

# Vertebral Artery Origin Stenosis in Patients with Posterior Circulation Strokes Due to Large Artery Atherosclerosis

Büyük Arter Aterosklerozuna Bağlı Posterior Dolaşımda İnmesi Olan Hastalarda Vertebral Arter Orjin Stenozları

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## Abstract

**Objectives:** The origin of the extracranial vertebral artery (V1 segment) is a common site for large artery atherosclerosis (LAA). The aim of this study was to determine the risk factors, prevalence and prognosis of the patients presented with acute ischemic stroke due to vertebrobasilar atherosclerosis and additional V1 stenosis.

**Materials and Methods:** We reviewed the charts of 957 patients who were admitted with acute ischemic stroke between the dates January 2011 and May 2017, and selected cases with stroke related to posterior circulation (PC) atherosclerosis. The demographic data, risk factors, National Institutes of Health Stroke Scale (NIHSS) scores at admission, and modified Rankin scores (mRS) in the follow-up period were recorded.

**Results:** There were 80 (8.36%) patients with acute ischemic stroke in the PC due to LAA. Thirty (37.5%) patients [9 females (30%), mean age 67.4±14.3 years] had V1 stenosis. No between group differences in the history of vascular risk factors and mRS scores during the follow-up period were observed ( $p>0.05$ ). In logistic regression analysis, the admission NIHSS score was higher in patients with V1 stenosis than others ( $p=0.022$ ).

**Conclusion:** In our registry, more than one third of patients with acute PC stroke due to LAA had stenosis in the origin of the vertebral artery. The patients with coexisting V1 stenosis presented with relatively severe stroke.

**Keywords:** Vertebral artery origin, posterior circulation strokes, large artery atherosclerosis

## Öz

**Amaç:** Ekstrakraniyal vertebral arterin orjini (V1 segmenti), büyük arter aterosklerozunun sık görüldüğü bir bölgedir. Bu çalışmanın amacı vertebrobaziler aterosklerozu ve ek olarak V1 stenozu nedeniyle akut iskemik inme geçiren hastaların risk faktörlerini, prevalansını ve prognozunu belirlemektir.

**Gereç ve Yöntem:** Ocak 2011 ile Mayıs 2017 tarihleri arasında akut iskemik inme nedeniyle başvuran 957 hastanın dosyaları incelendi ve posterior dolaşım aterosklerozuna bağlı inme geçiren hastalar çalışmaya dahil edildi. Demografik veriler, risk faktörleri, başvuru anındaki Ulusal Sağlık İnme Ölçeği (NIHSS) skorları ve takip dönemindeki modified Rankin scores (mRS) değerleri kaydedildi.

**Bulgular:** Büyük arter aterosklerozu nedeniyle arka sirkülasyonda akut iskemik inme geçiren 80 (%8,36) hasta vardı. [Otuz (%37,5) hastada 9 kadın (%30), ortalama yaş 67,4±14,3 yıl] V1 darlığı vardı. Vasküler risk faktörleri öyküsü ve takip süresi boyunca mRS skorları açısından gruplar arasında fark gözlenmedi ( $p>0,05$ ). Lojistik regresyon analizinde V1 darlığı olan hastaların başvuru NIHSS skoru diğerlerine göre daha yüksekti ( $p=0,022$ ).

**Sonuç:** Merkezimizde büyük arter aterosklerozuna bağlı akut posterior sirkülasyon inmesi geçiren hastaların üçte birinden fazlasında vertebral arter çıkışında darlık vardı. Eşlik eden V1 darlığı olan hastalar nispeten daha şiddetli inme ile başvurmuştu.

**Anahtar Kelimeler:** Vertebral arter orjini, posterior dolaşım inmeleri, büyük arter aterosklerozu

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## Introduction

Prognosis and clinical management differ significantly among stroke subgroups according to anatomical localization and infarct mechanism in patients with acute ischemic stroke. One fifth of strokes and transient ischemic attacks (TIA) occur in the posterior circulation (PC) area (1). The most common causes of PC ischemia are large artery atherosclerosis (LAA), cardiac embolism and small vessel occlusion (2,3).

Anatomically, the vertebral artery is traditionally evaluated in four parts (V1-4). The first segment (V1) is the part from the origin of the vertebral artery to the foramen in the transverse processes of the fifth or sixth cervical vertebra. In the PC, atherosclerosis usually occurs at the origin of the vertebral artery. Autopsy and angiography studies have shown that up to 40% of patients with cardiovascular risk factors have stenosis or occlusion at the origin of the vertebral artery (2-4). Moreover, V1 segment stenosis of the vertebral artery accounts for almost 20% of PC strokes (2).

