CLINICAL RESEARCH

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Received: 2015.08 Accepted: 2015.11 Published: 2016.05	.20 .24 .21	Morphological Characte Vertebrobasilar Arterial with Vertebrobasilar Do	ristics of the System Are Associated lichoectasia			
Authors' Contribution Study Design A Data Collection E Statistical Analysis (Data Interpretation E Manuscript Preparation E Literature Search I Funds Collection C	ABE 1 ABE 2 CDF 1 ABG 1	Xi Wu* Yanjun Li* Qinghai Huang Jianmin Liu	1 Department of Neurosurgery, Changhai Hospital, Shanghai, P.R. China 2 Department of Medical Imaging, Nanjing General Hospital of Nanjing Militar Command, Nanjing, Jiangsu, P.R. China			
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Background: Material/Methods:		Vertebrobasilar dolichoectasia (VBD) is characterized by abnormal dilation, distortion, and extension of the ver- tebral artery (VA) and basilar artery (BA). This study investigated whether BA and VA morphological character- istics were factors predicting VBD. Individuals aged ≥18 years undergoing contrast-enhanced magnetic resonance angiography (CE-MRA) of the head/neck were enrolled in 2012 at Changhai Hospital, Shanghai. Data concerning cardiovascular risk factors were recorded. Bilateral VA diameter and lateral displacement. BA diameter and lateral displacement. VA con-				
Results:		fluence displacement, and dominant VA (DVA) presence/absence were determined from CE-MRA. VBD was di- agnosed using established criteria. DVA and no-DVA groups were compared. Logistic regression analysis was used to identify variables independently associated with VBD. Our study included 1153 individuals, of which 614 (53.3%) had DVA. The DVA group had higher mean age, hypertension prevalence (44.6% vs. 37.5%), and VBD prevalence (8.1% vs. 4.5%), and lower smoking preva- lence (24.3% vs. 30.6%), than no-DVA patients. Univariate analysis revealed that age, female sex, hyperten- sion, hyperlipidemia, smoking, alcohol consumption, and DVA presence were associated with VBD occurrence. Multivariate analysis showed that age and presence of a DVA were independently associated with VBD.				
Conclusions:		Age and presence of DVA are independently associated with VBD.				
MeSH Keywords:		Basilar Artery • Risk Factors • Vertebral Artery • Vertebrobasilar Insufficiency				
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MEDICAL SCIENCE MONITOR

Background

Vertebrobasilar dolichoectasia (VBD) is an arteriopathy characterized by abnormal dilation, distortion, and extension of the vertebral artery (VA) and basilar artery (BA) [1,2]. VBD is associated with various neurologic deficits, including cranial nerve syndromes, brainstem compression, hydrocephalus, ischemic stroke, subarachnoid hemorrhage, and central sleep apnea [2–4]. Although numerous investigations have examined the neuroradiologic and pathologic features of VBD [4,5], little is known about the mechanisms that underlie its pathogenesis or its treatment [6].

Previous studies have shown that hypertension, atherosclerosis, older age, male sex, obesity, smoking, dyslipidemia, and diabetes mellitus are more common in individuals with VBD [1,2,7]. However, about 20% of patients with VBD have no recognized risk factors for cardiovascular diseases [2,4], suggesting that additional factors may also contribute to the pathogenesis of VBD.

VBD is the most common type of intracranial arterial dolichoectasia [4], suggesting that the vertebrobasilar arterial (VBA) system may have unique characteristics that predispose to dolichoectasia [4]. The human BA is the only major blood vessel formed by the confluence of 2 arteries [4], and the bilateral VAs can differ significantly in diameter (termed VA asymmetry) [4]. Doppler ultrasound studies have found that morphologically asymmetric VAs may cause asymmetric blood flow within these arteries [2,4,8], but it is still unknown if these differences are congenital or acquired. Since hemodynamic factors are thought to be involved in the occurrence of many cerebrovascular diseases, it is possible that deviations in blood flow during the course of VBA atherosclerosis could promote the occurrence of VBD.

The aim of this study was to investigate whether variations in the vascular structure of the VBA system, in addition to known risk factors such as smoking and alcohol consumption, are associated with VBD. Specifically, the study was designed to determine if a dominant VA (DVA) is associated with VBD by making the VA vessels broader and more laterally shifted. Because it is challenging to perform radiological follow-up of a fixed cohort, for several decades VBA system morphological parameters were measured in populations, and the relationships were determined between these parameters and the presence or absence of a DVA (as an approach to determining the role of a DVA in morphological changes of the VBA system). We used regression analysis to determine if DVA is independently associated with VBD.

