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Association Between Vertebral Arterial Tortuosity and Aneurysm Growth in Intracranial Vertebral Artery Dissection

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Background and Purpose An intracranial vertebral artery dissecting aneurysm (iVADA) increases the risk of future subarachnoid hemorrhage, which is a severe complication with high rebleeding rates and poor outcomes. Identifying potential risk factors associated with iVADA growth is crucial for their effective management.

Methods This observational study was carried out at a single center and included patients who had been diagnosed with iVADA based on neuroimaging findings. We divided the patients into two groups: with and without iVADA growth. Growth was defined as any enlargement of a dilated region or a morphological change in follow-up imaging. We measured the vertebral artery tortuosity index (VTI) in the contralateral vertebral artery (VA), defined as its actual length divided by its straight length. We investigated the factors associated with iVADA growth.

Results This study included 124 patients. The median follow-up period was 7 months. We observed iVADA growth in 54 patients (43.5%), who were more likely to be current smokers (33.3% vs. 14.3%, p=0.012) and have a higher VTI (1.14±0.11 [mean±standard deviation] vs. 1.06±0.12, p=0.035) compared with those without iVADA growth. A multivariate analysis revealed that the VTI (adjusted odds ratio=28.490, 95% confidence interval=1.025−792.046, p=0.048) was independently associated with iVADA growth.

Conclusions This study has identified an independent association between VA tortuosity and iVADA growth.

Keywords dissecting vertebral artery aneurysm; arterial tortuosity; aneurysm growth.

INTRODUCTION

An intracranial vertebral artery dissecting aneurysm (iVADA) can manifest in various ways, ranging from incidental findings to symptoms such as headaches, signs of brainstem compression, and ischemic strokes.[1] iVADA generally has a favorable prognosis.[2] However, the devastating complication of subarachnoid hemorrhage (SAH) can result from the growth and rupture of iVADA.[3,4]

iVADA is becoming easier to detect using various imaging modalities, which is facilitating interventions before rupture occurs.[5] Factors such as the size, neck/height ratio, and coexistence of arterial stenosis adjacent to an iVADA have been linked to the risk of rupture.[6] We previously demonstrated an association between higher vertebral artery (VA) tortuosity and the occurrence of dissection or intracranial aneurysms, which can be attributed to a weakened vascular structure that can lead to increased tortuosity and dissection.[7]

Arterial tortuosity can also affect the growth of an aneurysm.[8] Although dissecting aneurysms have different pathophysiological factors, the growth rates of dissecting and intracranial aneurysms may be influenced by similar factors, since they can share a common condition of fragmentation or a lack of internal elastic lamina.[9,10] This study aimed to iden-

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tify the factors associated with iVADA growth, including consideration of the VA tortuosity.

METHODS

Participants

This observational study was conducted at Asan Medical Center and involved patients diagnosed with iVADA between January 2017 and December 2021. iVADA was diagnosed based on neurovascular imaging findings, including from digital-subtraction angiography (DSA), magnetic resonance angiography (MRA), computed tomography angiography (CTA), and/or high-resolution magnetic resonance imaging (HR-MRI). These imaging modalities revealed 1) fusiform or saccular aneurysmal dilatation at the distal VA, and 2) intramural hematoma, intimal flap, double lumen sign, pearl-and-string sign, or their combination.

We excluded patients with 1) poor image quality, 2) bilateral VA involvement, 3) ruptured iVADA associated with SAH as diagnosed in initial brain imaging, 4) any hypoplastic VA on either side for which tortuosity was unmeasurable, or 5) laboratory or radiographic findings indicating angiitis, fibromuscular dysplasia, or any other causes (e.g., atherosclerosis) (Fig. 1).

We obtained demographic data and risk factors by reviewing the patients' medical records and a stroke registry database. We assessed the presence of vascular risk factors, comorbidities, family history of stroke, and medication use at the time of the iVADA diagnosis. The study was approved by the Institutional Review Board of Asan Medical Center (IRB number: 2021-1782). The need to obtained informed consents from patients was waived due to the retrospective design of the study.