This study aimed to investigate the prevalence, demographic and clinical characteristics of ischemic stroke patients diagnosed with vertebral artery V1 stenosis due to LAA.

## Materials and Methods

The medical records of patients hospitalized with a diagnosis of acute ischemic stroke at the Ankara University Faculty of Medicine Neurology Department between January 2011 and May 2017 were reviewed. Age, gender, drug history, vascular risk factors [hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), atrial fibrillation (AF), coronary artery disease (CAD), congestive heart failure (CHF) and malignancy], history of stroke or TIA, history of myocardial infarction in the last month, recurrent stroke status, admission National Institutes of Health Stroke Scale (NIHSS) score, pre-stroke and follow-up modified Rankin scores (mRS), and laboratory results were recorded. The etiologic workup included cerebral and cervical vascular imaging studies [carotid Doppler ultrasonography, computerized tomography angiography, magnetic resonance angiography, or digital subtraction angiography (DSA)], transthoracic or transesophageal echocardiography, 24-hour cardiac rhythm monitoring, and laboratory tests for hypercoagulability and vasculitis. Automated Causative classification of stroke system was used to determine the etiological type of ischemic stroke (5). Patients with acute ischemic stroke in the PC due to LAA (PC infarction-LAA) were included in the study.

The Ankara University Faculty of Medicine Clinical Research Ethics Committee granted ethical approval for this study (date: 27.05.2019, approval no.: 10-772-19) and the study was

conducted in accordance with the ethical standards of the Declaration of Helsinki.

## Statistical Analysis

The analysis of the data was made in the SPSS for Windows 15 package program. Descriptive statistics are shown as mean  $\pm$  standard deviation for variables with normal distribution, and as median (minimum-maximum) for variables with non-normal distribution, and nominal variables are shown as number of cases and percentage (%). The significance of the difference between the two groups in terms of means was investigated with the t-test, and the significance of the difference in terms of median values was investigated with the Mann-Whitney U test. Nominal variables were evaluated with Pearson's chi-square or Fisher's exact test. Logistic regression analysis was performed for the risk factors affecting the dependent variable. Results for  $p < 0.05$  were considered statistically significant.

## Results

We reviewed the charts of 957 patients who were admitted with acute ischemic stroke between January 2011 and May 2017. A total of 80 (8.36%) patients had acute ischemic stroke in the PC due to LAA.

Thirty (37.5%) patients [27 females (90%), mean age  $67.4 \pm 14.3$  years] had symptomatic V1 stenosis and 15 (18.75%) patients [13 females (86.7%), mean age  $68.2 \pm 18.05$  years] of them had isolated V1 stenosis.

We compared the patients with acute ischemic stroke in the PC due to LAA with and without V1 stenosis. No between group differences in history of vascular risk factors and mRS in the follow-up period were observed ( $p > 0.05$ ). The admission NIHSS score was higher in patients with V1 stenosis ( $p = 0.049$ ). Serum C-reactive protein (CRP) levels were higher in patients without V1 stenosis, whereas serum magnesium levels were higher in patients with V1 stenosis. The demographic data, clinical and laboratory results are summarized in Table 1.

The distribution of arteries with significant stenosis in the PC is shown in Table 2.

In logistic regression analysis, admission NIHSS scores and serum magnesium levels were still significantly higher in patients with V1 stenosis ( $p < 0.05$ ) (Table 3). The mean admission NIHSS score  $\pm$  standard deviation in patients with coexisting V1 stenosis was  $11.5 \pm 11.7$ , while it was  $4.88 \pm 4.55$  in patients without V1 stenosis ( $p = 0.001$ ). The admission NIHSS score was significantly higher in patients with coexisting V1 stenosis in logistic regression analysis ( $p = 0.018$ ).

