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Vertebrobasilar ectasia in patients with lacunar stroke: The SPS3 trial

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Abstract

Objective—The clinical implications of vertebrobasilar ectasia (VBE) in patients with cerebral small artery disease are not well defined. We investigated whether VBE is associated with recurrent stroke, major hemorrhage, and death in a large cohort of patients with recent lacunar stroke.

Materials and methods—Maximum diameters of the vertebral and basilar arteries were measured by magnetic resonance angiography and computed tomographic angiography in 2621 participants in the Secondary Prevention of Small Subcortical Strokes (SPS3) trial. VBE was defined *a priori* as basilar artery >4.5 mm and/or vertebral artery >4.0 mm. Patient characteristics and risks of stroke recurrence and mortality during follow-up (median 3.5 years) were compared between patients with and without VBE.

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Results—VBE affecting 1 artery was present in 200 (7.6%) patients. Patient features independently associated with VBE were increasing age, male sex, white race-ethnicity, hypertension, and higher baseline diastolic blood pressure. Baseline systolic blood pressure was inversely associated with VBE. After adjustment for other risk factors, VBE was not predictive of recurrent stroke (HR 1.3, 95% CI 0.85-1.9) or major hemorrhage (HR 1.5, CI 0.94-2.6), but was of death (HR 1.7, CI 1.1-2.7).

Conclusion—In this large well-characterized cohort of patients with recent lacunar stroke, VBE was predictive of death, but not recurrent stroke or major hemorrhage. In these exploratory analyses, the frequency of VBE was directly related to diastolic blood pressure but inversely related to systolic blood pressure.

Keywords

lacunar stroke; prognosis; recurrent stroke; small vessel disease; death; arterial diameter; vertebrobasilar ectasia

Introduction

Intracranial arterial dolichoectasia is characterized by increased dilatation and tortuosity of the arteries compared to expected values. [1-5]. Since the basilar artery and vertebral artery are preferentially involved, the term “vertebrobasilar (dolicho-) ectasia (VBE)” is commonly used. Reports of the prevalence of VBE range from 0.06—6% among healthy individuals [6-10] to 1—11% in stroke patients [11-17], with variability of rates partially due to differences in radiological definitions, patient populations, and stroke subtypes across studies.

Currently, there is insufficient evidence regarding prognosis of lacunar stroke patients with VBE [4, 5, 7, 8, 10, 13, 18-25]. Several small case series and observational studies have reported an unfavourable prognosis in patients with VBE [7, 8, 10, 13, 18-25]. In addition, a few studies have also reported a relationship between VBE and small vessel disease including lacunar stroke [9, 11, 13-15, 25]

The aim of this study was to investigate the prevalence and prognostic implications of VBE in patients with recent lacunar stroke due to cerebral small artery disease.

Materials and methods

Subjects

Participants were from the Secondary Prevention of Small Subcortical Strokes (SPS3) trial. Details about the study rationale, design, patient characteristics, and main results have been previously reported [26-29]. Briefly, patients with a recent (>2 wks, <6 mo) small symptomatic subcortical stroke documented on magnetic resonance imaging (MRI) were randomized simultaneously in a 2×2 factorial design to an antiplatelet therapy (double-blind, aspirin + placebo vs. aspirin + clopidogrel) and a target level of systolic blood pressure (130-149 mmHg vs. <130 mmHg). Corresponding lesion of the lacunar syndrome was verified on MRI. MRI scans were submitted for central interpretation by a neuroradiologist

(CB). The baseline MRI had to demonstrate a qualifying lesion meeting at least one of the following four specific criteria: i) diffusion-weighted imaging (DWI) lesion ≥ 20 mm in size at the largest dimension (including rostrocaudal extent); ii) well delineated focal hyperintensity ≥ 20 mm in size at largest dimension on fluid-attenuated inversion recovery (FLAIR) or T2 and clearly corresponding to the clinical syndrome; iii) multiple hypointense lesions of size 3-15 mm in size at the largest dimension in the cerebral hemispheres on FLAIR or T1 in patients whose qualifying event is clinically hemispheric; and iv) well-delineated hypointense lesion ≥ 15 mm in size at the largest dimension on FLAIR or T1 corresponding to the clinical syndrome with the MRI carried out at least one-month after the qualifying stroke.

