

Is Vertebral Artery Hypoplasia a Predisposing Factor for Posterior Circulation Cerebral Ischemic Events? A Comprehensive Review

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Key Words

Vertebral artery hypoplasia · Ischemic stroke · Transient ischemic attacks · Posterior circulation stroke · Brainstem infarction · Cerebellar infarction · Cerebral blood flow

Abstract

Vertebral artery hypoplasia is not currently considered an independent risk factor for stroke. Emerging evidence suggest that vertebral artery hypoplasia may contribute to posterior circulation ischemic events, especially when other risk factors coexist. In the present literature review, we present published data to discuss the relationship between a hypoplastic vertebral artery and posterior circulation cerebral ischemia. Despite difficulties and controversies in the accurate definition and prevalence estimation of vertebral artery hypoplasia, ultrasound studies reveal that the reduced blood flow observed ipsilateral to the hypoplastic vertebral artery may result in local cerebral hypoperfusion and subsequent focal neurological symptomatology. That risk of cerebral ischemia is related to the severity of the hypoplasia, suggesting that the smaller of paired arteries are more vulnerable to occlusion. Existing cohort studies further support clinical observations that hypoplastic vertebral artery enhances synergistically the vascular risk for posterior circulation ischemic events and is closely associated with both atherosclerotic and prothrombotic processes.

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Introduction

Congenital anatomical variations of both vertebral arteries are relatively frequent; left vertebral artery dominance presents in 50% of the population, while similar size vertebral arteries present with an only 25% prevalence. Due to this high prevalence, vertebral artery hypoplasia (VAH) has not yet been considered an independent risk factor for ischemic stroke [1, 2]. However, emerging evidence from case reports (table 1) and recent imaging (table 2) and cohort studies (table 3) suggest that VAH may contribute to ischemic events, even in young patients, especially when other risks factors are present [3].

In the present literature review, we present published data from case reports, imaging protocols and cohort studies to discuss thoroughly the relationship between VAH and posterior circulation cerebral ischemia. Our literature search through Medline and Embase was based on the combination of terms: vertebral artery hypoplasia, stroke, transient ischemic attacks, brainstem and cerebellar infarcts, and posterior circulation ischemia. References of retrieved articles were also screened. Only papers in English were included. The last search was done in PubMed on October 13, 2012.

Table 1. Case reports from patients with vertebral artery hypoplasia and posterior cerebral ischemia

Author	Age	Sex	VAH	Risk factors	Imaging findings
Giannopoulos et al. [3]	37	M	unilateral	hypertension, dyslipidemia	lateral medular infarction
Giannopoulos et al. [3]	38	M	unilateral	hypertension, Crohn's disease	lateral medular infarction
Giannopoulos et al. [3]	40	F	unilateral	hypertension	lateral medular infarction
Kawakami et al. [8]	8	M	unilateral	sport injury	cerebellar infarct
Mestan [7]	67	F	bilateral	–	cerebellar infarct
Orimo et al. [5]	36	M	bilateral	hypertension, hypercholesterolemia	pons, medulla oblongata and right cerebellar infarctions
Tai et al. [6]	60	M	bilateral	hypertension, hypercholesterolemia, history of TIA	bilateral medial medulla infarcts

Table 2. Imaging findings from ultrasound protocols in patients with vertebral artery hypoplasia

Author	Patients no	Patients status	Imaging method	VAH definition	VAH percentage	Main outcome
Chen et al. [12]	1,000	free of CVD	TCD	<2.5 mm	9.2% (5.9% R – 3.3% L)	patients with VAH had significantly lower MnfV and higher frequency of VA flow insufficiency
Jeng et al. [27]	447	free of CVD	TCD	<2.2 mm	11.6% (7.8% R – 3.8% L)	reduced MFV ipsilateral to the VAH and larger MFV contralateral to the VAH
Lovrencic-Huzjan et al. [10]	59	migraine	TCD	–	36%	higher frequency of VAH in migraine with aura patients
Min et al. [13]	410	free of CVD	TCD, MRA	<50% of the contralateral side	3.4% (2.14% R – 1.26% L)	increased MFV of unilateral VA may indicate contralateral VAH or VAP
Wang et al. [9]	82	children with PCI	TCD	–	7.3%	decreased VA diameter related with reduced blood flow and inadequate blood supply to the posterior circulation

VAH = Vertebral artery hypoplasia; CVD = cerebrovascular disease; TCD = transcranial Doppler; R = right vertebral artery; L = left vertebral artery; MnfV = mean net flow volume; VA = vertebral artery; MFV = mean flow volume; MRA = magnetic resonance angiography; VAP = vertebral artery aplasia; PCI = posterior circulation ischemia.