Measuring geometric parameters

MRI and MRA were performed using a 3.0-T Philips scanner (Philips Healthcare, Eindhoven, The Netherlands), while CTA and DSA were performed using a Siemens scanner (Siemens Healthneers, Erlangen, Germany). All morphological parameters were evaluated on two-dimensional (2D) angiographic images obtained from reconstructed coronal sections perpendicular to the anterior-posterior commissure plane.[11]

We determined the size of each dissecting aneurysm by measuring its most-dilated internal diameter.[12,13] The diameter of the basilar artery (BA) was measured 1 mm above the vertebrobasilar junction. We also measured the angle between the BA and the ipsilateral VA as well as the angle between the contralateral VA and VAs.[14] The aneurysm diameter ratio was calculated by dividing the most-dilated diameter by the vessel diameter at a point proximal to the dilatation where its diameter was normal. We considered a VA to be dominant if it had a larger diameter (a side-to-side diameter difference of ≥0.3 mm) or directly connected to the BA when the two VAs had comparable diameters.[15]

We determined the vertebral artery tortuosity index (VTI)

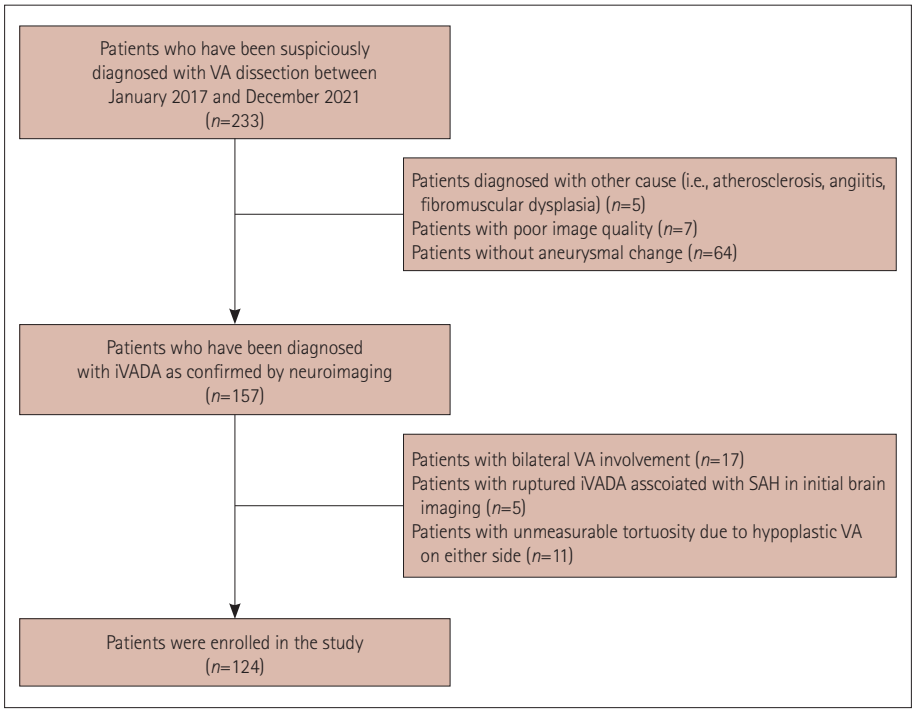

Fig. 1. Study flowchart. iVADA, intracranial vertebral artery dissecting aneurysm; SAH, subarachnoid hemorrhage; VA, vertebral artery.

by calculating the ratio of its actual length to its straight length. The VA actual length was determined by tracing the vessel's course from the union of both VAs to the dura mater, while it straight length was determined by measuring the linear distance from the origin to the end of its V4 portion (Fig. 2).[14,16] We measured the VTI from the contralateral VA, since the ipsilateral VA might have been deformed after the dissection, and in several patients the ipsilateral VA was not traceable.

Neuroimaging follow-up and aneurysm growth

Follow-up evaluations of iVADA growth were conducted in each patient using the same modalities (DSA, CTA, and/or MRA) utilized in the initial examination. The follow-up period was determined by the physician. iVADA growth was defined as any increase in the most-dilated internal diameter and any morphological changes such as bleb formation detected in the follow-up imaging (Fig. 3).[17,18] Two experienced researchers who were blinded to the patients' clinical information independently interpreted the images and reached consensus decisions.

Statistical analyses

We compared the characteristics of patients between those with and without iVADA growth, using chi-squared or Fisher's exact tests for categorical variables and Student's *t*-tests or Mann–Whitney U-tests for continuous variables. Univariate and multivariate logistic regression models were analyzed to identify the factors associated with iVADA growth. In the multivariable logistic regression we included age, sex, and variables with *p* values of <0.1 in the univariate analyses. The optimal predictor cut points for the VTI were determined by constructing receiver operating characteristic (ROC) curves. We used SPSS software (version 21.0, IBM Corp., Armonk, NY, USA) for the statistical analyses, and a *p* value of <0.05 was considered indicative of statistical significance.

