

# Association between Vertebral Artery Hypoplasia and Vertebral Artery Aneurysms: A Case-Control Study

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## Abstract

**Background** The aim of this retrospective case-control study was to determine the association of vertebral artery hypoplasia (VAH) and other anatomical variants with saccular vertebral artery posterior inferior cerebellar artery (VA-PICA) aneurysms.

**Methods** The frequency of VAH, vertebral artery (VA) atresia, VA aplasia, and PICA aplasia was analyzed using computed tomography (CT) angiography in 64 patients with VA-PICA aneurysms (43 ruptured and 21 unruptured) and compared with 128 age- and sex-matched controls. Logistic regression was performed to identify independent risk factors for aneurysm formation.

**Results** Univariate analysis showed that patients with VA-PICA aneurysms had a significantly higher frequency of VAH (53% versus 17%; odds ratio [OR] 4.8; 95% confidence interval [CI], 2.4–9.4;  $p < 0.0001$ ) and VA aplasia (14% versus 1%; OR 20.8; 95% CI, 2.5–168.0;  $p = 0.004$ ) compared with controls. VA-PICA aneurysms are detected significantly more often in the dominant VA, which is contralateral to VAH. Other anatomical variants are not related to aneurysm formation.

**Conclusions** VAH and VA aplasia are potential risk factors for VA-PICA aneurysms. Altered hemodynamics caused by VAH may result in intracranial aneurysm formation. Additional research should clarify the pathophysiologic association of VAH, VA aplasia, or vascular occlusion with arteriosclerosis and intracranial aneurysm formation.

## Keywords

- ▶ computed tomography angiography
- ▶ intracranial aneurysm
- ▶ posterior inferior cerebellar artery
- ▶ vertebral artery
- ▶ vertebral artery hypoplasia
- ▶ posterior circulation

## Introduction

The anatomy of the posterior circulation and the vertebral arteries (VAs) is highly variable.<sup>1,2</sup> Vertebral artery hypoplasia (VAH) is a relatively frequent variant with an incidence of up to 26%. Various publications described the association between VAH and posterior circulation ischemia, vestibular neuronitis, migraine, and VA dissection.<sup>3–6</sup> However, the effect of VAH on vertebral artery posterior inferior cerebellar artery (VA-PICA) aneurysm formation has not been studied. The aim of this retrospective case-control study was to

determine the association of VAH and other vessel variants with VA-PICA aneurysms. To achieve this, we assessed their frequency as determined by computed tomography angiography (CTA) in patients with ruptured and unruptured aneurysms, and in controls without a history of cerebrovascular disease. We analyzed clinical and anatomical data among patients with ruptured and unruptured aneurysms, and we conducted a case-control study to compare the frequency of VAH and related variants in patients with aneurysms and in controls.

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## Methods

### Study Population

Our study population consisted of 192 patients including 64 consecutive patients with VA-PICA aneurysms and 128 controls. Patients were admitted to our institution with ruptured or unruptured saccular aneurysms from January 2000 to March 2017. To exclude selection bias, we only included patients with saccular aneurysms at the VA-PICA origin. Patients with dissecting, fusiform, and giant thrombosed aneurysms were excluded. Controls were selected from our institutional trauma register between January 2015 and March 2017. Controls with head injury, cervical spine injury, traumatic VA dissection, intracranial hemorrhage, hemorrhagic shock, and any history of cerebrovascular diseases or stroke were excluded to avoid selection bias. Among the controls with suspected traumatic VA dissection on CTA, magnetic resonance angiography, digital subtraction angiography, and/or duplex ultrasound was also performed for further precise evaluation. The study was designed as a retrospective single-center hospital-based case-control study. The local ethics committee board approved the study.

### Radiologic Evaluation

Aneurysms were diagnosed using cranial CTA (GE Brightspeed QX/i; GE Medical Systems, Milwaukee, Wisconsin, United States). Controls underwent a CT whole-body scan, including cranial CTA, to exclude vascular injury. Radiologic images from patients and controls were stored in the hospital's central digital archiving system (Centricity RIS-I 4.2 Plus, GE Medical Systems), from which all relevant diagnostic images can be retrieved. For CTA, 75 mL highly iodinated contrast agent was administered intravenously, followed by 40 mL saline, both with a flow rate of 3 mL/s. CTA was performed from the axis to the vertex. Axial CTA images were reconstructed with a slice thickness of 1.25 mm at increments of 0.6 mm, using the multiplanar CTA reconstruction mode (► Fig. 1).