<b>Table 1: Demographic and clinical characteristics of patients with acute posterior circulation stroke due to large artery atherosclerosis</b>			
	<b>PC-LAA with V1 stenosis n=30</b>	<b>PC-LAA without V1stenosis n=50</b>	<b>p value</b>
Age, year, mean $\pm$ SD	67.4 $\pm$ 14.3	65.8 $\pm$ 13.1	0.38
<b>Sex, n (%)</b>			
- Female	9 (30)	24 (48)	0.088
- Male	21 (70)	26 (52)	
Stroke/TIA, n (%)	21 (70)/9(30)	28 (56)/22 (44)	0.157
<b>Medical history</b>			
- Hypertension, n (%)	22 (73.3)	40 (80)	0.336
- Diabetes mellitus, n (%)	9 (30)	21(42)	0.102
- Atrial fibrillation, n (%)	1 (3.3)	1 (2)	0.137
- Hyperlipidemia, n (%)	10 (33.3)	15 (30)	0.472
- CAD, n (%)	4 (13.3)	14 (28)	0.105
- CHF, n (%)	0 (0)	3 (6)	0.239
- Previous TIA history, n (%)	2 (6.7)	1 (2)	0.208
- Previous stroke history, n (%)	3 (10)	10 (20)	0.741
Admission NIHSS, mean $\pm$ SD	4.9 $\pm$ 4.5	4.9 $\pm$ 5.1	0.825
Median	5	3.5	<b>0.049</b>
(Min-Max)	(0-26)	(0-14)	
Hospital mortality, n (%)	4 (13.3)	8 (16)	0.105
Follow up mRS, Mean $\pm$ SD	1.79 $\pm$ 2.3	2.61 $\pm$ 2.3	0.515
Median	1	1	
(Min-Max)	(0-6)	(0-6)	
Recurrent stroke, n (%)	2 (6.7)	8 (16)	0.762
LDL, mg/dL, mean $\pm$ SD	112.38 $\pm$ 50.2	120.24 $\pm$ 49.6	0.967
CRP, mg/dL, mean $\pm$ SD	8.74 $\pm$ 5.92	16.97 $\pm$ 16.19	<b>0.017</b>
Mg mg/dL, mean $\pm$ SD	2.72 $\pm$ 3.58	2.02 $\pm$ 0.23	<b>0.019</b>

SD: Standard deviation, TIA: Transient ischemic attack, CAD: Coronary artery disease, CHF: Congestive heart failure, NIHSS: National Institutes of Health Stroke Scale, mRS: The modified Rankin scale, LDL: Low-density lipoprotein, CRP: C-reactive protein, Mg: Magnesium, Min-Max: Minimum-maximum, PC-LAA: Acute ischemic stroke in the posterior circulation due to large artery atherosclerosis

<b>Table 2: Distribution of arteries with significant stenosis in patients with acute ischemic stroke in the posterior circulation due to large artery atherosclerosis</b>			
	<b>PC-LAA with V1 stenosis n=30</b>	<b>PC-LAA without V1 stenosis n=50</b>	<b>p value</b>
Isolated V1 stenosis	15 (50%)	-	
V2 stenosis	14 (46.6%)	3 (6%)	<b>&lt;0.001</b>
V3 stenosis	12 (40%)	1 (2%)	<b>&lt;0.001</b>
V4 stenosis	14 (46.6%)	27 (54%)	0.5
BA stenosis	6 (20%)	8 (16%)	0.64
PCA stenosis	9 (30%)	12 (24%)	0.55

PC-LAA: Acute ischemic stroke in the posterior circulation due to large artery atherosclerosis, BA: Basiler artery, PCA: Posterior cerebral artery, V: Vertebral artery

<b>Table 3: Logistic regression analysis of PC-LAA with V1 stenosis</b>			
	<b>Beta</b>	<b>95%, confidence interval</b>	<b>p value</b>
Admission NIHSS, mean $\pm$ SD	0.006	0.001-0.012	<b>0.022</b>
Mg mg/dL, mean $\pm$ SD	0.051	0.036-0.066	<b>&lt;0.001</b>

SD: Standard deviation, PC-LAA: Acute ischemic stroke in the posterior circulation due to large artery atherosclerosis, NIHSS: National Institutes of Health Stroke Scale

## Discussion

Various vascular structures belonging to the intra- or extracranial as well as anterior or PC may be affected in ischemic stroke. Etiological, clinical and prognostic features may vary depending on the vascular structures affected by atherosclerotic stenosis (6). Investigating the subtypes of ischemic stroke according to the affected vessel and underlying causes may be beneficial in terms of better understanding the risk factors and clinical features of the disease.

In PC ischemic strokes, there may be different underlying causes, including cardio-embolism, LAA and small vessel disease (7). The rate of large vessel disease as the etiology of PC ischemic strokes varies among studies depending on the diagnostic criteria used and the diagnostic methods performed (8). Large artery disease was responsible for 32% of posterior cerebral artery territory infarcts in the New England Medical Center PC Registry (2).

