PAPER

Hypoplastic vertebral artery: frequency and associations with ischaemic stroke territory

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See Editorial Commentary, p 916

J Neurol Neurosurg Psychiatry 2007;**78**:954–958. doi: 10.1136/jnnp.2006.105767

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Received 29 August 2006
Revised 19 October 2006
Accepted 22 October 2006
Published Online First 10 November 2006

Background: In patients with posterior inferior cerebellar artery infarction (PICAI) or lateral medullary infarction (LMI), the ipsilateral vertebral artery is often hypoplastic and therefore at an increased risk of ischaemic stroke.
Objective: To investigate the frequency and clinical relevance of hypoplastic vertebral artery (HVA) in patients with ischaemic stroke with or without vertebral artery territory and in normal healthy people.
Methods: 529 patients with ischaemic stroke, including vertebral artery territory infarction (LMI or PICAI), were classified according to their stroke location (303 anterior circulation strokes (ACS) and 226 posterior circulation strokes (PCS)) by MRI. The frequency of HVA, defined as a diameter of $\leqslant 2$ mm by magnetic resonance angiography, was measured in comparison with 306 normal healthy people.
Results: 185 patients (35.2%) from the cohort had HVA (3.4%, bilaterally). Patients with PCS showed a higher rate of HVA than those with ACS (45.6% vs 27.1%, $p<0.001$). The HVA frequency of those with ACS was similar to that of the normal group (26.5%). Of the 112 patients with vertebral artery territory stroke, 58 (51.8%) had HVA (bilateral HVA in 10), and all of 48 showed ipsilateral HVA territory stroke. In 102 patients with vertebral artery territory stroke, classification of the ipsilateral vertebral artery as hypoplastic (vs dominant or symmetric) tended to predict the involvement of multiple and extensive lesions, and a higher incidence of steno-occlusion ($p<0.001$).
Conclusion: HVA is not rare in the normal population, and is frequent in patients with PCS. People with HVA may have a high probability of PCS, with atherosclerotic susceptibility and ipsilateral lesions in the vertebral artery territory.

Congenital variations in the arrangement and size of the vertebral arteries are frequently recognised, ranging from asymmetry of both vertebral arteries to severe hypoplasia of one vertebral artery on cerebral angiography. In a pathoanatomical study, hypoplastic vertebral artery (HVA) was defined as a lumen diameter of $\leqslant 2$ mm,[1] but there is no consensus on this value.

The absence of vertebrobasilar insufficiency symptoms among people with HVA indicates that even marked vertebral artery asymmetry is a normal variation,[2–4] and has led to an underestimation of the incidence and clinical relevance of HVA. However, ipsilateral HVA is common in patients with posterior inferior cerebellar artery infarction (PICAI) or lateral medullary infarction (LMI), suggesting that HVA confers an increased probability of ischaemic stroke. Although the relationship between hypoplasia of the vertebral artery or the basilar artery and the risk of posterior circulation ischaemia has been examined,[5] there have been few reports on the relationship between HVA and territorial ischaemic stroke, to our knowledge.

The objectives of this study were to determine the frequency of HVA in normal healthy people and in patients with stroke, and the clinical relevance of HVA in patients with ischaemic stroke with vertebral artery territory.

