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RESEARCH ARTICLE **ÖZGÜN ARAŞTIRMA**

THE RELATIONSHIP OF COLLATERAL CIRCULATION IN THE BRAIN AND INTERNAL CAROTID ARTERIAL STENOSIS AND CLINICAL FACTORS: EVALUATION WITH DIGITAL SUBTRACTION ANGIOGRAPHY (DSA)

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ABSTRACT

INTRODUCTION: The preservation of flow through collaterals is known to reduce ischemic brain damage and has been shown to have prognostic value for outcomes patients with ischemic stroke. However, it is not known exactly what the factor affecting the collateral circulation is. It is thought that carotid artery stenosis causes collateral development by inducing arteriogenesis as a result of metabolic changes in the brain.In our study, we aimed to investigate the clinical factors that will cause the collateral circulation in the brain and the effect of carotid artery stenosis on collateral circulation.
METHODS: Patients who were diagnosed with stenosis by carotid vertebral arterial doopler USG and underwent digital subtraction angiography (DSA) between January 2020 and January 2022 were included in the study. The degree of carotid stenosis, sociodemographic and clinical data of the patients were recorded. Collateral structure in DSA was divided into four groups based on the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading grading. For statistical significance, the patient group was divided into two as good collateral (Grade 3-4) and poor collateral (Grade 1-2), and their clinical data were compared.
RESULTS: The mean age of 80 patients included in the study was 67.1±10.2 and 37.5% (n=30) were female.When grouped according to collateral grading, Grade 1: 38.75% (n=31), Grade 2: 35% (n=28), Grade 3: 21.25% (n=17), Grade 4: 6.25% (n=5) there were patients. When the age, diabetes, hypertension, LDL and clinical variables of patients with good collaterals and patients with bad collaterals, carotid arterial stenosis were analyzed between the two groups, no significant difference was found (p>0.05).
DISCUSSION AND CONCLUSION: In conclusion, collateral circulation is very important in stroke patients. In our study, it was found that carotid artery stenosis had no effect on collateral circulation, and no correlation was found between clinical variables and collateral circulation.This shows that there are different clinical factors affecting collateral development.
Keywords: Carotid artery, cerebrovascular disease, collateral circulation, digital subtraction angiography (DSA).

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BEYİNDEKİ KOLLATERAL DOLAŞIMIN İNTERNAL KAROTİT ARTER DARLIĞI VE KLİNİK FAKTÖRLER İLE İLİŞKİSİ: DİGİTAL SUBTRACTION ANGIOGRAPHY (DSA) İLE DEĞERLENDİRME

ÖZ

GİRİŞ ve AMAÇ: Kollateral dolaşımın iskemik inmenin hasarını azalttığı ve iskemik inmede prognostik önem taşıdığı bilinmektedir. Ancak kollateral dolaşımı etkileyen faktörün ne olduğu tam olarak bilinmemektedir. Karotis arter darlığının beyinde yarattığı metabolik değişiklikler sonucunda arteriogenezisi indükleyerek kollateral gelişimine neden olduğu düşünülmektedir. Biz de çalışmamızda beyinde kollateral gelişimine neden olacak klinik faktörleri ve karotis arter darlığının kollateral gelişimine etkisini araştırmayı amaçladık.

YÖNTEM ve GEREÇLER: Çalışmaya Ocak 2020-Ocak 2022 arasında renkli doopler ultrasonografi ile karotis arterlerinde darlık saptanan ve digital subtraction angiography (DSA) uygulanan hastalar dahil edildi. Hastaların karotis darlıklarının yüzdesi, sosyodemografik ve klinik verileri kaydedildi. DSA'da kollateral yapısı American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading derecelendirmesi örnek alınarak dört gruba ayrıldı. İstatistiksel anlamlılık için iyi kollateral (Grade 3-4) ve kötü kollateral (Grade 1-2) olmak üzere hasta grubu ikiye ayrılarak klinik verileri karşılaştırıldı.