Case Reports' Hypothesis: Vertebral Artery Hypoplasia May Lead to Posterior Circulation Ischemia, when Combined with Conventional Risk Factors

Giannopoulos et al. [3] have reported three cases of young adults (average age 38 years) with lateral medullar ischemic events and associated these events with the presence of an ipsilateral hypoplastic vertebral artery on MRA. All 3 patients had two additional atherosclerotic or non-

atherosclerotic risk factors for stroke, suggesting that vertebral artery hypoplasia combined with other conventional risk factors may provide an optimal background for brainstem ischemia. None of these patients had recurrent transient ischemic attack (TIA) or stroke after the secondary stroke prevention treatment and none of them had on MRI scans other ischemic strokes in other vascular territories, except those in the lateral medulla. The authors concluded that both their uneventful outcome and medical history further support their initial hypothesis

Table 3. Cohort Studies from patients with vertebral artery disease and cerebral ischemia

Author	Stroke subtype	Number of patients	VA abnormality	Risk factors	Main outcome
Chuang et al. [19]	IS	191	VAH (<3 mm) 11.51%	53.4% one and 42.4% more than two risk factors	VAH was significantly more frequent in brainstem/cerebellar infarction
Delcker et al. [15]	TIA (VBS)	62	VAH (<2 mm), stenosis or occlusion	carotid artery atherosclerosis	patients with combined carotid and VA disease had increased TIAs
Hu et al. [20]	IS	841	VAH (<2 mm)	–	VAH was an independent risk factor for PCS
Lochner et al. [24]	IS or TIA	88	VAH (<2 mm or >50% difference in VA)	FTC (100%), atherosclerosis in VA, BA	the simultaneous occurrence of VAH and FTC may predispose to PCS
Park et al. [17]	PICAI or LMI	529	VAH (<2 mm) 35.2% (3.4% bilaterally)	–	both PICAI and LMI were dominant in patients with VAH
Perren et al. [18]	IS	725	VAH (<2.5 mm)	risk factors equally distributed	patients with VAH had significantly more frequent PCS
Toghi et al. [16]	CI	293	VAH, stenosis or occlusion	–	2/3 of the patients with SCA and AICA infarcts had unilateral VA occlusion or severe stenosis

VA = Vertebral artery; IS = ischemic stroke; VAH = vertebral artery hypoplasia; TIA = transient ischemic attack; VBS = vertebro-basilar system; FTC = fetal type circulation; BA = basilar artery; PCS = posterior circulation ischemia; PICAI = posterior inferior cerebellar artery infarction; LMI = lateral medulla infarction; CI = cerebellar infarction; SCA = superior cerebellar artery; AICA = anterior inferior cerebellar artery.

that their strokes can be attributed to the presence of a hypoplastic vertebral artery [4].

Locked-in syndrome due to brainstem infarction has been reported by Orimo et al. [5] in a 36-year-old male with hypertension and hypercholesterolemia. Brain MRI imaging showed pons, medulla oblongata and right cerebellum infarction, while cerebral angiography revealed bilateral VAH, a persistent right primitive trigeminal artery and retrograde blood flow of basilar artery from the primitive trigeminal artery.

Tai et al. [6] have recently presented a case of bilateral medial medullary infarction in a 60-year-old man with VAH, uncontrolled hypertension, hypercholesterolemia and a single episode of transient ischemic attack 15 years ago. MRA confirmed the presence of a hypoplastic left vertebral artery with atherosclerotic changes, occlusion after the posterior inferior cerebral artery and stenosis of the proximal basilar artery. Bilateral hypoplasia – an uncommon vertebral artery anomaly with an estimated frequency of 0.75% – has also been revealed in a 67-year-old female patient with cerebellar infarction by Mestan [7]. However, the angiogram in this particular case report

failed to display any evidence of vertebral atherosclerotic occlusive disease.

Finally, Kawakami et al. [8] considered VAH to be a predisposing factor for ipsilateral vertebral artery dissection and concomitant cerebellar infarction after sport injury in an 8-year-old boy.