PATIENTS AND METHODS

Participants

This study was approved by the appropriate institutional review board at Seoul National University Hospital, Seoul, Republic of Korea. Participants were selected from 901 consecutive patients with acute stroke who were admitted to our institute between July 2003 and June 2005. We excluded those who had had haemorrhagic stroke (n = 167) or those who did not undergo brain MRI owing to aneurysm clipping (n = 32), pacemaker insertion (n = 46) or unstable vital signs (n = 20). We selected 636 patients with ischaemic stroke who underwent brain MRI and three-dimensional time of flight (3D TOF) magnetic resonance angiography (MRA) at 2.9 (1.8) days after the onset of symptoms. The acute ischaemic lesion was assessed by high signal intensity on diffusion-weighted imaging with low signal intensity on apparent diffusion coefficient. If both vertebral arteries were not well visualised on 3D TOF MRA, their courses were entirely evaluated by contrast-enhanced MRA. The exclusion criteria included patients (1) with other determined aetiology, such as vasculitis (n = 3), dissection (n = 4), moyamoya disease (n = 8) or venous thrombosis (n = 4); (2) with transient ischaemic attack, which showed no ischaemic lesion on diffusion-weighted imaging and apparent diffusion coefficient (n = 25); (3) with incomplete angiographic investigation (n = 44); (4) who had cardioembolic disease with stenotic or occlusive vertebral artery, ipsilateral to the ischaemic lesion (n = 7); and (5) whose vertebral artery, ipsilateral to ischaemic lesion, was not visualised at all (n = 12). Finally, 529 patients (mean (SD) age 64.5 (11.8) years, 335 men) were selected for this analysis. Vertebral artery territory infarct is defined as either LMI or PICAI, or both, although those infarctions are not always due to the vertebral artery disease. Vertebral artery dissection was diagnosed by transfemoral cerebral angiography (string sign) or source view of MRA (double lumen).[6]

To compare the HVA frequency of patients with ischaemic stroke with that of the normal population, we evaluated brain

Abbreviations: ACS, anterior circulation stroke; or HVA, hypoplastic vertebral artery; LMI, lateral medullary infarction; MRA, magnetic resonance angiography; PCS, posterior circulation stroke; PICAI, posterior inferior cerebellar artery infarction; TOF, time of flight

MRI and 3D TOF MRA of 313 healthy people without stroke history who visited Seoul National University Hospital Healthcare System Gangnam Center, Seoul, Republic of Korea from March 2003 to May 2003. They underwent brain MRI as part of their routine health check. Informed consent was obtained for each participant. Participants who reported that they had experienced stroke or transient ischaemic attack were excluded. The term healthy was defined as the absence of symptoms or signs of neurological manifestations before and at the time of study enrolment, and all participants satisfied this criterion. Those people whose unilateral vertebral artery was not visualised at all ($n = 7$) were excluded. As a result, 306 healthy people (mean age 62.1 (10.3) years, 189 men) were recruited in this study as controls.

Definition of risk factors

We assessed demographic features and risk factors for stroke. Hypertension was defined as systolic blood pressure $\geqslant$140 mm Hg and/or diastolic blood pressure $\geqslant$90 mm Hg at least two times in a sitting position at 2 weeks (at least 10 days) after stroke onset, or patients receiving treatment for hypertension. Patients receiving treatment for diabetes, with a fasting plasma glucose concentration $\geqslant$126 mg/dl or a fed glucose concentration (2 h after a meal) of $\geqslant$200 mg/dl were considered to have diabetes mellitus.[7 8] Smokers included current smokers or those who had stopped for <1 year. Cardioembolic disease was defined as atrial fibrillation, mitral valve disease, congestive heart failure, patent foramen ovale, ventricular hypokinesia or akinesia or acute myocardial infarction. We performed electrocardiography and transthoracic echocardiography to rule out any cardioembolic source for all patients, and performed further studies such as transechocardiography or 24-h Holter monitoring if any abnormalities were found on initial investigation. The echocardiographic images were acquired with a Sonus 5500 imaging system (Agilent Technologies, Andover, Massachusetts, USA) equipped with a 3.5 MHz (for transthoracic echocardiography) or 6 MHz multiplane probe (for transoesophageal echocardiography).

Laboratory investigations

Blood glucose and lipid determination (total cholesterol, triglyceride, and high-density lipoprotein cholesterol levels) were performed after fasting overnight. Low-density lipoprotein-cholesterol (LDL-C) was calculated by Friedewald's equation.[9] Other laboratory investigations included complete blood count, fibrinogen and haemoglobin Alc (Hb A1c).