In addition to VA-PICA aneurysm size and side, cerebral aneurysms in other locations were assessed in each patient.

The diameter of V4 segments within 10 mm cranial to the foramen magnum, the diameter of both PICAs at their origin from the VA, and that of the basilar artery at the vertebrobasilar junction were measured in patients and controls. VAH was defined by a V4 segment diameter  $\leq 2.0$  mm. VA aplasia and PICA aplasia/hypoplasia were assumed when vessels remained undetected by CTA ( $< 0.5$  mm). We defined the PICA in accordance with other main series as an artery originating from the VA to supply the cerebellum.<sup>1,7</sup> Moreover, we studied other anatomical variants, such as VA atresia (unilateral termination of the VA into the PICA), complete or partial fetal distribution, and a persistent trigeminal or hypoglossal artery.

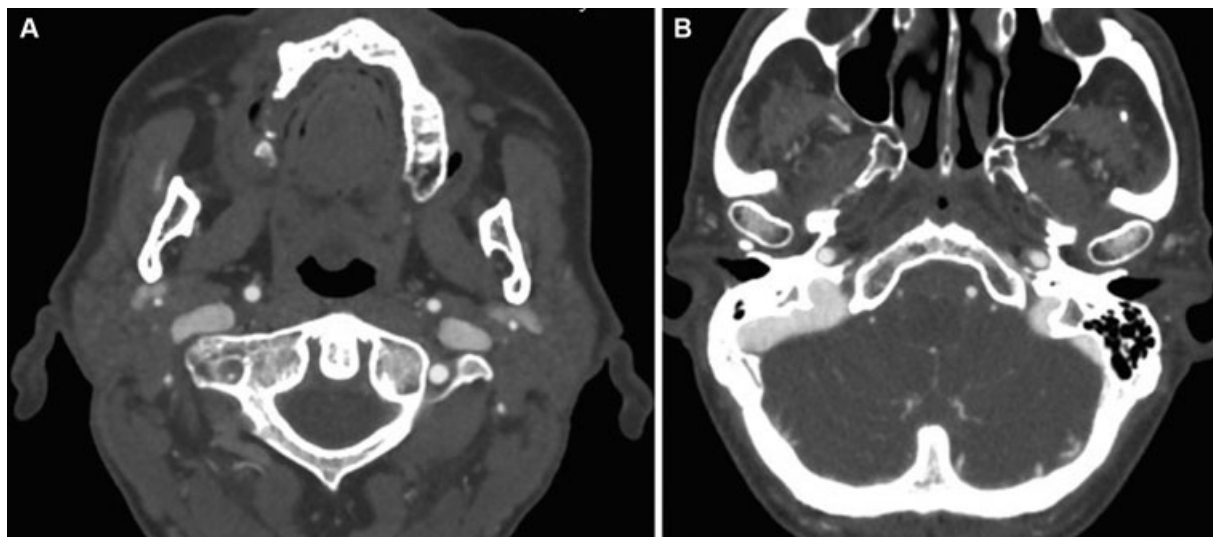
### Statistical Analysis

Data sets were analyzed using SPSS v.23 (SPSS, Inc., Chicago, Illinois, United States). Categorical variables were compared using the Fisher exact two-tailed test and Pearson's chi-square test, and continuous variables were compared between groups using the Mann-Whitney *U* test. A  $p < 0.05$  was considered significant. Univariate analysis was performed to determine the odds ratio of potential factors linked to VA-PICA aneurysm formation.