Imaging Studies Illustrate that Neurological Symptoms in Subjects with Vertebral Artery Hypoplasia Are due to Reduced Blood Flow and Subsequent Cerebral Hypoperfusion

Decreased vertebral artery diameter has been associated with both reduced blood flow and inadequate blood supply to the posterior circulation in a sonographic evaluation of pediatric patients with a history of headache, vertigo or syncope [9]. The role of VAH in the pathogenesis of migraine has also been examined with color Doppler ultrasound in 59 patients with migraine. Migraine with aura patients had a higher frequency of VAH (29%) compared to migraine without aura patients (7%), sug-

gesting that VAH presumably contributes to the hypoperfusion in the posterior circulation during the aura phase [10]. Even further, Simon et al. [11] have also proposed VAH as the main etiologic vascular factor for the marked ipsilateral cerebellar hypoplasia that was observed in a 48-year-old patient.

In a retrospective analysis of color Doppler ultrasonography data, healthy subjects with VAH had significantly lower mean flow volume (MFV) in the hypoplastic vertebral artery and slightly increased MFV in the contralateral one, when compared to those without VAH. The mean net flow volume (MnFV) – the sum of the MFV of bilateral VA – was also significantly lower and the prevalence of vertebral artery flow volume insufficiency was, respectively, higher in subjects with unilateral VAH. Moreover, both the MFV and the MnFV were found to have a strong positive relation with the diameter of the vertebral artery [12]. Likewise, Min et al. [13] showed that the MFV was augmented in the contralateral (nonhypoplastic) side of the vertebral artery hypoplasia or aplasia, although the respective ipsilateral decrease in MFV in the hypoplastic artery did not reach statistical significance in their study.

Despite literature controversy, embolism and impaired vertebral blood flow volume are considered the major mechanisms of vertebrobasilar ischemia [14]. When blood flow on the one VA is temporarily reduced, the flow on the opposite VA is compensatory augmented to provide sufficient flow in the basilar artery. However, under certain prices in the diameter of the VAH the blood flow is reduced to a greater degree that results in unbalanced hemodynamics and in inadequate blood supply to the brain [9].

Cohort Studies Further Test and Support the Hypothesis

Patients with combined carotid and vertebral artery disease were found to have an increased incidence of TIAs in the vertebrobasilar system (71%), when compared with patients with isolated carotid artery disease (8%). This pronounced difference highlighted the dominant role of vertebral arteries in the pathogenesis of TIA in the posterior circulation [15]. Surprisingly, in another large multicenter study vertebral artery abnormalities were more strongly related with cerebellar ischemia when compared with the abnormalities of cerebellar arteries that distribute directly to the ischemic areas. More specifically, two thirds of the patients with superior cere-

bral artery or anterior inferior cerebral artery infarct had unilateral vertebral artery occlusion or severe stenosis [16].

A retrospective analysis of 529 patients with ischemic stroke by Park et al. [17] demonstrated that even though VAH is a common finding in the asymptomatic population, it is highly associated with posterior circulation strokes. Perren et al. [18] confirmed that among 725 first-ever stroke patients, those with posterior circulation strokes had significantly more frequent VAH (13%) compared to those with stroke in other territories (4.6%). Similarly, Chuang et al. [19] reported that the overall incidence of unilateral VAH, measured in a study group of 191 acute ischemic stroke patients, was 11.5% and this percentage was significantly higher in cases of brainstem or cerebellar infarction. More than half of the study group patients had a single vascular risk factor and 79.4% of them had an additional vascular risk factor. Finally, a very recent retrospective study by Hu et al. [20] found a similar prevalence of VAH (10.8%) in Chinese patients with acute ischemic stroke. The presence of VAH also appeared to be an independent risk factor for posterior cerebral ischemia, after multivariate logistic regression analysis.

Even in a pediatric population of children between 3 and 14 years old, hypoplasia of the vertebrobasilar system accounted for 3% of the total cerebrovascular hypoplasias, and VAH particularly was regarded as the main cause for transient ischemic attacks [21]. Additional reports suggested that children with congenital hypoplastic vertebral artery were more susceptible to arteriosclerosis either at a young age or later in adulthood [9, 14, 22].