Material and Methods

Patients

This study was approved by the Ethics Committee of the Changhai Hospital (Shanghai, China). All participants provided written informed consent. This was a retrospective study of adult individuals who underwent contrast-enhanced magnetic resonance angiography (CE-MRA) of the head and neck in our hospital between June 1st 2012 and November 30th 2012. The inclusion criteria were: 1) age \geq 18 years and 2) CE-MRA of the neck and head.

The study participants included patients undergoing investigations for suspected cerebral ischemia and symptoms such as headache, as well as individuals undergoing routine health examinations that included CE-MRA for any reason. Individuals were excluded from the study if they had any diseases that might seriously affect the blood flow or morphology of the VBA system, including the presence of moderate-to-severe stenosis from the proximal part of the VA (neck side) to the bilateral VA confluence; VA aneurysm; Moyamoya disease; VBA dissection; VBA fenestration malformation; VBA arterio-venous shunt; abnormal VA origin (from the intracervical artery or aortic arch); and posterior fossa tumors as shown by MRA. Patients with stroke were not excluded, because cardiovascular and cerebrovascular diseases have been reported to be associated with VBD.

The following cardiovascular variables were collected from all recruited participants: histories of hypertension, diabetes mellitus, serum cholesterol, smoking, and alcohol consumption. The criteria used for determining these risk factors have been described previously [1].

CE-MRA technique

CE-MRA was performed using the 1.5T MR system (Avanto, Siemens, Munich, Germany) and the 3D FLASH sequence. The MRA parameters are listed in Table 1. Gd-DTPA (0.1 mmol/kg body weight) was used as a contrast enhancement agent and was administered intravenously via the antecubital vein at a rate of 3 mL/s (Medrad Spectris Solaris MR Injection System, Bayer, Leverkusen, Germany), followed by an intravenous bolus injection of 20 mL of 0.9% normal saline at 3 mL/s [9].

Image analysis

All CE-MRA images were 3-dimensionally rebuilt on the workstation using the maximum intensity projection technique and the volume scanning method (NUMARIS/4 syngo MR B17, Siemens). All VBA system morphological parameters were measured independently and in a blinded fashion by 2 radiologists,

Imaging parameter	Head MRA	Neck MRA
Repetition time (ms)	2.94	3.21
Echo time (ms)	1.06	1.08
Flip angle (degrees)	25	30
Bandwidth (Hz/pixel)	500	380
Field of view (mm)	228×157	340×223
Matrix size	256×141	384×164
Slice thickness (mm)	1.1	1
Voxel size (mm)	1.1×0.9×1.1	1.4×0.9×1.0
Slices per slab	80	88
Parallel acquisition (iPAT)	2	2
Acquisition time (s)	10	14

Table 1. Imaging parameters used for contrast-enhanced magnetic resonance angiography.

iPAT – integrated parallel acquisition technique; MRA – magnetic resonance angiography.

each with more than 8 years of experience. The data were entered into an Excel spreadsheet (Microsoft Corp, Washington D.C.) for comparison. Differences ≥ 0.2 mm between the 2 interpreters were resolved by repeat measurements until the difference was <0.2 mm.

The following parameters were measured (Figure 1) [1,10]: the diameter of the bilateral VA (measured 3 mm from the VA confluence); lateral displacement of the bilateral VA (a straight line was drawn from the cranial access point of the VA to the confluence site, and the maximum distance from the VA to the line was measured); the maximal diameter of the BA (along its entire course); lateral displacement of the BA (a straight line was drawn between the distal end of the BA and the bilateral VA confluence, and the maximum distance from the BA to the line was measured); and lateral displacement of the bilateral VA confluence (the maximum distance between the VA confluence and the median sagittal plane crossing the midpoint of the horizontal line between the 2 VA transverse foramens). In addition, the presence or absence of a DVA was established



Figure 1. Image analysis and measurements of basilar artery and vertebral artery parameters. (A) Representative contrast-enhanced magnetic resonance angiography (CE-MRA) images showing measurements of the basilar artery (BA) and vertebral artery (VA). The right VA had a diameter that was more than 0.3 mm larger than the left VA, and joined the BA at a greater angle; therefore, the right VA was considered dominant. (B) Measurement of the maximum lateral displacement of the VA. (C) Measurement of the maximum lateral displacement of the BA. (D) Measurement of the lateral displacement of the VA confluence. The white line indicates the sagittal plane. (E) Conversion of the curved BA into a straight line, to allow measurements. (F) Measurement of the BA length as the distance between the distal end of the BA and the VA confluence along the reconstructed BA midline. (G) Conversion of the curved VA into a straight line, to allow measurement of its length. The white line marks the center of the VA was exposed; this was converted into a straight line using surface measurements. (H) Measurement of the VA length as the distance between the VA confluence to the VA cranial access point along the reconstructed VA midline.