## Results

### Patient Group

The patient group included 45 women (70%) and 19 men (30%). Mean age at rupture or at diagnosis was 57 years (range: 29–81 years). Forty-one patients (64%) presented with ruptured VA-PICA aneurysms. Twenty-nine (70%) presented with Fischer grade 4, six (15%) with Fischer grade 3, and the remaining 6 patients (15%) with Fischer grade 1 and 2 bleeding. Of the 23 patients with unruptured VA-PICA aneurysms, 11 patients presented with hemorrhage from a cerebral aneurysm at another site. Altogether 21 patients had multiple aneurysms. The aneurysm size among patients with ruptured and unruptured aneurysms did not show normal distribution. The median size of ruptured aneurysms was significantly higher than in unruptured aneurysms. However, categorical



**Fig. 1** (a, b) Axial computed tomography angiography demonstrating vertebral artery hypoplasia in the V3 and the V4 segment on the right side.

distribution did not show any significant differences among both groups. Only 31 patients (48%) had a symmetrical contribution of the VAs. ► **Table 1** lists the characteristics of patients with ruptured and unruptured aneurysms. In addition to aneurysm size, no statistically significant differences were observed in morphometric parameters and anatomical variants. Aneurysms on the left side presented more frequently with rupture than those on the right side. Aneurysms were also more frequently located contralateral to VAH ( $p = 0.022$ ). This finding was more pronounced on the left side (► **Table 2**).

**Case-Control Study**

Groups were adjusted for age and sex, with VAH detected in 52% of patients with VA-PICA aneurysms and 17% of con-

trols ( $p < 0.0001$ ). In both patients and controls, VAH was more frequently observed on the right side. Mean diameter of the right VA was smaller than the one on the left side in both groups, and it was significantly smaller in the aneurysm patient group compared with the controls (2.3 mm versus 3.1 mm;  $p < 0.0001$ ). The incidence of VAH, VA aplasia, and PICA aplasia was significantly higher in the aneurysm patient group, whereas other anatomical variants such as fetal distribution and VA atresia did not differ between groups. Rare anatomical variations such as persistent fetal arteries, duplication, or fenestrations of the VA or PICA were not observed in our series. Baseline characteristics of patient and control groups are presented in ► **Table 3**.

**Predictors of VA-PICA Aneurysms**

Univariate analyses identified VAH, VA aplasia, and PICA aplasia as significant determinants of VA-PICA aneurysms (► **Table 4**).

**Table 1** Clinical characteristics of patients with VA-PICA aneurysms

Characteristic	Ruptured (N = 41)	Unruptured (N = 23)	p value
Age	57.2 ± 14.2	55.8 ± 11.5	0.690
Sex F/M	29/12	16/7	0.922
Aneurysm size, mm (%)			
Large: 15–25	1 (2)	2 (9)	0.091
Medium: 7–14	15 (37)	3 (13)	
Small: < 7	25 (61)	18 (78)	
Aneurysm size, mm, median (range)	6 (2–19)	4 (2–20)	<b>0.038</b>
Aneurysm side (%)			
Left	28 (68)	10 (39)	0.052
Right	13 (32)	13 (61)	
Vertebral artery hypoplasia (%)	23 (56)	9 (39)	0.193
Vertebral artery aplasia (%)	6 (15)	3 (13)	0.861
PICA aplasia (%)	15 (37)	7 (30)	0.619
Vertebral artery atresia (%)	2 (5)	2 (9)	0.545
Fetal distribution (%)			
Partial	12 (29)	4 (17)	0.347
Complete	2 (5)	3 (13)	

Abbreviations: F, female; M, male; PICA, posterior inferior cerebellar artery. Note: Significant results bold.

**Table 2** Characteristics of the aneurysm side and VAH

	Normal	VA aplasia or hypoplasia, left	VA aplasia or hypoplasia, right	VA hypoplasia, bilateral	p value
Left aneurysm	17	1	18	2	<b>0.022</b>
Right aneurysm	14	6	5	1	

Abbreviations: VA, vertebral artery; VAH, vertebral artery hypoplasia.

**Discussion**

Our results confirm that VAH, VA aplasia, and PICA aplasia are potential risk factors for VA-PICA aneurysms. Other anatomical variations such as VA atresia and fetal distribution were not related to VA-PICA aneurysms. To our knowledge, this is the first study to confirm the association between VAH and VA-PICA aneurysms with VA-PICA aneurysms more likely to develop contralateral to a hypoplastic VA. This correlation may result from increased flow in the dominant VA, resulting in chronic hemodynamic wall shear stress, especially at the VA-PICA origin.

