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Does Migraine Attack Cause Cognitive Impairment and White Matter Lesions?

Migren Atağı Kognitif Bozukluğa ve Beyaz Cevher Lezyonlarına Neden Olur mu?

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Abstract

Objectives: The aim of the study is to better assess the association between cognitive impairment during migraine attacks and white matter lesions, in conjunction with the relation of anatomical localizations in migraineurs with white matter lesions.

Materials and Methods: Study questionnaires were filled during routine medical visitations. In the context of cognitive functions evaluation, the standardized mini-mental status examination was utilized. Patient demographics and migraine characteristics were carefully recorded. The Migraine Disability Assessment Score, the Headache Impact Test, and the Mig-SCog questionnaires were used to test the ultimate severity of the migraine. Brain magnetic resonance imaging (MRI) scans were evaluated with the benefit of hindsight; for detecting and scoring white matter lesions, the Scheltens scoring system was brought into play. Depending upon perceived presence or absence of hyperintense lesions in brain MRI, the patients were divided into a pair of specific subsections.

Results: One hundred twenty female (86%) and 19 (14%) male patients were evaluated, respectively. Statistically significant differences were uncovered between the two groupings related to their intrinsic demographics, age, and educational levels. Patients demonstrating normal MRI had shorter disease duration when juxtaposed with the grouping possessed of white matter lesions. As per Mig-SCog questionnaires, cognitive complaints during migraine attacks were statistically significant within the tranche with white matter lesions. Interestingly, longer durations of migraine and higher Mig-SCog scores were correlated with deep white matter hyperintensities.

Conclusion: During instances of migraine attack, the underlying migraine pathophysiological process can significantly influence cognitive impairment and noticeable alterations to white matter.

Key Words: Migraine, Cognition, White Matter

Öz

Amaç: Çalışmanın amacı migren atağı sırasındaki kognitif bozulma ile beyaz cevher lezyonları arasındaki ilişkinin yanı sıra migrenin, beyaz cevher lezyonlarının anatomik lokalizasyonları ile ilişkisini ortaya koymaktır.

Gereç ve Yöntem: Çalışma anketleri rutin muayene sırasında doldurduldu. Kognitif işlevleri değerlendirilmek için standartize mini-mental durum muayenesinden yararlanıldı. Hastaların demografik özellikleri ve migren özellikleri kaydedildi. Migrenin şiddetini test etmek için Migraine Disability Assessment Score, Headache Impact Test, ve Mig-Scog anketleri kullanıldı. Beyin manyetik rezonans görüntülemeleri (MRG) değerlendirildi; Beyaz cevher lezyonlarının tespiti ve skorlanması için Scheltens skorlama sistemi kullanıldı. Beyin MRG'sinde hiperintens lezyonların varlığına veya yokluğuna bağlı olarak hastalar iki alt gruba ayrıldı.

Bulgular: Yüz yirmi kadın (%86) ve 19 (%14) erkek hasta değerlendirildi. İki grup arasında demografik özellikler, yaş ve eğitim düzeylerine ilişkin istatistiksel olarak anlamlı farklılıklar ortaya çıktı. MRG'i normal olan hastaların hastalık süresi, beyaz cevher lezyonlarının olduğu grupla karşılaştırıldığında daha kısaydı. Mig-SCog anketlerine göre migren atakları sırasındaki bilişsel yakınmalar beyaz cevher lezyonları olan grupta istatistiksel olarak anlamlıydı. Migren süreleri daha uzun olan ve daha yüksek Mig-SCog skorları, derin beyaz cevher hiperintensiteleri ile koreleydi.

Sonuç: Migren atakları sırasında, altında yatan patofizyolojik süreç kognitif bozulmaya ve beyaz cevher değişikliklerine neden olabilir.

Anahtar Kelimeler: Migren, Kognisyon, Beyaz Cevher

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Introduction

Migraine is a chronic neurological disorder characterized by episodes of headaches and reversible neurological or systemic symptoms. It affects millions of productive-age people worldwide (1). In studies conducted in the United States of America, its annual prevalence was 14.6% (2), and in Turkey, it was reported as 16.4% (3,4). Migraine is also ranked sixth among the diseases that cause the most disability worldwide (5). Increased rates of migraine-related disability, which often affects young adults, leads to a loss of workforce and an increased financial burden on healthcare systems (6,7). Besides the core symptoms of the migraine attack (pulsatile pain, nausea-vomiting, photophobia, and phonophobia), cognitive impairment is also a significant cause of disability.