Magnetic resonance analysis

MRI was performed in the horizontal plane using a 1.5 Tesla full system (Sonata, Siemens, Germany) with a T2-weighted image of TR/TE 5000/99 ms, a diffusion-weighted image of TR/TE 6500/110 ms, and fluid-attenuated inversion recovery image of TR/TE 9000/119 ms. All MRA included intracranial and neck vessels and was performed using a 3D TOF technique (TR 35 ms, TE 7.2 ms) with or without 3D contrast-enhanced MRA, which was performed by means of an intravenous bolus injection of magnevist 10 ml with a TR of 35 ms and TE of 7.2 ms. A three-dimensional spoiled gradient-echo acquisition was applied with the following parameters: excitation angle 25°; field of view 240×6/8; acquisition matrix 288×512.

Patients were classified according to the location of stroke as either anterior circulation stroke (ACS) or posterior circulation stroke (PCS). We assessed HVA in all patients and normal healthy people. We also measured the frequency of symptomatic HVA (ipsilateral to the territorial lesion), demographic features and vascular risk factors in patients with vertebral artery territory stroke (LMI or PICAI). Vertebral artery symmetry means that both vertebral arteries have a diameter >2 mm. Although there is no clear definition of HVA, it was defined as a vertebral artery with a diameter of $\leqslant$2 mm, and the larger (contralateral) one was defined as a dominant vertebral artery in this study. We chose to examine the mid-portion level of V_2 (the portion in the vertebral columns) of the vertebral artery using magnified images of MRA on a picture archiving communication system because other levels, including V_3 (after exit from the C2 transverse foramen),[10] V_4 (the intracranial portion beginning at the atlanto-occipital membrane and terminating at the formation of the basilar artery)[10] and V_1 (proximal to entry into the transverse foramen), are more susceptible to atherosclerotic steno-occlusion or have more artefacts than V_2. We initially evaluated TOF, but when steno-occlusion or hypoplasia was obscure, we further used contrast-enhanced MRA with same magnetic resonance sequence as that of TOF in <5% of stroke cases.

To assess reliability, the MRA of each patient was independently reviewed by two investigators (J-HP and J-MK), both of whom were blinded to all clinical information. The consensus for the presence of HVA was standardised according to neuroradiological interpretation reports and was acceptable ($\kappa = 0.88$, $p<0.01$).

In 102 patients with vertebral artery territory stroke, as most were elderly and showed combined atherosclerotic stenosis or occlusion in the vertebral artery, the stenosis degree of the distal vertebral artery (V_4) responsible for vertebral artery territory stroke (LMI or PICAI) was defined as ''occlusion'', ''stenosis'' (>50% reduction of arterial column width) and ''normal''. Distribution of acute ischaemic lesions of vertebral artery territory was examined and analysed by the group of vertebral arteries.

Statistical analysis

Categorical variables were performed by χ^2 tests. The one-way analysis of variance test was used for analysis of continuous variables. After post hoc testing (Tukey–B method), they were re-evaluated to determine which variables were significant. For multiple comparisons between patients with ischaemic stroke (ACS, PCS) and normal healthy people, the Bonferroni method was used. All statistical analyses were conducted using the SPSS package for Windows, V.11.5. Two-sided p values of 0.05 (0.017 (0.05/3) in Bonferroni method) were considered significant.

RESULTS

Analysis of HVA frequency

Table 1 illustrates HVA frequency between the study group and normal healthy people. HVA was detected in 186 (35.2%) patients (102 (19.3%) on the right side, 66 (12.5%) on the left and 18 (3.4%) bilaterally) among the 529 patients with ischaemic stroke. When classified by stroke location (303 ACS and 226 PCS), patients with PCS showed more significant frequency of HVA than those with ACS and normal healthy people (all $p<0.001$, table 1). The frequency of HVA in the 306 normal healthy people (26.5%; 1.6% bilateral) was similar to that in patients with ACS. In the Bonferroni method, the PCS group showed higher frequency of HVA than the ACS group and normal healthy people (all $p<0.017$).