VAH is defined by a small vessel diameter and termination by forming the basilar artery;<sup>2</sup> its prevalence is highly variable and ranges between 2% and 26%,<sup>4,6,8–14</sup> which may result from different definitions of VAH. Cutoff diameter and measure points differ between the series.<sup>6,9,15,16</sup> The characteristics of the screened cohort, such as ethnic origin or underlying cerebrovascular disease, may be associated with other potential causes such as different diagnostic methods.<sup>6,17,18</sup> In our series, the frequency of VAH was 17% in the control group. In accordance with our study, Thierfelder et al demonstrated a prevalence of 15.6% in a German population with suspected stroke,<sup>6</sup> and also consistent with our study, they defined VAH as a vessel diameter < 2 mm in the V4 segment using CTA.<sup>6</sup> The VAH frequency was consistent with previous reports and depended on the approach and definitions for diagnosis.<sup>6,11</sup>

Despite its high prevalence, the clinical significance of VAH has been underestimated for a long time. VAH was

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**Table 3** Characteristics of cases and controls

Characteristic	Case group (n = 64)	Control group (n = 128)	p value
Age, y, mean ± SD	57.2 ± 17.5	56.7 ± 13.4	
Sex, F/M	45/19	81/47	
Vertebral artery hypoplasia, %			
All	(33) 52%	(22) 17%	<b>&lt; 0.0001</b>
Left	(7) 11%	(7) 4%	
Right	(23) 36%	(15) 12%	
Both	(3) 5%	0	
Vertebral artery aplasia, %			
All	(9) 14%	(1) 1%	<b>&lt; 0.0001</b>
Left	(3) 5%	0	
Right	(6) 9%	(1) 1%	
PICA aplasia	(22) 34%	(26) 20%	<b>0.034</b>
All			
Left	(7) 11%	(9) 7%	0.47
Right	(15) 23%	(17) 13%	
Vertebral artery atresia	(4) 6%	(5) 4%	
Fetal distribution			
Partial	(16) 25%	(35) 27%	0.79
Complete	(5) 8%	(8) 6%	
Diameter vertebral artery left, mm, median (range)	3.0 (0–5.3)	3.2 (1.2–5.5)	<b>0.023</b>
Diameter vertebral artery right, mm, median (range)	2.3 (0–4.6)	3.1 (0–4.6)	<b>&lt; 0.0001</b>
Diameter basilar artery, mm, median (range)	3.2 (1.6–4.5)	3.2 (0.8–4.6)	0.42

Abbreviations: F, female; M, male; PICA, posterior inferior cerebellar artery; SD, standard deviation.

Note: Significant results bold.

**Table 4** Univariate analysis of anatomical factors predicting VA-PICA aneurysms

Variable	Odds ratio	95% CI	p value
Vertebral artery hypoplasia	4.8	2.4–9.4	<b>&lt; 0.0001</b>
Vertebral artery aplasia	20.8	2.5–168.0	<b>0.004</b>
PICA aplasia	2.1	1.1–4.0	<b>0.036</b>
Vertebral artery atresia	1.6	0.4–6.3	0.470
Fetal distribution	1	0.5–1.8	1.0

Abbreviations: CI, confidence interval; PICA, posterior inferior cerebellar artery; VA, vertebral artery.

Note: Significant results bold.

recognized recently as an independent risk factor for a reduction of posterior circulation blood flow, and it was associated with PICA and lateral medullary ischemia.<sup>3,4,6,8–11,19</sup> In another case-control study, VAH was also associated with VA dissection.<sup>5</sup> VAH may also lead to regional hypoperfusion with complex neurovascular sequelae, such as vestibular neuropathy and migraine.<sup>11</sup>

VA atresia is defined by unilateral termination of the VA into the PICA with the contralateral VA continuing into the basilar artery.<sup>2</sup> Reported estimates of VA atresia range between 1.0% and 6.3%.<sup>1,20</sup> In a recent study, VA atresia was associated with a significantly higher prevalence of cerebrovascular events in the posterior circulation.<sup>20</sup> VA atresia is also associated with complex VA aneurysms.<sup>21</sup> However, in our series, VA atresia was not associated with a higher incidence among patients with VA-PICA aneurysms.