Park et al. [23] demonstrated in another study protocol that most of the 37 acute stroke patients with vertebral artery diameter of less than 3 mm in the V2 segment had relatively small or scattered lesions in the VA territory (cerebellum and/medulla), when compared with stroke patients without small vertebrobasilar system. The most common angiographic finding in patients with small vertebral artery and/or small basilar artery was VA stenosis or occlusion and the most common vascular risk factors were hypertension (83.3%) and diabetes (22.2%). All these patients had fetal posterior circulation, with an absent or hypoplastic P1 segment of the posterior cerebral artery, supporting the hypothesis that their vertebral arteries must be congenitally small rather than acquired. In the FTP circle of Willis there is an embryonic derivation of the posterior cerebral arteries from the internal carotid artery instead from the basilar artery, or alternatively there is a communication with the basilar artery through

a hypoplastic P1 segment of the PCA. The presence of the aforementioned nonfunctional collateral pathway was strongly associated with both a hypoplastic vertebrobasilar system and posterior circulation ischemia in another case series of 13 patients [24].

Both studies by Park et al. [17, 23] and Chuang et al. [19] converge that the majority of patients with VAH related ischemic stroke is based on large-artery atherosclerosis. A hypoplastic vertebral artery, because of its decreased flow volume and flow velocities, could presumably be more susceptible to prothrombotic or atherosclerotic processes than normal vertebral arteries. Blood rheology at a low shear rate was found significantly impaired in symptomatic patients with VAH compared to those VAH patients who were asymptomatic, providing further evidence that an altered blood rheology in the vertebral artery could result in posterior cerebral ischemia [25].

Discussion and Conclusion

The prevalence of VAH is roughly estimated to range from 1.9 to 11.6%, since neither consensus on a standardized measuring system nor on the cut-off diameter (range 2.0–3.0 mm) for the definition of a VAH has been achieved to date. Thus, comparison of data from different research groups is difficult if not impossible [12, 26]. Results from two separate ultrasound protocols indicate that right-sided VAH is twice as more common than left-sided VAH [12, 27]. As for the degree of hypoplasia, severe unilateral hypoplasia was detected in 5.3% of the total study population and in 12.3% of the hypoplastic subgroup in MRI scans of patients with cervical pain [26]. VAH has also been related to basilar artery hypoplasia or stenosis, which further increases the risk of posterior circulation hypoperfusion [28].

Among imaging techniques, Doppler ultrasonography is a valuable, quick and noninvasive technique in the assessment of the vertebral arteries, even though the differential diagnosis between vertebral artery hypoplasia, aplasia, occlusion or dissection may be difficult [22]. Even conventional angiography or MRA may fail to distinguish reliably vertebral artery hypoplasia or aplasia from vascular occlusion, as they only demonstrate the intraluminal flow and cannot visualize the vascular walls [29]. Therefore, the difficulty for standard angiographic techniques to differentiate congenital variants from secondary thrombosis in the vertebral arteries leads primary to VAH underdiagnosis [30].

Caplan and Baker [31] were the first to notice that smaller of paired arteries are more likely to occlude compared with their larger counterparts, and raised the question if the congenital hypoplastic vessels are by nature more prone to occlusion. The aforementioned hypothesis was later stated in case reports from patients with posterior cerebral ischemia ipsilateral to a hypoplastic vertebral artery [3, 5–8] and further investigated in large cohort studies [15–19, 24].

Clearly the explanation cannot be size alone as many intracranial arteries are smaller than the hypoplastic or smaller arteries identified in these studies, and they are not predisposed to occlude. The answer must lie somehow in the physics of blood flow and sheer forces. There must be an interaction between blood pressure, blood constituents and the rheology and physics of blood flow at various arterial locations that explains the data [32]. A small-diameter artery appears to be more vulnerable to stenosis or occlusion, as its low flow velocity predisposes to prothrombotic or atherosclerotic processes in the presence of conventional vascular risk factors. Finally, a posterior circulation stroke may occur due to artery-to-artery embolism from the low-flowed stenotic VA [23]. Consistent literature data about the association of VAH with a specific pathogenetic mechanism do not exist. The hypothesis by Park and coworkers is in accordance with the clinical observation that proximal embolism (cardiac or arterial) is the leading cause of infarction in posterior circulation, especially in cases of superficial posterior cerebral artery infarction, with the source of embolism remaining undetermined in more than one third of the cases [33, 34]. However, we may note that in our series of patients with VAH and medullary ischemia, *in situ* atherothrombosis in the territory of perforators could be the most likely mechanism [3].

Therefore, the posterior circulation is presumably more vulnerable to ischemia in patients with VAH, particularly in those with severe hypoplasia. Most of these individuals remain asymptomatic, but the stroke risk increases further when additional atherosclerotic factors coexist.

Disclosure Statement

The authors report no potential conflict of interest.

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