Smyrna Tıp Dergisi ***Araştırma Makalesi***

The Analysis of Virchow-Robin Spaces using Magnetic Resonance Imaging in Women Patients with Migraine
Kadın Migren Hastalarında Manyetik Rezonans Görüntüleme ile Virchow-Robin Boşluklarının Analizi

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Summary
Aim: Migraine is a chronic condition characterized by recurrent moderate or severe headache, mostly in the autonomous nerve system. Virchow-Robin spaces (VRS) are perivascular areas in laid with pia matter surrounding small arteries and arterioles perforating the brain surface and invading the tissue. This study looks into the VRS of migraine patients through magnetic resonance imaging (MRI) to investigate the neurovascular basis of migraine.
Material and Method: Patient group consist of 83 female who were diagnosed with migraine and had been taken MRI; and control group consist of 87 female subjects were formed. Whether there were correlations between migraine and number of VRS at the hippocampus, white matter and basal ganglia was investigated.
Results: In all three levels, there were statistically significant differences between the patient and control groups, favoring the patient group. The correlation of the white matter to the basal ganglia and hippocampus was very weak, and the correlation of the basal ganglia to hippocampus was weak.
Conclusion: Statistically significantly higher results in the patients group with migraine compared the controls in all three levels may provide guidance in diagnosing the disease and/or confirming the diagnosis.
Key Words: Magnetic resonance imaging, migraine, Virchow-Robin spaces, women

Özet
Amaç: Migren çoğunlukla otonom sinir sisteminde görülen tekrarlayıcı, orta şiddette veya şiddetli baş ağrısıyla karakterize kronik bir hastalıktır. Virchow-Robin boşlukları (VRB) beynin yüzeyini delerek dokunun içine doğru ilerleyen küçük arter ve arteriyollerin etrafını saran pia ile döşeli perivasküler alanlardır. Bu çalışmada migren hastalığının nörovasküler temelini araştırmak amacıyla migren hastalarındaki VRB, manyetik rezonans görüntüleme (MRG) üzerinden incelenmektedir.
Gereç ve Yöntem: MRG'si çekilen ve migren tanısı almış 83 kadından hasta grubu ve 87 kadın ile kontrol grubu oluşturuldu. Beyaz cevher, bazal ganglionlar ve hippocampus düzeyindeki VRB sayısı ile migren hastalığı arasında ilişki olup olmadığı araştırıldı.
Bulgular: Her üç seviyede de hasta ve kontrol grubu arasında hasta grubunu destekleyen istatistiksel olarak anlamlı farklılıklar vardı. Beyaz cevherin bazal ganglionlar ve hippocampus ile korelasyonu çok zayıftı ve bazal ganglionların, hipokampus ile korelasyonu zayıftı.
Sonuç: Migren tanılı hastaların kontrol grubuna göre her üç seviyede istatistiksel olarak anlamlı şekilde yüksek çıkması, hastalığın tanısını koymak ve/veya doğrulamak için bir yol gösterici olabilir.
Anahtar Kelimeler: Manyetik rezonans görüntüleme, migren, Virchow-Robin boşlukları, kadın

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Introduction

Migraine is a condition characterized by recurrent, moderate to severe headache mostly in the autonomous nervous system. It affects about 10 to 15% of the general population and is more prevalent in women than in men (1,2,3). It is considered to be a neurovascular disorder although its exact mechanism is not known. The basis of this notion is the close relation between vascular activity and neural function (4).

Virchow-Robin spaces (VRS) are defined as enlarged perivascular spaces located at the entrance of small vessels from the subarachnoid space to the brain parenchyma. VRS are perivascular areas covered by pia mater surrounding the small arteries and arterioles which perforate the brain surface and advance into the tissue (5). They can be seen in all age groups and are usually asymptomatic and are detected incidentally. The most common symptom is headache (6). They can be unilateral and symmetric or asymmetric (7,8,9). Studies are being performed to investigate the relevance of VRS in several conditions and in normal subjects. Pathologic dilatation of VRS (dVRS) is associated with age, diabetes mellitus, hypercholesterolemia, incidental white matter lesion, smoking, hypertension and arteriolar abnormalities related with other vascular risk factors (5,10,11). Histopathological studies link dVRS to cases of inflammatory brain disease (9). Migraine is considered an independent vascular risk factor in young women (12).