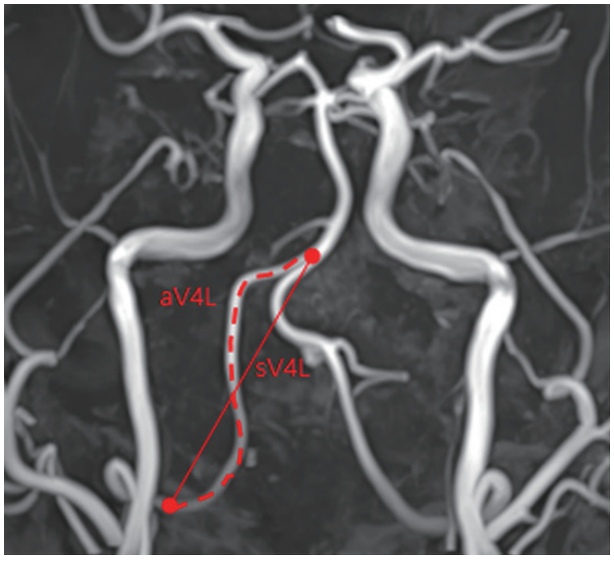

Fig. 2. Measurement of the VTI. If the actual length of the VA is aV4L and its straight length is sV4L, then VTI is calculated as aV4L/sV4L. VA, vertebral artery; VTI, vertebral artery tortuosity index.

RESULTS

This study included 124 patients aged 54±12 years (mean± standard deviation), of whom 64.2% were male. The median follow-up period was 7 months (interquartile range= 1–28 months).

iVADA growth occurred in 54 (43.5%) patients, with 2 showing morphological changes and 52 having an enlarged dilated region. There were no significant differences between those with and without iVADA growth in vascular risk factors or symptoms, except for the prevalence of current smoking being higher in patients with iVADA growth (33.3% vs. 14.3%, p=0.012) (Table 1). The only significant intergroup difference in geometric parameters was for VTI, which was higher in those with iVADA growth (1.14±0.11 vs. 1.06± 0.12, p=0.035) (Table 2).

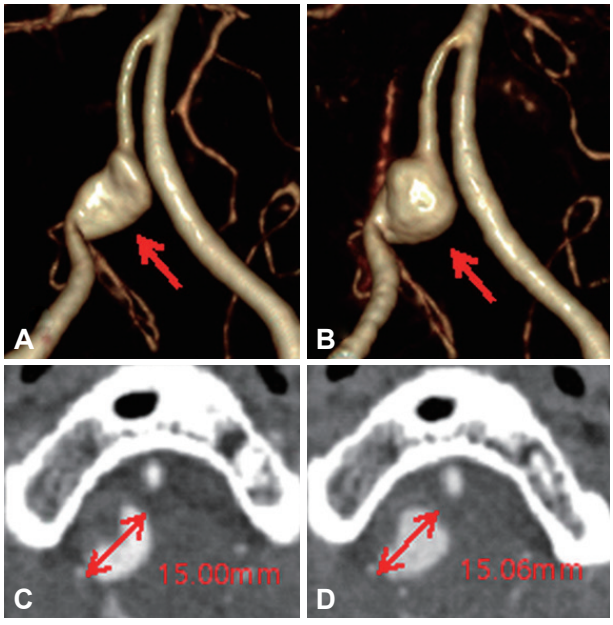

Fig. 3. Image of growth in the right iVADA. A: At the initial presentation, three-dimensional CTA demonstrated the pearl-and-string sign with dilatation (arrow) of the right VA where it branched from the posterior inferior cerebellar artery. B: 1-Year follow-up CTA showed an enlarged aneurysm sac and changes in the morphology of the right iVADA. C and D: Images showing the diameter of the dissecting aneurysm at the initial presentation and at the 1-year follow-up in axial CTA. CTA, computed tomography angiography; iVADA, intracranial vertebral artery dissecting aneurysm; VA, vertebral artery.