Old subcortical infarcts, remotely symptomatic or asymptomatic, were defined as hypointense lesions on FLAIR and/or T1 measuring ≥ 3 mm, but no more than 15 mm in maximum dimension. Lesions at the level of the anterior commissure, convexity, or midbrain, were interpreted as enlarged peri-vascular spaces and not classified as infarcts, unless the lesion was surrounded by a hyperintense halo on FLAIR.¹ Patients were required to have vascular imaging of the intracranial arteries to qualify for study entry. Magnetic resonance angiography (MRA), computed tomography angiography (CTA), or angiogram images were submitted to the Coordinating Center.

Baseline systolic and diastolic blood pressures were determined by the average of two blood pressure measurements taken at least 1 week apart and at least two weeks after the qualifying stroke. Each measurement was the average of three blood pressure readings separated by at least two minutes in the seated position. History of hypertension pertained to prior to the qualifying stroke and was based on physician review of the patient's medical records or participant use of at least one antihypertensive medication at study entry.

Dilatation of arteries and intracranial arterial dolichoectasia

All available MRA and CTA were reviewed by a neurologist (MN) blinded to clinical information. MRA/CTAs with no scale and those visualizing only 4 or less of the 7 intracranial arteries within the image were not included. To measure arterial diameters, reconstructed maximum intensity projection images were used for MRA and source images were used for CTA. Maximum diameters at any point along the course of each of the basilar artery, intracranial internal carotid arteries, M1 segment of the middle cerebral arteries, and V4 portion of the vertebral artery were measured. MRA and CTA were assessed on digital (n = 2505) or film images (n = 289) as submitted to the Coordinating Center from each study site. Arterial diameters on digital images were measured manually using a DICOM viewer software available online (<http://www.radiantviewer.com>), and those on film images were measured using a graduated lens with scales (Supplemental figure) [14].

Intra-rater reliability (correlation coefficient) was assessed for each of the 7 intracranial artery measurements on a random sample of images for 50 patients re-read more than 6 months after initial reading. Readings for the intracranial internal carotid arteries and M1 segment of the middle cerebral arteries were not sufficiently reproducible (correlation coefficients ≤ 0.70) such that we did not include those results further in these analyses. Patients included in these analyses have a measurement for the basilar artery and at least one

vertebral artery. Correlation coefficients for the first and second readings of the basilar and vertebral artery measurements ranged from 0.84-0.89. The random sample was also read by a second reader (NO), and inter-rater reliability for the basilar and vertebral artery measurements ranged from 0.78-0.87.

Vertebrobasilar ectasia (VBE) was defined *a priori* as diameters of >4.5 mm for the basilar artery [32, 33] and >4.0 mm for the vertebral artery [4, 25]. The maximum dimension of the right and left vertebral arteries was used. The tortuosity of the basilar artery was not part of the definition of VBE.

Statistics

Artery measurements were described using medians and interquartile ranges (IQR) and assessed for normality using Kolmogorov-Smirnov test. Patient characteristics were compared between groups using chi-square tests, Student's t-test, or Mann-Whitney U test as appropriate. Stepwise multivariable binomial logistic regression of patient characteristics was used to determine patient characteristics independently associated with VBE. Multivariable Cox proportional hazards models were used to assess independent contributions of VBE for risk of recurrent stroke, myocardial infarction, major hemorrhage, and death during follow-up after adjusting for assigned antiplatelet therapy and blood pressure control target groups, and other possible confounders as noted. Statistical significance was accepted at the 0.05 level, and no adjustment was made for multiple comparisons. All confidence intervals (CI) are two-sided. Analyses were done using SPSS Statistics for Windows, Version 20 (Armonk NY).

Results

Technically adequate intracranial vascular imaging was available for review for 2621 SPS3 participants (87% of all participants; 2530 magnetic resonance angiographies (MRAs) and 91 computed tomography angiographies (CTAs)). Participants without adequate imaging available were not statistically different from those included in the study with respect to age, blood pressure, and prevalence of hypertension, diabetes, prior symptomatic stroke, or ischemic heart disease, but were less often female and hyperlipidemic (Supplemental table 1).

Maximum diameters of the arteries were not normally distributed ($p < 0.001$ for each artery). Respective medians (IQR) for the basilar and vertebral arteries were 3.3 (0.8) mm, and 2.7 (0.8) mm. VBE was present in 1 artery in 200 (7.6%) patients: 155 involved the basilar artery and 116 the vertebral arteries.