	Female (N=518)		Male (N=635)			
	DVA (251)	No-DVA (267)	Р	DVA (363)	No-DVA (272)	Р
Age, years (range)	57.40±13.29	53.86±15.02	0.005	56.97±13.33	54.18±14.30	0.012
BMI, mean ±SD (kg/m²)	21.56±3.08	21.19±2.75	<0.160	22.93 ± 2.44	22.93 ± 2.94	0.976
Hypertension, n (%)	125 (49.8%)	101 (37.8%)	0.008	149 (41.0%)	101 (37.1%)	0.326
Hyperlipidemia, n (%)	25 (10.0%)	432 (12.0%)	0.485	47 (12.9%)	22 (8.1%)	0.054
Diabetes, n (%)	32 (12.7%)	33 (12.4%)	0.895	43 (11.8%)	40 (14.7%)	0.341
Smoking, n (%)	6 (2.4%)	9 (3.3%)	0.605	143 (39.4%)	156 (57.4%)	<0.001
Alcohol consumption, n (%)	8 (3.2%)	10 (3.7%)	0.813	103 (28.4%)	90 (33.1%)	0.222
BA diameter (mm)	3.86±0.48	3.86±0.40	0.960	3.99±0.50	0.394±0.44	0.193
BA displacement (mm)	4.56±2.35	4.11±2.32	0.030	4.43±2.50	4.19±2.45	0.215
VA confluence displacement (mm)	4.11±3.71	4.21±3.85	0.772	4.41±3.59	4.48±3.67	0.806
VBD, n (%)	15 (6.0%)	8 (3.0%)	0.134	35 (9.6%)	16 (5.9%)	0.104

 Table 2. Clinical and demographic characteristics of the study participants.

BA – basilar artery; DVA – dominant vertebral artery; SD – standard deviation; VA – vertebral artery; VBD – vertebrobasilar dolichoectasia. Data for BA and VA morphological characteristics are presented as value (range).

using the following criteria to define DVA: a difference in the bilateral VA diameters of \geq 0.50 mm, with the larger VA joining the BA at a greater angle [1,11].

The diagnosis of VBD from CE-MRA images required consensus between 2 neuroradiologists working independently.

A diagnosis of VBD [12] was made if the diameter of any segment of the BA was \geq 4.5 mm, and 2 or more of the following criteria were also fulfilled: BA length >29.5 mm; a displacement of the BA from its starting point to the initial bifurcation of the posterior cerebral artery of >10.0 mm; length of the V4 segment of the VA >23.5 mm; and any VA segment displaced >10.0 mm from the line joining the VA cranial access point to the VA confluence point.

Statistical analysis

Statistical analysis was performed using SPSS 19.0 (IBM, Armonk, NY). Data are presented as values with percentages, means \pm standard deviations, or medians with ranges, as appropriate. Comparisons between groups were made using the Mann-Whitney U test. Univariate and multivariate logistic regression analyses with calculation of odds ratios (ORs) and 95% confidence intervals (95% CIs) were performed to identify variables independently associated with VBD. *P*<0.05 was considered statistically significant.

Results

Clinical and demographic characteristics of the study participants

A total of 1153 individuals were included in the study – 614 with DVA and 539 without DVA. The clinical and demographic characteristics of the study participants are presented in Table 2. In both the DVA and no-DVA groups, mean BMI was significantly lower in females than in males, and significantly fewer females (as compared with males) were smokers or consumed alcohol (P<0.05). In both groups, there were no significant differences between males and females with regard to age, hyperlipidemia, or diabetes. In the DVA group, the prevalence of hypertension was significantly higher in females (P<0.05), but no difference between sexes was observed in the no-DVA group.