During prodromal and migraine attack periods, one in three patients suffers subjective cognitive complaints such as difficulty finding words and reading, impaired concentration, difficulty maintaining attention, and delayed processing time. Studies show that patients with subjective complaints during a migraine attack have impaired neuropsychological assessments. Therefore, treatments for headaches during an attack may not be beneficial in treating cognitive complaints (8). Functional imaging studies during a migraine attack revealed increased activity in the cingulate cortex, insula, prefrontal cortex, and temporal areas, which regulate executive functions (9). Although studies have shown that chronic migraine patients have decreased cognitive performance, longitudinal research has not discovered sufficient evidence that migraine is a risk factor for cognitive impairment (10,11).

Migraine patients have a two to four times higher incidence of white matter hyperintensities, defined as white matter lesions (WMLs), than control patients (12,13). These lesions can be detected in various localizations, such as periventricular, deep-subcortical, basal ganglia, and infratentorial hyperintensities, on magnetic resonance imaging (MRI) utilizing T2 and fluid-attenuated inversion recovery (FLAIR) sequences. Although periventricular WMLs have been attributed to an increased risk of stroke, dementia, and cognitive impairment in elderly non-migraineurs, a link between the detection of WMLs and cognitive decline in migraineurs has not been identified (14).

This study aims firstly to reveal the possible relationship between subjective cognitive involvement during migraine attacks and WMLs, in which similar mechanisms are identified in developmental mechanisms, and secondly to determine the relationship of anatomical localizations in migraineurs with WMLs.

Materials and Methods

Researchers performed the study's questionnaires face-to-face with patients during their routine visits to the neurology outpatient clinic. Inclusion criteria for the study were as follows:

(1) Patients should be between 18 and 50 years old;

(2) Patients have at least five years of education;

(3) Patients do not have a disease that may cause white matter hyperintensities (diabetes, hypertension, vasculitis, heart disease, rheumatic diseases and a history of head trauma, a history of drug and alcohol abuse);

(4) Patients without cognitive impairment (mini-mental state examination score of 24 and above); and

(5) Patients have had a brain MRI performed within the last year.

The standardized mini-mental status examination (sMMSE), whose validity and reliability studies were conducted in Turkey, was also used to evaluate the general cognitive performance of the participants (15). The forms applied to the participants questioned demographic characteristics (age, gender, body mass index, medical and family history, usage of drugs, habits of smoking and alcohol) and migraine characteristics (duration of the disease, frequency, severity according to visual analog scale, accompanying findings, presence of aura, medical treatments).

Migraine was evaluated using the International Classification of Headache Disorders criteria, 3rd edition (ICHD-3), by professional neurologists (16).

In addition, the Migraine Disability Assessment Score (MIDAS) questionnaire (3,17), the headache impact test (HIT-6) questionnaire (18,19), and the Mig-SCog questionnaire (7,20), which are also Turkish validity and reliability studies, were applied to the participants. MIDAS is a questionnaire that assesses the impact of headaches in the previous three months by asking five questions about work and school, housework, spending time with family, and social status. It was utilized in our study to evaluate migraine-related disability (17). The questionnaire determines the MIDAS total score for the number of days the specified activities cannot be performed. There are four disability levels: no disability (0-5), mild disability (6-10), moderate disability (11-20), and severe disability (>21) (12).

The HIT-6 test is a 5-point Likert scale questionnaire that assesses the impact of headaches on quality of life (6=never, 8=seldom, 10=occasionally, 11=very often, 13=always). The final score is determined from the summation of six items, with a range between 36 and 78, with higher scores indicating greater impact, as categorized into four groups including scores ≤49 (little or no impact), scores 50-55 (some impact), scores 56-59 (substantial impact) and scores ≥60 (severe impact) (18,19).