More than 50% of the patients with VA-PICA aneurysms in our series had associated anatomical variants within the posterior circulation; the most frequent was VAH.<sup>7,22</sup> Other characteristics included a small size rupture compared with other intracranial aneurysms.<sup>22–24</sup> Consistent with other series, women and older patients were more often affected.<sup>7,22</sup> In the largest series to date, Lehto et al found that 89% of VA-PICA aneurysms were located on the dominant VA.<sup>7</sup> In their series, VA-PICA aneurysms presented more frequently on the left side, which is consistent with previous reports.<sup>7,25</sup> In accordance with other series, the left VA was larger, and VAH was more frequent on the right side.<sup>3,4,6,7,19</sup> The reason for this asymmetry remains unclear. The left subclavian artery, from which the left VA is derived, arises directly from the aortic arch. Therefore, it is likely to undergo more shear stress during development, potentially leading to posterior circulation blood supply that is dominated by the left VA. Pressure and blood flow are potential stimuli for morphological vessel changes. Numerous studies have examined flow-dependent remodeling. Hemodynamic stress favors aneurysm formation, and it may also promote growth and rupture.<sup>26,27</sup> This was demonstrated in anterior communicating artery aneurysms. A dominant anterior cerebral artery A1 segment that supplies both A2 segments is a well-recognized risk factor for anterior communicating artery aneurysm formation and rupture.<sup>28,29</sup>

This study has several methodological strengths. Given the need for sophisticated imaging to identify VAH properly, and the rare occurrence of VA-PICA aneurysms, a case-control design is feasible to investigate the associations between these conditions. Moreover, controls were recruited from a trauma register, and we excluded patients with a history of cerebral ischemia and cerebral bleeding and avoided a selection bias that could overestimate VAH frequency.

However, the present study has some limitations. First of all, the study design is not suitable to calculate prevalences/incidences for a larger target population. Because of the rare occurrence of VA-PICA aneurysms (< 5% among all cerebral aneurysms), a time span of 17 years was affordable for the retrospective analysis. Recent technical advances and better

imaging may provide better information on the shape and the three-dimensional anatomy of the aneurysms, which was not possible in all patients. Additionally, we were not able to assess precisely other risk factors such as diabetes mellitus, smoking, and hypertension retrospectively and include them in the analysis. Moreover, CTA was performed in 41 patients after subarachnoid hemorrhage and most of them with Fischer grade 4 bleeding. Vasospasm-related irregularities and potential local mass effect of a subarachnoid clot could have influenced diameters of the intracranial vessels.

Multicenter studies with a larger population including other vascular territories may be more feasible for future analysis. Despite using a high-resolution CTA for assessment of the posterior circulation, small vessel variants (< 0.5 mm) may have been missed that could have possibly influenced the results. Digital subtraction angiography is still the gold standard for intracranial vascular imaging, but compared with angiography, CTA is fast, noninvasive, and more readily available. Additionally, it is difficult to distinguish vascular occlusion or vasospasm from hypoplasia or aplasia with CTA because it only shows intraluminal flow and cannot clearly visualize the vascular wall.<sup>4</sup> In the case of ruptured VA-PICA aneurysms, VAH may also influence the clinical course and probably the outcome. Thus the results of this pilot study should be confirmed by further prospective studies.

## Conclusion

Our case-control study shows that VAH and VA aplasia are significant risk factors, with a prevalence of 52% in patients with VA-PICA aneurysms. In addition to A1 dominance, we were able to identify another variant as a potential risk factor for aneurysm formation. The pathogenic mechanisms linking VAH and aneurysms may be associated with altered hemodynamics and are not completely understood, but we emphasize increased attention to VAH because it is related to numerous cerebrovascular diseases. VA-PICA aneurysms are rare, and VAH is a relatively frequent condition. Therefore, our results did not generally support any staging for patients with VAH. However, the effect of hypoplasia/aplasia or vascular occlusion by arteriosclerosis on intracranial aneurysm formation in other locations may be of major interest because they will affect diagnostic staging and the choice of diagnostic intervals and possibly treatment modalities and timing in the future.

### Conflicts of Interest

None.

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