Table 1. Baseline characteristics of patients with and without iVADA growth

Characteristics	Growth (*n*=54)	No growth (*n*=70)	*p*
Age (yr)	54±11	57±11	0.097
Sex, male	36 (66.7)	44 (62.9)	0.660
Follow-up period (months)	2 [0–8]	13 [3–36]	0.709
Risk factors			
Hypertension	31 (57.4)	43 (61.4)	0.651
Diabetes mellitus	3 (5.6)	12 (17.1)	0.050
Hyperlipidemia	14 (25.9)	16 (22.9)	0.692
Coronary artery disease	2 (3.7)	6 (8.6)	0.464
Current smoking	18 (33.3)	10 (14.3)	0.012
Initial blood pressure			
SBP (mm Hg)	140.30±17.01	139.98±21.39	0.924
DBP (mm Hg)	86.15±10.24	86.79±16.62	0.804
Family history	14 (25.9)	11 (15.7)	0.160
Previous stroke history	4 (7.4)	1 (1.4)	0.166
Medication			
Antiplatelets	16 (29.6)	13 (18.6)	0.149
Anticoagulants	1 (1.9)	2 (2.9)	0.999
Antihypertensives	16 (29.6)	28 (40.0)	0.231
Antidiabetics	3 (5.6)	7 (10.0)	0.511
Antihyperlipidemics	16 (29.6)	16 (22.9)	0.393
Ischemic stroke	7 (12.7)	4 (5.6)	0.208
TIA	1 (1.8)	1 (1.4)	0.999
Symptom			0.564
Headache	31 (58.5)	40 (57.1)	
Dizziness	9 (16.6)	6 (8.6)	
Others	4 (7.5)	9 (12.9)	
Asymptomatic	10 (18.9)	15 (21.4)	

Data are *n* (%), mean±standard-deviation, or median [interquartile range] values.
DBP, diastolic blood pressure; iVADA, intracranial vertebral artery dissecting aneurysm; SBP, systolic blood pressure; TIA, transient ischemic attack.

Table 2. Vascular geometry in patients with and without iVADA growth

Geometric characteristic	Growth (*n*=54)	No growth (*n*=70)	*p*
VTI	1.14±0.11	1.06±0.12	0.035
Size of aneurysm (mm)	6.88±3.00	6.24±2.79	0.248
BA–ipsiVA angle (degrees)	145.56±22.56	150.18±19.54	0.243
VA–VA angle (degrees)	57.03±28.02	49.62±26.08	0.144
Aneurysm ratio	2.83±1.32	2.42±0.83	0.054
BA diameter (mm)	3.10±0.91	3.16±0.65	0.677
VA diameter ratio	1.48±0.39	1.54±0.58	0.533
Ipsilateral dominant	24 (44.4)	33 (47.1)	0.765
Other cerebral aneurysm	11 (20.0)	13 (18.3)	0.397

Data are *n* (%) or mean±standard-deviation values. The VA diameter ratio was calculated by dividing the diameter at the initiation of the affected V4 segment by the diameter at the termination of the affected V4 segment. Other cerebral aneurysm refers to an aneurysm located in any intracranial and/or extracranial artery other than the ipsilateral or contralateral distal VA.
BA, basilar artery; ipsiVA, ipsilateral VA; iVADA, intracranial vertebral artery dissecting aneurysm; VA, vertebral artery; VTI, vertebral artery tortuosity index.

Factors associated with iVADA growth

Current smoking (odds ratio [OR]=3.000, 95% confidence interval [CI]=1.249–7.208, *p*=0.014) and the VTI (OR=31.003, 95% CI=1.160–828.675, *p*=0.041) were associated with iVADA growth. In the multivariate analysis, VTI remained significantly associated with growth after adjusting for age, sex, diabetes mellitus, and current smoking (adjusted OR=28.490, 95% CI=1.025–792.046, *p*=0.048) (Table 3). ROC curve analysis showed that VTI had predictive value for iVADA growth, with an area under the ROC curve of 0.633 (95% CI=0.529–0.738, *p*=0.015). The optimal cutoff value for VTI was 1.065, which yielded sensitivity and specificity values for predicting iVADA growth of 63.0% and 61.8%, respectively (Supplementary Table 1 and Supplementary Fig. 1 in the online-only Data Supplement).

DISCUSSION

iVADA growth was present in 43.5% of the patients in this study. These patients were more likely to be current smokers and had a higher VTI compared with those without iVADA growth. VTI was independently associated with iVADA growth.

iVADA growth has been attributed to repeated hemodynamic injuries to the aneurysm wall. Elastin is a protein that is important for the maintenance of mechanical tension, and is functionally impaired in arterial walls with aneurysm. These walls progressively weaken due to turbulent blood flow in the aneurysm sac, which makes the wall less able to resist pulsatile stresses, resulting in aneurysm growth.[19] A recent study demonstrated that preserved endothelial function, as measured by flow-mediated dilatation, is associated with a reduction in the iVADA size, whereas aneurysmal enlargement is more common in individuals with a lower arterial stiffness.[20]