LAA is defined as >50% stenosis or occlusion of a large cervical or cerebral artery (9). In the PC, atherosclerosis commonly occurs at the origin of the vertebral artery (7). However, atherosclerosis can also occur in the distal vertebral, basilar and posterior cerebral arteries. In this study, we focused on posterior system strokes due to LAA. We investigated whether there were differences in the demographic and clinical characteristics between patients with and without V1 stenosis.

Vertebral artery stenosis (24.8%) ranks second among extracranial stenosis after internal carotid stenosis (59.4%) (10). The rate of V1 stenosis among patients with acute ischemic stroke in the PC due to LAA was 37.5% in our registry. In a prospective cross-sectional study conducted in Iran examining 3703 acute stroke patients, vascular imaging with DSA was performed in 342 patients with large vessel disease, and stenosis was detected in the extracranial segment of the right and/or left vertebral artery in 32% of them (10). The researchers noted that these results were similar to the North American and European data. Similarly, in the Oxford Vascular Study, severe stenosis of the vertebral or basilar artery was responsible for 26% of patients with posterior system minor stroke or TIA (11).

Although male dominance was noted in patients with V1 stenosis (70% vs. 52%), no statistically significant difference was detected between the two groups in terms of age and gender. There was also no group difference in the history of vascular risk factors, including HT, AF, DM and HL as well as history of CAD and CHF. In this study, median admission NIHSS score was higher in patients with V1 stenosis ( $p=0.049$ ) suggesting that stroke may be clinically more severe in patients with coexisting V1 stenosis. The higher frequency of additional vertebrobasilar stenosis (V2, V3 segment, basilar artery and posterior cerebral

artery) in half of the patients with V1 segment stenosis included in the study may be related to the higher severity of stroke and high NIHSS scores in this group.

Signs and symptoms seen in PC infarcts include dizziness, vertigo, dysarthria, diplopia, dysphagia, nausea or vomiting, impaired consciousness, weakness, ataxia and nystagmus (2,3). However, in our study, we did not analyze which symptoms and findings were responsible for the higher NIHSS scores in patients with V1 stenosis. Although patients with V1 stenosis had a higher admission NIHSS score, there was no difference between the two groups in terms of hospital mortality rates and mRS scores or recurrent strokes at follow-up. In patients without V1 stenosis, presentation with TIA was more common (46% vs. 30%). However, the difference between the two groups in terms of stroke or TIA presentation was not significant.

Interestingly, serum CRP levels were higher and serum magnesium levels were lower in patients without V1 stenosis when compared with patients with V1 stenosis. Both higher CRP and lower magnesium (Mg) levels may be associated with an increased risk for atherosclerosis (12,13). On the other hand, both may point to poor prognosis in patients with stroke (14-16). A recent study revealed that although admission NIHSS scores were similar between patients with normal and high CRP levels, high CRP levels could predict poor prognosis (15). In our study, the admission NIHSS score was lower in patients without V1 stenosis, even though serum CRP levels were higher and serum magnesium levels were lower. The outcomes were similar in both groups despite these differences.

## Conclusion

This study is a retrospective study and included only a small number of patients from a single center; therefore, the results should be interpreted cautiously. However, we can conclude that PC stroke with coexisting V1 stenosis may be associated with stroke severity in the acute stage. The associations between localization of stenosis, stroke severity and serum biomarkers, including CRP and Mg levels need to be further investigated which may help to understand the pathogenesis and choose better prevention and treatment methods.

### Ethics

**Ethics Committee Approval:** The Ankara University Faculty of Medicine Clinical Research Ethics Committee granted ethical approval for this study (date: 27.05.2019, approval no.: 10-772-19).

**Informed Consent:** This study is a retrospective study and included only a small number of patients from a single center; therefore, the results should be interpreted cautiously. However, we can conclude that PC stroke with coexisting V1 stenosis may be associated with stroke severity in the acute stage.

## Authorship Contributions

Concept: S.E., C.T.I., M.H.S Design: S.E., C.T.I., M.H.S Data Collection and/or Processing: T.Ş., M.H.S., T.K., Z.Ö.A., E.Y., O.B., B.Ö., A.Y.Y., Z.Y., C.Ö., A.N., M.E., E.A., T.A., Analysis and/or Interpretation: M.E, Literature Search: S.E., C.T.I., Writing: S.E., C.T.I., M.H.S

**Conflict of Interest:** There is no potential conflict of interest to declare.

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