Patients with VBE were on average 2 years older ($p = 0.004$), more often male (81% vs. 61%, $p < 0.001$), and more often had history of hypertension (83% vs. 74%, $p = 0.004$) vs. those without VBE, while diabetes (37% vs. 29%, $p = 0.02$) and current smoking (22% vs. 15%, $p = 0.02$) was more frequent in patients without VBE (Table 1). By multivariable analysis, risk factors from Table 1 independently associated with VBE were age, male sex, body mass index, non-current smoking, white race-ethnicity, a history of hypertension, and higher diastolic blood pressure at entry (Table 2). The frequency of VBE was inversely

related to systolic blood pressure (Table 2). Multiple small subcortical infarcts (30% vs. 17%, $p < 0.001$) and severe white matter hyperintensities (33% vs. 21%, $p < 0.001$) were more common in patients with VBE vs. those without VBE.

During a median follow-up of 3.5 patient-years, 250 patients had a recurrent stroke (ischemic and hemorrhagic), 142 had a major hemorrhage (intra- and extracranial), and 176 died (Table 3). Of the 21 patients with VBE and ischemic stroke, 9 were in the middle cerebral artery territory, 4 in the brainstem, 1 in the cerebellum, and 1 in the brainstem and posterior cerebral artery territory (undetermined 6 patients). Patients with VBE were not at significantly increased risk of recurrent stroke, myocardial infarction, or major hemorrhage (Table 3). Risk of all-cause death however was increased for patients with VBE (adjusted HR 1.7, CI 1.1-2.7, $p = 0.02$). Of the 23 deaths in VBE patients, 4 were cerebrovascular, 6 vascular, non-cerebral, 9 non-vascular (6 cancer, 3 non-cancer), and the remainder uncertain or unknown causes.

Neither the maximum diameter for the basilar or the vertebral artery was predictive of recurrent stroke or major hemorrhage (Table 4). Increased basilar artery diameter was predictive of death (adjusted HR 1.3 per mm, CI 1.1-1.7, $p = 0.008$), while increased vertebral artery diameter showed a trend towards significance (adjusted HR per mm 1.2, CI 0.99-1.5, $p = 0.06$).

Discussion

In this large cohort of recent lacunar stroke patients, the basilar and vertebral arteries were assessed to elucidate the prevalence and relationships between clinical characteristics and clinical outcomes and VBE. In our cohort, VBE was not associated with risk of any of recurrent stroke, myocardial infarction, or major hemorrhage, but was associated with increased risk of death. Increased maximum basilar artery diameter was predictive of death, and maximum vertebral artery diameter showed a strong trend.

Previous studies of VBE also focused on the basilar and vertebral arteries, but only a few small studies investigated clinical significance of VBE as a predictor of future stroke or intracranial hemorrhage [7, 13, 21, 22]. Unlike in those studies, we did not find patients with VBE at increased risk of recurrent stroke or major hemorrhage. Differences in stroke subtype, patient characteristics, and the definition of VBE may explain the different findings, however the influence of antiplatelet therapy and blood pressure control in this clinical trial should be noted. The assignment of all SPS3 participants to either aspirin or aspirin and clopidogrel as well as a systolic blood pressure target of either 130-149 mmHg or <130 mmHg may have contributed to a lower incidence of recurrent stroke than most previous studies (Supplemental table 2) [8, 10, 23, 25].

On the other hand, we did find patients with VBE at increased risk of death. Furthermore, when each arterial diameter was investigated separately as a continuous variable, basilar artery dilatation was independently related to risk of subsequent death. The basilar artery is considered particularly susceptible to ectasia [13, 14, 24, 25, 32], presumably due to anatomical factors such as less sympathetic innervation of posterior circulation [1]. A

relationship between basilar artery dilatation and higher risk of cardiovascular events or mortality has also been reported, although the reason remains unclear [24, 33-35]. One speculation is that the basilar artery dilatation might reflect the influence of traditional atherosclerotic risk factors more strongly than for other intracranial arteries [35]. We did not compare the significance of arterial diameter in predicting clinical outcome between the anterior and posterior circulation because we did not find measurements of the internal carotid and middle cerebral arteries adequately reproducible.