BULGULAR: Çalışmaya dahil edilen 80 hastanın yaş ortalaması 67,1±10,2 olup, %37,5 (n=30)'i kadındı. Kollateral derecelendirmesine göre gruplandırıldığında Grade 1: %38,75 (n=31), Grade 2: %35 (n=28), Grade 3: %21,25 (n=17), Grade 4: %6,25 (n=5) hasta vardı. İyi kollateralle sahip hastalar ve kötü kollaterale sahip hastaların yaş, diyabet, hipertansiyon, LDL düzeyleri, trigliserit düzeyleri, klinik değişkenleri ve karotis arter darlıkları iki grup arasında analiz edildiğinde anlamlı farklılık saptanmamıştır (p>0,05).

TARTIŞMA ve SONUÇ: Sonuç olarak inme hastalarında kollateral dolaşım oldukça önemlidir. Bizim çalışmamızda karotis arter darlığının kollateral dolaşıma etkisinin olmadığı saptanmıştır, klinik değişkenler ile kollateral gelişimi arasında korelasyon saptanmamıştır. Bu da kollateral gelişimini etkileyen farklı klinik faktörlerin olduğunu göstermektedir..

Anahtar Sözcükler: Karotis arter, serebrovasküler hastalık, kollateral dolaşım, digital subtraction angiography (DSA).

INTRODUCTION

Cerebrovascular diseases are a leading cause of death and disability in adults worldwide (1). In patients with obstructive cerebrovascular disease, collateral circulation is essential for maintaining cerebral perfusion, metabolism, and function. Numerous studies have demonstrated the importance of adequate hemodynamic balance via the collaterals in patients with cerebral artery stenosis and the association of collateral flow with infarct volume in predicting stroke outcome (2–5). Carotid stenosis is thought to cause the development of collaterals due to decreased cerebral blood flow or hypercapnia induced by decreased cerebral blood flow (6). Therefore, patients with carotid stenosis may not show signs of worsening cerebral hemodynamics because collateral circulation compensates for the decrease in cerebral blood flow (7). Digital subtraction angiography (DSA) is considered the gold standard for assessing collateral circulation. Determining the factors affecting collateral circulation in the brain is essential for determining precautions that can be taken in patients with ischemic stroke. It is believed that half of the cerebrovascular diseases can be reduced by measures taken before acute ischemic stroke (8). These measures are crucial because they increase the individual's quality of life and significantly reduce the cost to society.

The clinical factor affecting collateral blood flow to the brain is still unknown. There are few studies on this topic in the literature. In our study, we investigated the relationship between collateral circulation in the brain of patients who underwent DSA, clinical factors, and carotid artery stenosis.

METHODS

Our study was designed as a retrospective, observational, cross-sectional study conducted in line with the ethical standards of the Declaration of Helsinki . An approval was obtained from the Ethics Committee of Adana City Training and Research Hospital for our study (Date: 20.05.2020, Number: 870). Color Doppler ultrasound examination of the vertebral carotid artery (CDUSGVCA) was planned due to ischemic stroke, transient ischemic attack, or vertigo and evaluated in our outpatient clinic in 2020-2021, and patients with stenosis of the carotid artery in the

CDUSGVCA were included in the study. Exclusion criteria were determined as neurodegenerative diseases, diseases other than ischemic stroke leading to neurological deficits, mental retardation, presence of conditions preventing imaging, patients with non-atherosclerotic (arterial dissection or cardioembolic causes) large vessel occlusions, patients with heart failure, patients not wishing to undergo a DSA procedure and patients not willing to participate in the study.

Patients: The sociodemographic data and concomitant diseases of patients enrolled in the study were recorded. Routine blood tests, CDUSGVCA, electrocardiography, cardiac rhythm Holter ECGs, and echocardiograms were performed for at least 24 hours, and the results were recorded. A DSA procedure was performed on all patients. After diffusion-weighted (DWI) MRI examination, patients were divided into three groups: Patients without MRI lesions, those with lacunar infarcts, and those with major hemispheric infarcts. Depending on the stenosis of the internal carotid artery (C1 cervical segment) and the vertebral artery (V2 segment), patients were divided into those with right-sided, left-sided, or bilateral stenosis of the carotid artery and those with more than 50% stenosis according to the degree of stenosis of the carotid artery, and 50% divided into two groups as those with less than stenosis. The vertebral artery was divided into two groups: those with right-sided, left-sided, bilateral vertebral artery stenosis, and those with more than 50% stenosis and those with less than 50% according to the degree of vertebral artery stenosis.