Frequency of HVA and baseline characteristics in patients with vertebral artery territory stroke

Out of 226 patients with PCS, there were 112 patients (mean (SD) age 61.7 (12.8) years, 75 men) with vertebral artery territory stroke. HVA was present in 58 patients (51.8%, bilateral HVA in 10) and all 48 patients had ipsilateral vertebral artery territory stroke (100%).

Table 1 Comparison of hypoplastic vertebral artery frequency between study group and normal healthy people

	HVA (+)	HVA (–)	p Value*
ACS group (n = 303)	82 (27.1)	221 (72.9)	<0.001
PCS group (n = 226)†	103 (45.6)	123 (54.4)	
ACS group (n = 303)	82 (27.1)	221 (72.9)	0.869
Normal healthy people (n = 306)	81 (26.5)	225 (73.5)	
PCS group (n = 226)†	103 (45.6)	123 (54.4)	<0.001
Normal healthy people (n = 306)	81 (26.5)	225 (73.5)	

ACS, anterior circulation stroke; HVA, hypoplastic vertebral artery; PCS, posterior circulation stroke; +, HVA present; −, HVA absent.
Values are number (%) of patients.
*By χ^2 test.
†By Bonferroni method (significant value is <0.017).

Table 2 shows the results of demographic features, risk factors and laboratory findings in the vertebral artery feature groups (hypoplastic, dominant and symmetric). The mean vertebral artery diameter of the hypoplastic group was significantly smaller than that of the dominant and symmetric vertebral arteries ($p<0.001$). After post hoc tests, these values showed significant differences between the three groups ($p<0.001$). Cardioembolic stroke was more prevalent in the symmetric group ($p = 0.016$). In others, there were no significant differences.

Ischaemic lesion distributions in patients with vertebral artery territory stroke

Acute ischaemic lesions of the vertebral artery territory stroke were present in the PICA territory in 51 patients (50%), lateral medulla in 36 patients (35.3%), PICA territory and lateral medulla in 10 patients (9.8%), and PICA territory and basilar artery territory or more in 5 patients (4.9%). Of these, the number of patients with cardioembolic stroke was 19 in PICA territory, 4 in lateral medulla and 4 in PICA territory and lateral medulla. No cardioembolic stroke was noted in PICA territory and basilar artery territory or more. Table 3 illustrates ischaemic lesion distributions in the vertebral artery feature groups. LMI and PICAI were dominant in the hypoplastic vertebral artery group. Multiple infarctions, such as LMI and PICAI, and PICAI and basilar artery territory infarction or more were also more prominent in the hypoplastic vertebral artery group than in the symmetric group. In the dominant vertebral artery group, the largest in vertebral artery diameter, the lesions were present dominantly in the cerebellum (PICA territory), and then in the lateral medulla.

Stenosis degree of responsible vertebral artery (V_4)

As the severity of stroke correlated with the presence of ipsilateral HVA, we analysed the presence or degree of stenosis in the intracranial symptomatic vertebral artery (table 4). Stenosis or occlusion of the distal (intracranial) vertebral artery was significantly more prevalent in the hypoplastic group ($p<0.001$).

DISCUSSION

We have described the frequency of HVA and association of HVA with vertebral artery territory ischaemic stroke by retrospective analysis.