The prevalence of VBE observed in our study was 7.6%. This result is lower than reported in other studies despite using a similar definition of VBE: 15.5% in the Northern Manhattan Study [32] and 13.2% in a Korean study [36]. The former is a community-based study in which the 718 participants were older (average 72 years) than in our study. The latter is a hospital-based cohort of 182 transient ischemic attack/stroke patients who underwent MRI including 23% with small vessel disease, also with patients somewhat older (average ~65 years).

Among clinical factors, we found white race-ethnicity to be independently associated with VBE patients. This is in contrast to one small cohort study reporting that VBE was equally distributed between whites and African-Americans [8, 10] and a community-based study reporting increased VBE prevalence in Hispanics (23%) and blacks (22%) compared to whites (12%) [37]. Although most other studies did not report the race/ethnicity of participants, it seems reasonable that prevalence of VBE or arterial diameter itself varies with race-ethnicity group. Further investigation in other settings is needed to clarify this issue.

In these exploratory analyses, we observed an unanticipated difference in the relationship between systolic and diastolic blood pressure measured at entry and VBE: by multivariable analysis, both increasing diastolic blood pressure and decreasing systolic blood pressure were associated with VBE. The systolic and diastolic blood pressures used in our analysis were determined via protocol based on multiple measurements proximate to study entry. Whether the differential association of higher systolic and diastolic blood pressures and VBE offers a clue to blood pressure mechanisms influencing the development of VBE or is explained by the play of chance requires confirmatory data from other studies.

Like other investigators [9, 14], we found multiple small infarcts and severe white matter hyperintensity on MRI more prevalent in patients with VBE than in those without VBE. A pathological study reported that the media of the artery was affected both in VBE and small vessel disease, which suggests involvement of matrix metalloproteinase metabolism [9]. Not only matrix metalloproteinase or traditional atherosclerotic risk factors, but also other genetic or environmental factors might link VBE and small vessel disease, however, further investigation is needed to clarify the relationship and the underlying common pathogenesis.

Controversy regarding the definition of VBE exists [5, 38, 39] with the two most widely used methods being 1) visual inspection, and 2) basilar artery diameter >4.5 mm with/without elongation (height of bifurcation and lateral displacement) of basilar artery based on Smoker's criteria [30, 31]. No studies have demonstrated a clear threshold effect of basilar

artery elongation on the risk of stroke or death [39]. Consequently, we *a priori* focused on maximum vessel diameters only in our study, analyzing them in two ways: first, vs. commonly used cutoff points for vertebral and basilar arteries and, second, as a continuous variable for each artery [6-17, 34].

The study has several strengths including the study group being a large well-characterized cohort of patients with recent lacunar stroke verified by MRI with a long term follow-up. To our knowledge this is the largest series of lacunar stroke patients with VBE studied. Because this study was based on a post-hoc analysis of a clinical trial though, the data are limited, and some factors possibly associated with patient outcome, such as progression of VBE during follow-up, arterial morphology, or other clinical manifestations of VBE, therefore could not be investigated [1-5, 25, 34, 40]. Another limitation of this study was that imaging quality, modality, and equipment were not standardized across clinical centers, however, this may increase the generalizability of our results. Measurements were done using both MRA and CTA images, and MRA has been found to be as accurate as CTA in correctly identifying dolichoectatic arteries [5, 41]. Lastly, measurements were performed by a single individual which could potentially introduce systematic bias, however the intra- and inter-rater reliabilities were excellent.

In short, in this large cohort of lacunar stroke patients, VBE was predictive of death but not recurrent stroke, major hemorrhage, or myocardial infarction. The mechanistic relationship between basilar and/or vertebral artery dilatation and death and the intervening factors requires validation and additional study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Patient features at study entry according to VBE status

	VBE absent (n = 2421)	VBE present (n = 200)	p-value
Age in years, mean (SD)	63 (11)	65 (11)	0.004
Males, %	61	81	< 0.001
Race-ethnicity, %			0.003
Non-Hispanic white	51	63	
Hispanic	28	26	
Black	18	9	
Other/multiple	3	3	
Body mass index, kg/m ² , mean (sd)	29 (6)	30 (7)	0.3
Current smoker, %	22	15	0.02
Modified Rankin Score at entry, %			0.1
0	15	17	
1	52	50	
2	24	29	
3	9	5	
Prior symptomatic S3, %	10	13	0.1
Hypertension, %	74	83	0.004
Diabetes mellitus, %	37	29	0.02
Hyperlipidemia, %	49	54	0.2
Ischemic heart disease, %	11	11	0.9
Severity of HTN, %			0.1
normotensive	2	1	
pre-HTN	18	13	
stage I	41	48	
stage II	39	39	
Blood pressure on entry, mmHg			
systolic, mean (SD)	143 (19)	144 (19)	0.2
diastolic, mean (SD)	78 (10)	82 (11)	< 0.001
Qualifying lesion on MRI, %			0.003
basal ganglia	4	2	
thalamus	27	20	
internal capsule	13	10	
corona radiata	27	33	