Comparisons between the DVA and no-DVA groups revealed that the DVA group had a higher mean age, higher prevalence of hypertension (44.6% vs. 37.5%), and lower prevalence of smoking (24.3% vs. 30.6%) (all P<0.05). When dividing the patients according to sex and then by DVA, older age was associated with DVA both in men and in women (P=0.005 and P=0.01, respectively). Men with DVA had a higher frequency of hypertension (P=0.008) and a greater BA displacement (P=0.03). Women without DVA had a higher frequency of smoking (P<0.001) (Table 2). There were no significant differences between the DVA and no-DVA groups with regard to BMI, the

Table 3. Vertebral artery characteristics in study participants with a dominant vertebral artery (DVA group).

		DVA (<i>N</i> =614)		
	Female (<i>N</i> =251)	Male (N=363)	Р	
Dominant VA diameter (cm)	0.34 (0.20, 0.52)	0.35 (0.23, 0.54)	<0.001	
Non-dominant VA diameter (cm)	0.23 (0, 0.40)	0.24 (0, 0.43)	0.112	
Dominant VA displacement (cm)	0.610 (0, 1.415)	0.600 (0, 1.840)	0.804	
Non-dominant VA displacement (cm)	0.500 (0, 1.725)	0.450 (0, 1.605)	0.178	
Ratio of bilateral VA diameters	0.700 (0, 0.870)	0.706 (0, 0.863)	0.702	

DVA - dominant vertebral artery; VA - vertebral artery. Data are presented as value (range).

Table 4. Univariate and multivariate logistic regression analyses of the variables associated with vertebrobasilar dolichoectasia.

Verichler	Univariate an	alysis	Multivariate analysis		
variables	Odds ratio (95% CI)	P	Odds ratio (95% CI)	Р	
Age	1.029 (1.011, 1.048)	0.002	1.028 (1.008, 1.048)	0.007	
Male gender	1.879 (1.132, 3.119)	0.015	1.231 (0.655, 2.314)	0.518	
Hypertension	2.069 (1.284, 3.336)	0.003	1.499 (0.899, 2.499)	0.121	
Hyperlipidemia	2.015 (1.091, 3.722)	0.025	1.574 (0.821, 3.018)	0.172	
BMI	1.050 (0.968, 1.138)	0.239			
Diabetes	1.490 (0.797, 2.785)	0.211			
Smoking	1.909 (1.177, 3.095)	0.009	1.774 (0.976, 3.222)	0.060	
Alcohol consumption	1.854 (1.092, 3.147)	0.022	1.599 (0.883, 2.894)	0.121	
Dominant vertebral artery	1.902 (1.152, 3.140)	0.012	1.809 (1.082, 3.02)	0.024	

CI – confidence interval.

prevalence of hyperlipidemia or diabetes mellitus, or alcohol consumption (Table 2).

BA and VA morphological characteristics and prevalence of VBD

Data for the morphological characteristics of the BA and VA, determined from analysis of CE-MRA images, are shown in Tables 2, 3. BA diameter and DVA diameter were significantly larger in males in the DVA group, while BA displacement was significantly larger in males in the no-DVA group (P<0.05). Within each group, there were no significant differences in the other parameters measured.

The prevalence of VBD did not differ significantly between males and females in either the DVA or no-DVA group, despite numerically higher values in males in both groups (Table 2). The prevalence of VBD was 6.4% overall, and was significantly higher in the DVA group than in the no-DVA group (8.1% vs. 4.5%; P<0.05).

Logistic regression analysis of factors associated with VBD

Univariate logistic regression analysis revealed that older age, male sex, hypertension, hyperlipidemia, smoking, alcohol consumption, and the presence of a DVA were all associated with the occurrence of VBD (Table 4). Multivariate logistic regression showed that only older age and the presence of a DVA were independently associated with VBD (Table 4).

Discussion

The main findings of the present study were that individuals with a DVA tended to be older and have a higher prevalence of hypertension, lower prevalence of smoking, and higher prevalence of VBD than individuals without a DVA. Furthermore, older age and the presence of a DVA were both independently associated with the occurrence of VBD. These novel findings indicate that certain morphological changes of the VBA system, including the presence of a DVA, may be associated with VBD occurrence. The overall prevalence of VBD in the present study was 6.4%, consistent with values reported in previous investigations ranging from 3.7% (in patients with posterior circulation ischemic stroke) to 18.8% (in patients with isolated pontine infarct) [5]. The prevalence of VBD in asymptomatic Japanese individuals was recently determined to be 1.3% [5], illustrating the fact that VBD is often associated with neurologic pathology and symptoms.

