of right-sided VA hypoplasia The corresponding vestibular evoked myogenic potentials testing disclosed an ipsilateral delayed response.

The side accordance rate between VAH and VN was higher in the left (83.3%) than in the right side (60.8%) (p=0.037) VN subjects were stratified to two subgroups for comparison:VN with (N=51; age: 63.29±8.5 years old; F/M: 28/23) and without medical atherosclerotic risk factors (N=18; age:48.55+-6.5; F/M: 12/6). The side accordance rate between VAH and VN was much higher (80.9%) in the vascular risk group than in the non-vascular risk group (25%). In both groups, left VAH assumed a significantly higher accordance rate than the right side. Demographic data showed older age and male predominance in the vascular risk group, while the prevalence of VAH was comparable between the two groups. (Table 2)

Our study revealed that VN subjects had a statistically higher incidence of VAH, and there is a significant side accordance rate between VAH and VN, especially on the left side and in those with vascular risk factors.

VAH is associated with a delayed P13 response in vestibular evoked myogenic potentials, suggesting labyrinthine injuries, probably related to VAH-associated hypoperfusion[17]. Although AICA is a branch of the caudal basilar artery (BA), the ipsilateral relationship between VAH and VN can be explained by the asymmetrical junction geometry. Ravensbergen found a BA 'double hump' axial velocity profile just downstream of the VA confluence[21]. A larger-calibre dominant VA with the highest 'hump' crosses the centre-line of BA and restricted blood of the hypoplastic VA from flowing into the ipsilateral AICA. However, with the Fahraeuse Lindqvist effect, small-calibre VAH will reduce its blood

Table 2. Clinical characteristics in 69 VN patients stratified by VAH and medical atherosclerotic risk factors

	VN with VAH	VN without VAH	p
No. of cases	29	40	
Age, year	50.29±8.5	48.55±6.5	0.073
Radiological findings			
Asymmetry index of VA	0.49±0.06	0.28±0.11	0.018*
No. of right VAH	23		
No. of left VAH	6		0.019*
No. of ipsilateral VAH according to VN lesion side	Global	19/29 (65.52%)	
Right VAH with ipsilateral. VN	14/23 (60.87%)		
Left VAH with ipsilateral. VN	5/6 (83.33%)		0.037*
	Vascular risk group	Non-vascular risk group	p
No. of cases	51	18	
Age, year	63.29±8.5	48.55±6.5	0.019*
Risk factors (%)	Hypertension	31	0
Diabetes mellitus	18	0	
Smoking	20	0	
Coronary artery disease	10	0	
Hyperlipidemia	32	0	
Radiological findings			
VAH	21 (41.17%)	8 (44.44%)	0.230
	R/L: 17/4	R/L: 6/2	
No. of ipsilateral VAH according to VN lesion site			
Global	17/21 (80.95%)	2/8 (25%)	0.009
Right VAH with ipsilateral VN	13/17 (76.47%)	1/6 (16.6%)	0.009
Left VAH with ipsilateral VN	4/4 (100%)	1/2 (50%)	0.068

* left VAH versus right VAH

viscosity and speed up dominant laminar flow to ipsilateral AICA.

VAH-related vestibular hypoperfusion may increase vulnerability to more severe viral infection through impeded immunity and restricted neuronal repair capacity[22]. Hypoperfusion with impaired oxidative killing by neutrophils, a primary defense against pathogens, is directly related to tissue oxygenation[23,24]. Comorbid intracranial VAH may also serve as a risk factor for severe vestibular neuronitis[25].

CONCLUSION

In this review, we gave an overview of the literature concerning vertebral artery hypoplasia. VA hypoplasia served as an independent factor of a reduction of the posterior circulation blood flow velocity rather than of the anterior circulation. VA hypoplasia can play a negative role in cases of occlusion of a major brain vessel since it limits the potential of compensatory blood circulation. VA hypoplasia may also lead to regional hypoperfusion and complex neurovascular consequences which correspond to vestibular neuronitis and migraine pathogenesis.

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