Mig-SCog is an accessible, intelligible, and reliable test developed by Gil-Gouveia et al. (20) in 2011, subjectively questioning patients' cognitive decline during migraine attacks. It is a 3-point Likert-type scale with a total score ranging from 0 to 18. The first three questions are about attention, processing speed, and orientation; questions four and five deal with planning and attention; questions six to nine deal with language and naming (7,20).

Following the patients' approval for the study, their brain MRI scans were assessed retrospectively. The same methods were used to acquire whole-brain MRI scans for all subjects and utilized a 3T MRI scanner (Signa VH/I General Electric). Axial T2-weighted, axial FLAIR, and axial T1-weighted images were all included in the scans. The slices were 5 mm thick, with a 1 mm gap between them, and no intravenous contrast was used.

MRI scans were analyzed retrospectively by a single specialist who did not know the clinical characteristics of the patients. Scheltens scoring system, a semiquantitative visual rating system, was used to detect and score WMLs. This scoring system evaluates hyperintense lesions with scores varying according to the diameters of the lesions in four different anatomical regions. The areas described are: periventricular hyperintensities (0-6); deep white matter hyperintensities (0-24); basal ganglia hyperintensities (0-30); and infratentorial hyperintensities (0-30) (17).

The simultaneous detection of hyperintense lesions on T2-weighted and FLAIR sequences was evaluated. Furthermore, lacunar infarcts (well-defined areas of >2 mm with a hypointense lesion and a hyperintense rim on FLAIR images), perivascular spaces, and ischemic infarct areas with previous sequelae were not scored. The participants were divided into two groups based on the presence of hyperintense lesions in brain MRI. The two groups were then compared in terms of demographic and migraine-related characteristics.

Statistical Analysis

All statistical analyses in the study were carried out using the IBM SPSS statistic program version 23.0 (Chicago, IL, USA). The Mann-Whitney U test or Student's t-test was applied according to the normal distribution characteristics of parametric data. Chi-square analysis was used to compare categorical variables. Pearson correlation analysis was used to show the correlation between migraine-related features and white matter hyperintensity localizations. A p-value less than 0.05 (typically ≤0.05) was accepted to be statistically significant.

This retrospective cross-sectional study was performed in Ankara City Hospital from March to November 2021 and approved by Ankara City Hospital No: 1 Clinical Research Ethics Committee (date: 02.17.2021, decision no: E1/1476/2021). All procedures were organized based on the ethical rules and principles of the Declaration of Helsinki.

Results

The study included 120 (86%) female patients and 19 (14%) male patients with mean ages of 33.4±9 and 29.7±7.5, respectively. The average years of education of the participants were 10.2±3.8, and the average body mass index was 25.8±5.

There was a statistically significant difference between the two groups regarding demographic characteristics, age, and duration of education (p=0.001, p=0.03, respectively). However, there was no statistically significant difference between the two groups in terms of gender, BMI, smoking, and sMMSE scores. The disease duration was longer in the group with WMLs than in the group with normal MRI (p=0.03). There was no statistically significant difference in the presence of aura, frequency of migraine attacks, number of painful days, relationship with menstruation, use of NSAIDs, or use of prophylactic treatment between the two groups.

There was no statistically significant difference between the two groups in visual analogue scale, HIT-6, and MIDAS, which gives an idea of the severity, impact, and related disability of migraine attacks.

Mig-SCog scores questioning subjective cognitive complaints during migraine attacks were statistically significant in the group with WMLs (p=0.003) (Table 1).

The study used the Scheltens scoring system, which allows the quantitative localization of hyperintensities in the brain to be evaluated. Subgroup analysis was performed in the group with white matter hyperintensities. In addition, Pearson correlation analysis was used to assess the relationship between the location of existing lesions and migraine-related features in patients with hyperintensities on MRI. These findings are shown in Table 2. According to correlation analysis, deep white matter hyperintensities, which are frequently demonstrated in migraine, have a positive relationship with migraine duration (r=0.381 p<0.01) and Mig-SCog scores (r=0.259 p<0.05) and a negative relationship with duration of education (r=-0.327 p<0.05).