The present study examined dVRS of female patients with migraine using MRI to investigate the neurovascular basis of migraine.

Material and Methods

This study was approved by the Clinical Research Ethics Committee of the Dumlupınar University (14.04.2016/2016-5-4).
Patient group including 83 female patients, aged 18 to 60 years, who had presented to the Neurology outpatient clinic of the Afyon Kocatepe University, Faculty of Medicine (Currently Afyonkahisar Health Sciences University) between January 2010 and April 2016 and had been taken MRI which were included in the study. Control group including 87 females, aged 18 to 60 years, who were not diagnosed with migraine or did not suffer from headache complaint or didn't have any neurological findings and had normal findings with MRI which obtained randomly and retrospectively was formed for this study.

T2 sequence and FLAIR were used for analyses. Signal intensity of dVRS has the same characteristics as cerebrospinal fluid that appear hypointense with T2 sequence. FLAIR differentiates VRS from lesions by suppressing cerebrospinal fluid. Whether there was a relationship between migraine and the VRS count in the hippocampus, brain white matter and the basal ganglia was investigated.

When all sections of the white matter were measured; (VRS are indicated by black arrows in all figures) dVRS count below 10 were considered as grade 1, dVRS count above 10 were considered as grade 2. Also, when the section that contained the most dVRS were examined; dVRS count below 10 were considered as grade 2. When the section containing the maximum dVRS were examined, dVRS count above 10 were considered as grade 3 (Figure 1).

For the basal ganglia; dVRS count below 5 were considered grade 1, dVRS count between 5 and 10 were considered grade 2, dVRS count above 10 were considered grade 3 (Figure 2).

For hippocampus, same as in basal ganglia; dVRS count below 5 were considered grade 1, dVRS count between 5 and 10 were considered grade 2, dVRS count above 10 were considered grade 3 (Figure 3).

Statistical analysis
Descriptive statistics were used to evaluate the data. Spearman's correlation coefficient was used to evaluate the correlation of dVRS values in white matter, basal ganglia and hippocampus level. Chi-Square test was used to compare percent distributions between patient and control groups. SPSS 20.0 (Statistical Package for the Social Science, version 20.0). The results were evaluated as 95% confidence interval and $p<0.05$.