Weakening of the arterial connective tissue manifests as an increased vascular tortuosity of the cerebral arteries. For example, a mutation in the transforming growth factor β receptor activates signaling cascades in the vessel wall, resulting in selective deterioration of the extracellular matrix. This ultimately leads to aneurysm formation and high vascular tortuosity.[21-23] We previously found VA dissection to be associated with higher VA tortuosity due to a weakened vas-

Table 3. Factors associated with iVADA growth

	Univariate analysis		Multivariate analysis*	
	OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Age	0.972 (0.941–1.005)	0.100	-	
Sex, male	1.182 (0.561–2.490)	0.660	-	
Risk factors				
Hypertension	0.674 (0.328–1.385)	0.283		
Diabetes mellitus	0.284 (0.076–1.064)	0.062	0.246 (0.059–1.031)	0.059
Current smoking	3.000 (1.249–7.208)	0.014	1.348 (0.998–4.419)	0.064
Family history	1.877 (0.774–4.553)	0.163		
Previous stroke history	5.520 (0.599–50.892)	0.132		
Medication				
Antiplatelets	1.846 (0.798–4.272)	0.152		
Anticoagulants	0.639 (0.056–7.233)	0.717		
Antihypertensives	0.687 (0.326–1.446)	0.323		
Antidiabetics	0.527 (0.130–2.141)	0.371		
Antihyperlipidemics	1.410 (0.630–3.155)	0.403		
Vascular geometry				
VTI	31.003 (1.160–828.675)	0.041	28.490 (1.025–792.046)	0.048
Size of aneurysm	1.080 (0.947–1.231)	0.251		
BA–ipsiVA angle	8.989 (0.972–1.007)	0.242		
VA–VA angle	1.010 (0.996–1.024)	0.147		
Aneurysm diameter ratio	1.444 (0.998–2.089)	0.052	1.456 (0.994–2.132)	0.055
Other cerebral aneurysm	1.115 (0.456–2.726)	0.811		

*Multivariate analysis with adjustment for age, sex, diabetes mellitus, current smoking, VTI, and aneurysm diameter ratio.
BA, basilar artery; CI, confidence interval; ipsiVA, ipsilateral VA; iVADA, intracranial vertebral artery dissecting aneurysm; OR, odds ratio; VA, vertebral artery; VTI, vertebral artery tortuosity index.

cular structure being prone to deformity.[7] Another study showed that high tortuosity of the coronary artery disrupts laminar blood flow, increasing the artery wall shear stress (WSS) and weakening the artery. This may lead to spontaneous coronary artery dissection.[24]

Arterial tortuosity can also affect the growth of an aneurysm. A previous study showed that the high vessel tortuosity can change the local hemodynamics, such as the WSS and flow angle, which impacts aneurysm growth.[8] However, we found that iVADA growth was associated with high VA tortuosity on the contralateral side. The ipsilateral VA might have shown morphological changes following dissection. Most previous studies have found temporal changes in unruptured VA dissection in follow-up imaging.[25] Nevertheless, contralateral tortuosity can be represented by uncharacterized underlying systemic factors that weaken the arterial wall structure. Also, a previous study found that the contralateral tortuosity was similar to the ipsilateral tortuosity, which indicates that the contralateral tortuosity is particularly useful since ipsilateral measurements are often rendered infeasible due to various causes.[26]

The present study had several limitations. Firstly, it was conducted at a single center with relatively few patients. Secondly, the vascular geometry data relied on 2D images derived from reconstructed three-dimensional angiographic images. However, measuring tortuosity in the lateral dimensions seems highly feasible. Thirdly, although we suggest that an impaired hemodynamic status is associated with iVADA growth, this could not be assessed in the present retrospective study. Also, we could not make adjustments for all possible confounding factors such as the initial and follow-up systolic and diastolic blood pressures due to only a small number of patients being evaluated. Fourthly, the prevalence of iVADA in this study (43.5%) was higher than in previous studies, which was probably due to many patients being referred to our tertiary hospital for a second consultation.[27-30] It is known that iVADA aggravation often progresses within 1 month. In our study, most patients were followed up regardless of symptoms. Finally, although we investigated the family history, we did not perform genetic testing, and so the influence of genetics on the present results cannot be excluded.

Notwithstanding these limitations, VA tortuosity was found to be independently associated with iVADA growth, which is in turn associated with severe complications such as high rebleeding rates and poor outcomes. Therefore, patients exhibiting iVADA with high VA tortuosity should be carefully

managed in order to prevent further growth.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2024.0139.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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