Evaluation of collaterals: Diagnostic angiographies were performed in all patients with a biplane angiography device. The carotid and vertebrobasilar systems were examined at the level of the neck and intracranially. Each vascular angiogram was obtained in 2 projections (anterior and lateral projections) with the same amount of contrast agent and injection speed.

There is no adequate and uniform grading scale for angiographic collaterals in the literature. In our study, we used the American Society of Interventional and Therapeutic Neuroradiology /Society of Interventional Radiology (ASITN/SIR) collateral flow grading system as an example of collateral classification (9). However, because our patients were not patients with acute ischemic stroke, we determined the classification as follows: Grade 0 (no hemispheric collateral circulation), 1 (slow hemispheric collateral circulation), 2 (rapid hemispheric collateral circulation), 3 (monitoring of complete hemispheric blood supply in the late venous phase), and 4 (complete and rapid collateral flow). Grading was performed by experienced interventional neurology specialists (Z.A.), and grading was blinded to patients' clinical information.

Statistical analysis: IBM SPSS Statistical program version 20.0 was used. Categorical measurements were evaluated as numbers and percentages, numerical measurements were evaluated as mean and standard deviation (median and minimum-maximum, if necessary), and descriptive statistics were used. The distribution of data was assessed using the Shapiro-Wilk test. For comparisons between groups, the simple independent T-test was used for normally distributed data, and the Mann-Whitney U test was used for nonnormally distributed data. The statistical significance level was set at 0.05 for all tests.

RESULTS

The mean age of the 80 patients included in the study was 67.1±10.2 (age range=40-89 years) , and %37.50 (n=30) were female. 32.50% (n=26) of the patients were smokers. 38.75% (n=31) of patients had diabetes mellitus and 72.5% (n=58) had hypertension. The most common complaints of patients were dizziness (38.75%), sensory disturbances (32.5%), and speech disorders (21.75%). Hypoesthesia (30%), speech disorders (19%), and hemiparesis (12%) were the most common neurological examination findings. Mean LDL cholesterol levels in all patients were 123.9±35.2 mg/dL, and mean triglyceride levels were 187.5±130.2 mg/dL. When grouped by collateral grading, the number of patients by grades is as follows: Grade 1: %38.75 (n=31) patients, Grade 2: %35 (n=28) patients, Grade 3: %21.25 (n=17) patients, and Grade 4: %5 (n=4) patients (Table 1).

When patients were divided into two groups- patients with good collaterals (grades 3 and 4) and patients with poor collaterals (grades 1 and 2)- no significant difference was found between the two groups when age, diabetes, hypertension, LDL cholesterol levels, clinical variables, and carotid

stenosis were analyzed (p>0.05). Although the patients with more than 50% vertebral artery stenosis were more in the group with poor collaterals, no significant difference was found between the two groups (p=1.00) (Table 2).

Table 1. Sociodemographic and clinical data of all patients.

	All patients (n=80)
Age	67,1±10,2
Gender	
Female	%37,5 (n=30)
Male	%62,5 (n=50)
Smoking	
Yes	%32,5 (n=26)
No	%67,5 (n=54)
Diabetes	
Yes	%38,8 (n=31)
No	%41,2(n=49)
Hypertension	
Yes	%72,5 (n=58)
No	%27,5 (n=22)
LDL cholesterol (mg/dL)	123.9±35.2
Triglyceride (mg/dL)	187.5±130.2
Collateral grading	
Garade 1	%38,75 (n=31)
Garade 2	%35 (n=28)
Garade 3	%21,25 (n=17)
Garade 4	%5 (n=4)

Table 2. Sociodemographic and clinical data and carotid artery stenosis status of patients grouped according to collateral grading.