Figure 1. *Grading the count of dVRS in level of white matter in MRI sections*

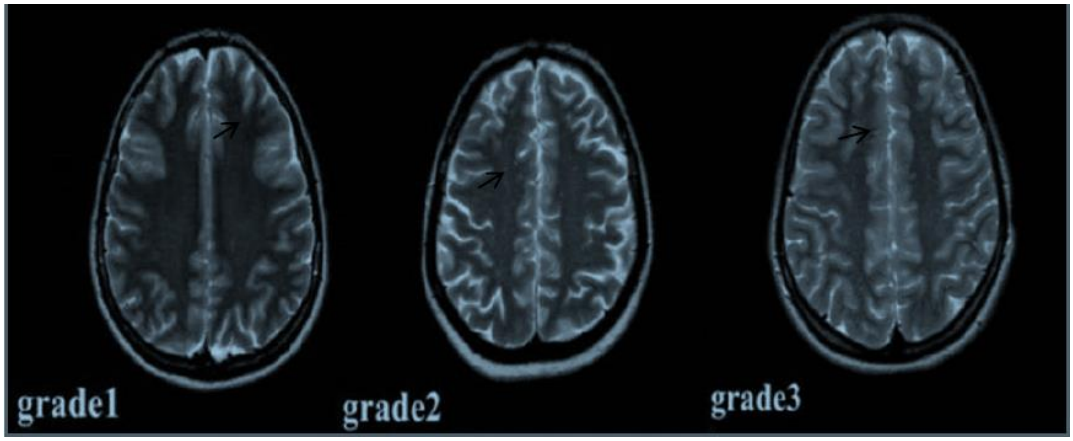


Figure 2. *Grading the count of dVRS in level of basal ganglia in MRI sections*

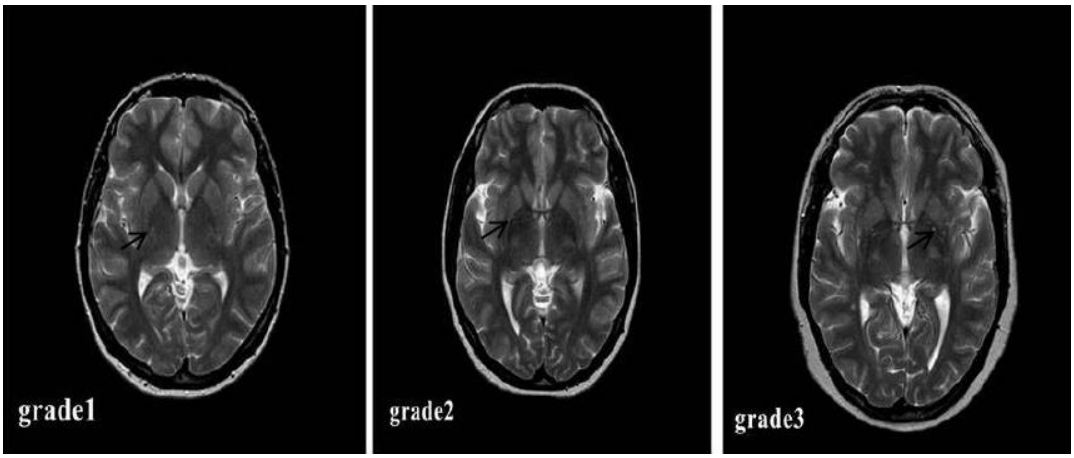
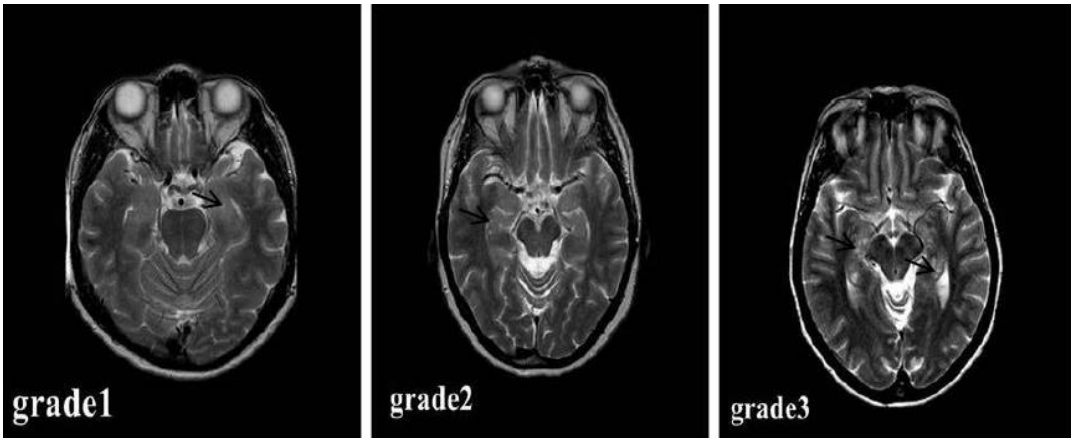


Figure 3*. Grading the count of dVRS in level of hippocampus in MRI sections*



Results

The mean age of the patients in the study was 39.56±10.7 year and in the control group was 40.12±13. There was no statistically significant difference between the mean age of the two groups (p:0.97).

For the white matter, 37% of the patient group was grade 1; 50% were grade 2 and 76% were grade 3. In the control group, 63% were grade 1; 50% were grade 2 and 28% were grade 3.

For the basal ganglia, 26% of the patient group was grade 1; 42% were grade 2 and the rest were grade 3. In the control group, 74% were grade 1; 43% were grade 2 and the rest were grade 3.

For the hippocampus, 34% of the patient group was grade 1; 47% were grade 2 and the rest were grade 3. In the control group, 66% were grade 1; 43% were grade 2 and the rest were grade 3. Significant differences between the patient and control groups, favoring the patient group, were found in all three parameters (Table 1).

The correlation of the white matter with basal ganglia (r:0.163 p:0.34) and hippocampus (r:0.215 p:0.005) was very weak, and the correlation of the basal ganglia with hippocampus (r:0.309 p:0.00) was weak (Table 2).