HVA has been defined as vertebral artery flow volume <30–40 ml/min using colour duplex sonography, or vertebral artery

Table 2 Characteristics by vertebral artery group in 102 patients with vertebral artery territory stroke

	Hypoplastic (n = 48)	Dominant (n = 26)	Symmetric (n = 28)	p Value
Age, years	61.7 (11.7)	65.2 (12.9)	58.2 (13.5)	0.112
Men, n (%)	30 (62.5)	20 (76.9)	17 (60.7)	0.372
Hypertension, n (%)	35 (72.9)	15 (57.7)	21 (75)	0.304
Diabetes, n (%)	19 (39.6)	8 (30.8)	6 (21.4)	0.259
Cardioembolic stroke, n (%)	8 (16.7)	6 (23.1)	13 (46.4)	0.016*
Smoking, n (%)	9 (18.8)	8 (30.8)	6 (21.4)	0.491
Haematocrit, %	41.2 (4.9)	42.6 (4.6)	39.8 (7.1)	0.188
Fasting glucose, mg/dl	129.2 (65.5)	117.4 (62)	128.9 (35.5)	0.672
HbA1c, %§	6.9 (1.7)	6.2 (1)	6.4 (2.1)	0.226
T-Ch (mg/dl)	184.5 (40)	175.8 (34.4)	189.8 (44.4)	0.455
LDL-C (mg/dl)	116.4 (38.2)	107.5 (27.7)	114.3 (38.2)	0.623
TG, mg/dl§	160.5 (139.5)	119.2 (60.3)	140.0 (132.6)	0.412
HDL-C, mg/dl	41.9(11.9)	43.9 (12.9)	46.7 (15.9)	0.353
Fibrinogen, mg/dl	405.2 (102.7)	390.1 (60.8)	380.1 (82.0)	0.498
Vertrebral artery (V_2) diameter, mm	1.3 (0.3)	3.5 (0.5)	2.6 (0.3)	<0.001†‡

HbAlc, haemoglobin Alc; HDL-C, high-density lipoprotein-cholesterol; T-Ch, total cholesterol; LDL-C, low-density lipoprotein-cholesterol.
Values are mean (SD) unless otherwise specified.
Ten patients with bilateral hypoplastic vertebral artery were excluded.
*χ^2 test.
† One-way analysis of variance test.
‡After post-hoc test, these values showed significant difference between the three groups.
§Statistical tests were performed using logarithmically transformed variables.

Table 3 Lesion distribution by vertebral artery group in 102 patients with vertebral artery territory infarction

	Hypoplastic	Dominant	Symmetric
LMI (n = 36)	18 (50)	9 (25)	9 (25)
PICAI (n = 51)	21 (41.2)	17 (33.3)	13 (25.5)
LMI + PICAI (n = 10)	6 (60)	0 (0)	4 (40)
PICAI + ⩾BA territory (n = 5)	3 (60)	0 (0)	2 (40)

BA, basilar artery; LMI, lateral medullary infarction; PICAI, posterior inferior cerebellar artery infarction.
Values are number (%) of patients.
Ten patients with bilateral hypoplastic vertebral artery were excluded.
Most ischaemic strokes in vertebral artery territory originated from hypoplastic vertebral artery.

diameter either <3 or <2 mm.[11–14] This lack of consensus on the definition of HVA results from the fact that studies were often not conducted on healthy subjects, the sample size was small or there were no other well-assessed sonographic findings to support HVA.[15] Recently, a cut-off point of <2.2 mm was determined for HVA, based on significant haemodynamic changes, which is further supported by an increase in ipsilateral flow resistance (resistance index ⩾0.75), contralateral diameter (side-to-side diameter difference ⩾0.12 cm) and flow volume (side-to-side flow volume ratio ⩾5) by colour-coded duplex ultrasonography.[15]

The reported frequency of unilateral HVA is dependent on the definition used for HVA. One study using an HVA definition of ⩽2 mm by ultrasonography found that the HVA frequency was 1.9% in 451 subjects.[16] A second study found an HVA (defined as lumen diameter <3 mm) frequency of 6% in 50 healthy subjects.[12] Another study documented that HVA was present in 2.34% of patients.[17] Recently, the frequency of HVA (defined as vertebral artery diameter <2.2 mm) was shown to be 11.6% (7.8% on the right and 3.8% on the left) in 447 subjects.[15] In our study, the frequencies of HVA were as high as 35.2% in 529 patients with ischaemic stroke. The reason for the higher percentage of HVA in our study compared with that in previous reports[12 15–17] may result from measurement differences (3D TOF or contrast MRA vs duplex ultrasonography). Therefore, it would be difficult to compare the frequency of our results directly with previous study results.[12 15–17] The left vertebral artery diameter is often larger than the right, as measured in duplex sonographic studies[14 18–21]—that is, HVA is predominant on the right side,[15 22] which is consistent with our finding.