	VBE absent (n = 2421)	VBE present (n = 200)	p-value
centrum semiovale	3	< 1	
pons	21	30	
medulla/midbrain/cerebellum	4	4	

Abbreviations: VBE, vertebrobasilar ectasia; S3, small subcortical strokes; HTN, hypertension

Table 2
Characteristics independently associated with intracranial vertebro-basilar arterial ectasia in patients with recent lacunar stroke due to cerebral small artery disease

	VBE in 1 artery OR (95%CI)	Basilar artery VBE OR (95%CI)
Age, per 10 year increase	1.5 (1.3, 1.7)	1.7 (1.4, 1.9)
Male sex	2.5 (1.7, 3.7)	2.5 (1.7, 3.6)
Body mass index, per 10 kg/m ² increase	1.3 (1.0, 1.7)	1.4 (1.1, 1.7)
Current smoker	0.60 (0.39, 0.92)	NS
White race-ethnicity	1.7 (1.3, 2.3)	1.7 (1.2, 2.2)
History of hypertension	1.8 (1.2, 2.7)	1.7 (1.2, 2.5)
Systolic blood pressure, per 20 mmHg increase	0.62 (0.49, 0.78)	0.55 (0.42, 0.72)
Diastolic blood pressure, per 10 mmHg increase	2.0 (1.6, 2.5)	2.1 (1.7, 2.7)

OR = odds ratio; CI = confidence interval; NS = not statistically significant.

Table 3
Risk of recurrent stroke, major hemorrhage, and death associated VBE in patients with recent lacunar stroke

	VBE absent (n = 2421)	VBE Present (n = 200)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Stroke, n (% per pt-yr)	225 (2.5)	25 (3.4)	1.3 (0.88, 2.0)	1.3 (0.85, 1.9)*
Ischemic + uncertain	199 (2.2)	21 (2.8)		
lacunar	111	11		
intracranial atherosclerosis	14	4		
extracranial atherosclerosis	9	1		
cardioembolic	18	2		
other specific cause	9	0		
uncertain	37	3		
Intracerebral hemorrhage	26 (0.3)	4 (0.5)		
Myocardial infarction, n (% per pt-yr)	60 (0.6)	8 (1.0)	1.6 (0.76, 3.3)	1.5 (0.70, 3.1)†
Major hemorrhage, n (% per pt-yr)	124 (1.4)	18 (2.4)	1.8 (1.1, 2.9)	1.6 (0.94, 2.6)*
Death, n (% per pt-yr)	153 (1.6)	23 (2.9)	1.8 (1.2, 2.8)	1.7 (1.1, 2.7)‡

* Adjusted for assigned antiplatelet therapy and blood pressure control target groups as well as age and hypertension at study entry

† Adjusted for assigned antiplatelet and blood pressure control target groups as well as age, hypertension, and ischemic heart disease at study entry

‡ Adjusted for assigned antiplatelet therapy and blood pressure control target groups as well as age, hypertension, diabetes, hemoglobin, systolic blood pressure, and eGFR at study entry

Table 4
Risk of recurrent stroke, major hemorrhage, and death according to maximum arterial diameter

	Stroke Adjusted HR* (95% CI)	Major Bleed Adjusted HR* (95% CI)	Death Adjusted HR [†] (95% CI)
Basilar artery, per 1 mm increase	1.0 (0.85, 1.2)	1.0 (0.83, 1.3)	1.3 (1.1, 1.7)
Vertebral arteries, per 1 mm increase	0.96 (0.79, 1.2)	1.1 (0.84, 1.4)	1.2 (0.99, 1.5)

* Adjusted for assigned antiplatelet therapy and blood pressure control target groups as well as age and hypertension at study entry

[†] Adjusted for assigned antiplatelet therapy and blood pressure control target groups as well as age, hypertension, diabetes, hemoglobin, systolic blood pressure, and estimated glomerular filtration rate at study entry