	Good collateral Grade 3-4, n =21	Poor collateral Grade 1-2, n =59	P
Age (year±SD)	67,61±9,29	66,86±10,57	1.00*
Gender			
Female	43% (n=9)	36% (n=21)	0.55*
Male	57% (n=12)	64% (n=38)	
Smoking			
Yes	33,3% (n=7)	33,3% (n=19)	0.92*
No	66,7% (n=14)	66,7% (n=36)	
Diabetes			
Yes	52,4% (n=11)	36,4% (n=20)	0.20*
No	47,6% (n=10)	63,6% (n=35)	
Hypertension			
Yes	71,4% (n=15)	78,2% (n=43)	0.63*
No	28,6% (n=6)	21,8% (n=12)	
LDL cholesterol (Mean±SD)	112,04±34,90	128,08±34,59	0.78*
Triglyceride (Mean±SD)	173,76±63,59	192,42±146,98	0.99*
Carotid artery stenosis>%50	75% (n=16)	76,28% (n=45)	0.99*
≤%50	25% (n=5)	23,72% (n=14)	
Bilateral carotid artery stenosis	29% (n=6)	12% (n=7)	0.075*
Vertebral artery stenosis > %50	1% (n=2)	14% (n=8)	1.00**

SD: Standart deviasyon, *Pearson chi square, **Fisher Exact Test's.

DISCUSSION AND CONCLUSION

The status of the collateral circulation can give the clinician an indication of the progression of the potential ischemic event that the patient will experience in the future. Carotid stenosis stimulates angiogenesis by decreasing cerebral blood flow and causing hypoxia or hypercapnia induced by decreased cerebral blood flow (10). This suggests that carotid stenosis is associated with good collateral development in the brain. In our study investigating the relationship between brain collateral development in carotid stenosis and clinical variables affecting good collateral development, no clinical factor was found to be associated with good collateral development. Contrary to our hypothesis, good collateral development was not found in our patients with carotid stenosis. Since we determined carotid artery stenosis above 50% in order to obtain meaningful analysis, we can interpret this result as the result of patients who did not reach the stenosis that could develop hemodynamic changes. The fact that our patients were composed of patients with symptomatic and asymptomatic carotid stenosis may also have influenced this result. Although studies (11,12) report an association between symptomatic carotid stenosis and the development of collaterals, there is no study including the asymptomatic group as in our study. When we evaluate similar studies in the literature, ASITN/SIR collateral classification was used in a study that analyzed the effect of different blood pressure parameters on collateral circulation in patients with carotid stenosis and acute ischemic stroke. Patients were divided into good and bad collaterals, and hypertension was reported to be significantly different between the two groups (13). The main difference between this study and our study is that all patients were evaluated in the first 72 hours after acute ischemic stroke, and the entire patient group consisted of patients with unilateral carotid stenosis.

In a study evaluating 42 patients with symptomatic carotid stenosis, collaterals in the Willis polygon, leptomeningeal, and ophthalmic collaterals were assessed. They reported that any ophthalmic or leptomeningeal collaterals were associated with increased cerebral metabolism and oxygen extraction fraction, and this

association was particularly noted in striatocapsular infarcts (2). In a study examining patients with severe carotid stenosis (stenosis >90%), the patients' carotid arteries were examined with MR angiography and CDUSGVCA, and it was reported that the condition, which has a positive effect on brain hemodynamics, was associated with the development of collaterals in the group with unilateral carotid stenosis (12).

Our study had several limitations. First, based on the subgroup analyses, we could have obtained more meaningful results if the number of patients had been larger. Because there is insufficient consensus in the literature on the classification of collaterals, we followed the ASITN/SIR collateral classification in our study, but this classification is used for acute ischemic strokes. In our study, some patients had an ischemic stroke, and some did not. We could not evaluate patients according to the disease duration in the analysis because we lacked information on the duration of concomitant diseases. The small number of patients with advanced carotid stenosis and the absence of patients with intracranial artery stenosis were also among the limitations of our study. If the study had been planned as a long-term study, we could have analyzed the change in collateral grades as a function of carotid stenosis and obtained more meaningful results.

As a conclusion, in our study, no contribution of carotid stenosis to good collateral development was found, and no significant relationship was found between clinical variables and collateral development. The results of our study indicate that more multifactorial, longer-term studies are needed to determine which factor determines collateral development and in people with which characteristics it develops better. However, our study is significant as it will shed light on these studies.

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Ethics

Ethics Committee Approval: The study was approved by Clinical Stıdies Ethics Committee of Adana City Training and Research Hospital (Date: 20.05.2020, Number: 870).

Informed Consent: The authors declared that informed consent was obtained from the patients.

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