A previous study found that for each 1-mm increase of the diameter of the basilar artery, stroke mortality hazard ratio increased 1.23 times; if the diameter was greater than 4.3 mm, the hazard ratio was 3.69; and if the height of the basilar artery bifurcation score was greater than 1 point, the hazard ratio was 2.08 [13]. Previous studies have reported a significant difference in BA diameter between normal male and female populations [4,14]. The present study found that in the population with a DVA, both BA diameter and DVA diameter were larger in males than in females. Therefore, it would seem necessary to re-define the diagnostic criteria for VBD in men and women, taking into account sex differences. However, few studies have focused on determining appropriate sex-specific diagnostic criteria for VBD. Some investigations have used cranial volume as a reference to adjust vascular parameters such as arterial diameter, and this seems to be a potentially promising correction method [1].

VA asymmetry is a very common clinical phenomenon [7,14,15] and can result in differences in blood volume and flow rate between the Vas [15]. Asymmetric blood flow may cause deviation of blood flow [16], producing high local shear stress on lateral regions of the BA wall on the side contralateral to the DVA, and low shear stress on the medial curvature of the vessel ipsilateral to the DVA. The VA confluence angle is also an important factor affecting the hemodynamic characteristics of the BA [14,15], including the direction of the confluenced blood flow. However, it remains unknown whether a DVA simply accompanies VBD or acts to promote the occurrence of VBD, and there is little information on eventual treatments for symptoms of abnormal DVA [17,18].

It has been reported that the BA in individuals with a DVA tended to bend toward the contralateral side and become thicker [4], although it was not established whether this phenomenon was congenital or the result of the DVA. The DVA itself may be at least partly congenital, but the resulting changes in the BA might be acquired. In addition, BA length has been found to increase with age, with this elongation promoted by the presence of a DVA [10]. Consistent with these findings, the present study observed that individuals in the DVA group were significantly older and exhibited significantly greater lateral displacement of the BA than those in the no-DVA group. This suggests that a DVA could promote morphological dilation and deviation of the VBA system, although the underlying mechanisms remain to be elucidated.

An important finding of the present study is that the prevalence of VBD in the DVA group was nearly double that in the no-DVA group. This suggests that the presence of a DVA is associated with the occurrence of VBD, and the odds may be greater still if displacement of the VBA system occurs. Since a DVA has been reported to promote the elongation and curvature of the BA [10], patients in whom this occurs may be particularly susceptible to VBD. Thus, the detection of certain morphological changes (such as DVA, BA displacement, and VA confluence displacement) with CE-MRA in individuals without VBD might identify individuals at higher risk of having VBD, allowing implementation of measures to control other risk factors as well as regular follow-up to reduce the risk of VBD development.

Previous studies have determined that male sex is associated with VBD [2,4]. However, the present study failed to demonstrate such a correlation, with sex being not associated with VBD after adjustment for other parameters. The observations in previous studies may be explained by male sex being associated with other parameters associated with VBD (including those reported previously), such as DVA diameter, smoking, and alcohol consumption. Smoking is generally recognized as an important risk factor for cardiovascular diseases, including stroke [3-5,10], and tobacco smoking may have multiple effects on vascular remodeling, possibly by promoting sclerosis of the vascular wall. The present study showed a significant difference in smoking between men and women (47.1% vs. 2.9%), although no significant sex-related difference in VBD occurrence was observed. Thus, the mechanism underlying the possible effect of smoking on the development of VBD needs to be further explored.

The present study has several limitations. First, this was a single-center study in China, and the findings may not be generalizable to other regions of China or other countries. Second, there is currently no unified diagnostic criteria for VBD [1] and using a cutoff of 4.5 cm for the BA might result in overestimation of DE in men and underestimation in women [10]. Additional studies are necessary to determine the best cutoff point. Third, the prevalence of VBD in our patients may not reflect the general population, as all the included patients had attended hospital and thus would be predicted to have a higher incidence of pathology. Fourth, only a limited number of parameters were investigated for their association with VBD. Fifth, it was not possible to investigate the mechanisms underlying the associations between age and the presence of a DVA on VBD.

Conclusions

Age and the presence of a DVA are independently associated with VBD. It is possible that VBA system displacement and other morphological changes contribute, in part, to age- and DVA-related associations with VBD. Further studies are needed to examine these associations in more detail and explore possible underlying mechanisms.

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Conflict of interest statement

The authors declare they have no conflicts of interest in this study.

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