Table 1. *Dilated VRS frequencies in different parts of the brain.*

	Patient n (%)	**Control n (%)**	**X^2**	**P**
White Matter				
1	26 (37%)	45 (63%)	12.756	P=0.002
2	35 (50%)	35 (50%)		
3	22 (76%)	7 (24%)		
Basal Ganglia				
1	18 (26%)	52 (74%)		
2	42 (57%)	32 (43%)	33.1745	P=0.001
3	23 (88%)	3 (12%)		
Hippocampus				
1	26 (34%)	51 (66%)		
2	47 (57%)	35 (43%)	17.152	P=0.001
3	10 (91%)	1 (9%)		

Table 2. *Correlation between different parts of the brain*

Spearman's rho		**White Matter**	**Basal ganglia**	**Hippocampus**
White Matter	**Correlation Coefficient**	1.000		
	p	-		
Basal ganglia	**Correlation Coefficient**	.163	1.000	
	p	.034	-	
Hippocampus	**Correlation Coefficient**	.215	.309	1.000
	p	.005	.000	-

Discussion

VRS are small canals that are covered with pia, filled with fluid and contain small vessels in the subarachnoid intracerebral layer. If the short axis of VRS are longer than 2 mm or, according to some authors, 3 mm, they are defined as dilated (9,13,14). When VRS observed microscopically, enlarges, it can also be observed clearly with MRI (5). In this study, it was considered that VRS were visible with MRI as dVRS.

Even in the normal brain, some VRS are seen in the substantia innominata of the anterior commissure. The other locations that it is frequently seen are the midbrain, deep white matter and subinsular cortex. It is seen in the basal ganglia in more than 60% of the subjects (5,15). In this study the numbers of dVRS were measured from the transverse sections of the MRI that involve the white matter, basal ganglia and hippocampus.

dVRS are associated with age, dementia and incidental white matter lesions (10,13). Many mechanisms including impaired permeability on arterial surface, cerebrospinal fluid disorders, spiral extensions of blood vessel, ex vacuum phenomenon brain atrophy or demyelination have been suggested as the cause of dVRS. VRS are involved in the homeostasis of interstitial fluids and the immune system regulation of the central nervous system, and these are the very reasons causing altered values and dimensions in inflammatory conditions such as multiple sclerosis (9). The reason for studying VRS in migraine patients was that; it was aimed to suggest increased VRS count, seen in migraine, defined as neurogenic inflammation (vasodilation and vascular permeability increased), as an option in establishing or confirming diagnosis.

In the study, the reason for using only female patients was due to insufficient images of male migraine patients in the hospital. It was also aimed to exclude the effect of undesirable gender factors by working with single sex.

There are articles in the literature investigating dVRS in different conditions and through different mechanisms. In a study with multiple sclerosis patients, VRS were shown to be a necessary pathway for drainage between lenticulostriate arteries and the lymphatic system, and it was shown that blood-brain barrier abnormalities and inflammation resulting from a disturbance in this barrier laid the groundwork for dVRS (9). In a study with atherosclerosis patients, local necrotizing angiitis causing increased permeability of the arterial walls cause dilatation of VRS as a result of slow leakage of interstitial fluid from the intercellular region to the pial space (16).

It was found that, highly significant relationship between internal carotid artery narrowness and VRS was underlain by the role of hypoperfusion resulting from the narrowness (17). In addition, several blood vessel abnormalities and vascular risk factors were found to lay the groundwork for dilatation in patients with myotonic dystrophy, who frequently present with VRS (18). Similar to this study, study by Machado et al found that VRS were significantly different between migraine patients and control group subjects. This difference was attributed to the filling of inflammatory cells as a result of immune stimulation to CNS-containing VRS (19).

This study may provide guidance to clinicians in diagnosing migraine. It was also believed that positive results may be obtained in migraine treatment if the link between migraine and VRS is supported by other studies.

Conclusion

The fact that the patients with migraine had statistically significantly higher values in all three parameters compared to the control group may provide guidance in establishing and/or confirming the diagnosis. In addition, these findings will provide background and support to other studies on the mechanism of occurrence and treatment of the disease.

Conflict of Interest: There is no conflict of interest. All authors have read and approved of the manuscript being submitted.

This study was presented orally with the title “Analysis of Virchow-Robin Spaces in female migraine patients with MRI” at the 17th International Participated National Anatomy Congress held in Eskişehir on September 5-9, 2016.

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