In our study, the facts that (1) the PCS group showed a higher frequency of HVA than the ACS group, which is in line with a study[22] in which HVA showed topographic preponderance of brain stem/cerebellar infarction and (2) all the patients with unilateral HVA among those with vertebral artery territory stroke showed ipsilateral ischaemic lesions, provide evidence that HVA may be aetiopathogenetically implicated in PCS. As expected, the HVA frequency in patients with ACS (27.1%) reflected that in the normal population; the HVA frequency in normal healthy people was 26.5% in this study, similar to the ACS group. In comparing patients with PCS with those with ACS, there was no significant difference between the groups with regard to age, gender and other risk factors (hypertension, diabetes, heart disease and smoking; data not shown).

Table 4 Stenotic degree of the distal vertebral artery in 102 patients with vertebral artery territory stroke

	Hypoplastic (n = 48)	Dominant (n = 26)	Symmetric (n = 28)	p Value
Normal	7 (14.6)	23 (88.5)	26 (92.9)	<0.001*
Stenosis/ occlusion	41 (85.4)	3 (11.5)	2 (7.1)	

Values are number (%) of patients.
Ten patients with bilateral hypoplastic vertebral artery were excluded.
*By χ^2 test.

In vertebral artery territory stroke, cardiac embolism and artery-to-artery embolism are the two most common stroke mechanisms.[23]

In this series, cardioembolic stroke was least prevalent in the hypoplastic group. It is thought that luminal narrowing of the HVA might make it less feasible for cardiogenic emboli to pass through it.

We observed that 46/102 (45.1%) patients with vertebral artery territory stroke had vertebral artery stenosis/occlusion, and most (89.1%) of them showed HVA. The HVA, which shows lower mean flow volume[3 14 22] and decreased flow velocities,[14] seems to be more susceptible to pro-thrombotic or atherosclerotic processes than normal or dominant vertebral arteries. Therefore, our findings could be supported by findings[5 22] that HVA-related ischaemic stroke is based on large-artery atherosclerosis. Some proportion of PCS might result from an atherosclerotic HVA because vertebral arterial thrombi can cause in situ strokes and are prone to cause distal embolisation.[23]

It should be noted that our study cohort may not be representative of the worldwide general population in the frequency of HVA because our data were limited to a single centre. Also, normal healthy people were enrolled from a population concerned about their health status. Furthermore, as the racial distribution of the population was Korean, it may also limit generalisations based on our study results. Secondly, we recruited patients with ischaemic stroke, who might have other risk factors that could precipitate atherosclerotic narrowing. However, in an attempt to overcome this limitation, we included data from normal visitors to a healthcare centre.

Considering that MRI is gaining more popularity in clinical practice, this study will inform patients with potentially vulnerable vertebral circulation systems.

In conclusion, HVA frequency is not rare in the normal population, as was previously reported. The strength of this study is that we demonstrated a high association of vertebral artery territory ischaemic stroke with ipsilateral HVA. A further detailed prospective study with larger cohorts would be useful for determining further pathophysiological and causal relationships between HVA and ipsilateral vertebral artery territory stroke.

ACKNOWLEDGEMENTS

We thank the Medical Research Collaborating Center of Seoul National University Hospital for statistical comments on the manuscript and the Healthcare System Gangnam Center of Seoul National University Hospital for allowing us to investigate the clinical data.

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Competing interests: None.

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