Discussion

Migraine is an independent risk factor in the development of subclinical, focal, deep WMLs in young adult healthy individuals (14). There was no significant link between the detection of WMLs and cognitive decline or dementia in several longitudinal studies (21). In recent years, migraine-related cognitive decline has been identified as a significant cause of disability, and simple, subjective, and accessible testing has facilitated its recognition

(7,20,22). In our study, we revealed that migraine patients with WMLs on brain MRI had statistically higher subjective cognitive complaints during a migraine attack (p=0.004). Also, the development of white matter hyperintensities is linked to older age and the duration of the disease, precisely as it is in the literature (23). In our study, no significant difference was found between the groups with and without WMLs in demographic and migraine-related features such as gender, body mass index, presence of aura, frequency of attacks, number of days with pain, relationship with menstruation, or use of medical treatment. Although some researchers have linked the presence of an aura and the frequency of attacks to white matter hyperintensities

Table 1: The relationship between demographic characteristics, migraine characteristics and MRI findings

		MRI findings		
		White matter lesions n=55 (39.5%)	Normal n=84 (60.5%)	
		Mean (± SD)	Mean (± SD)	p-value
Demographic characteristics				
Gender (n, %)	Female	51 (37%)	69 (50%)	0.07
	Male	4 (3%)	15 (10%)	
Age		35.5 (±8.3)	31.3 (±9.0)	**0.001***
Education duration (year)		9.4 (±3.8)	10.8 (±3.7)	**0.03***
BMI		26.0 (±5.0)	25.6 (±5.0)	0.68
Smoking (n, %)		11 (8%)	19 (13.8%)	0.67
sMMSE		28.6 (±1.17)	28.7 (±0.82)	0.45
Migraine features				
Disease duration		6.9 (4.2)	5.4 (4.0)	**0.03***
Presence of aura (n/%)		22 (16%)	33 (24%)	0.93
Number of attacks (n/month)		5.9 (±3.4)	6.3 (±3.5)	0.56
Number of painful days (n/month)		11.5 (±6.3)	11.8 (±6.3)	0.77
Relations with menstruation (n, %)		24 (20%)	34 (28%)	0.81
Usage of NSAIDs (n/month)		11.2 (±13.1)	9.2 (±9.5)	0.31
Presence of prophylactic treatment (n, %)		7 (5%)	12 (9%)	0.79
VAS		7.5 (±1.1)	7.1 (±1.2)	0.09
MIDAS		45.7 (±24.6)	46.3 (±27.7)	0.89
HIT-6		65.2 (±5.0)	65.7 (±5.1)	0.52
Mis-Scog score		10.6 (±4.1)	8.7 (±3.3)	**0.004***

*Significant difference between group with white matter lesions on MRI and group with normal MRI
BMI: Body mass index, VAS: Visual analogue scale, NSAID: Non-steroidal anti-inflammatory drugs, MIDAS: Migraine Disability Assessment Score, HIT-6: Headache impact test, sMMSE: Standardized minimental status examination

Table 2. Migraine features and white matter hyperintensities localizations

	Locations of hyperintensities on MRI				
	Periventricular hyperintensities (r)†	Deep white matter hyperintensities (r)†	Basal ganglia hyperintensities (r)†	Infratentorial hyperintensities (r)†	Sum Schelton scores (r)†
Age	0.309*	-	-	-	-
Education duration	-0.350**	-0.327*	-	-	-0.380*
Duration of migraine	-	0.381**	-	-	0.308*
VAS	-	-	-	-	-
MIDAS	-	-	-	-	-
HIT-6	-	-	-	0.286*	-
Mig-Scog	-	0.259*	-	0.259*	-

*p<0.05, **p<0.01, pearson correlation analysis
(r) †: Correlation coefficient rate
"-" is used to denote results that are not statistically significant
VAS: Visual analogue scale, MIDAS: Migraine Disability Assessment Score, HIT-6: Headache impact test, sMMSE: Standardized minimental status examination

(14,24), others have found the opposite (12,25). In addition, no difference was found between the two groups in terms of migraine-related disability and the severity of pain and attacks.

In previous studies, white matter hyperintensities have been associated with stroke, dementia, and cognitive decline in the elderly group without migraine [14], and they are often localized in the periventricular regions (26). Therefore, we excluded patients over 50 years of age and those with diseases that may cause white matter hyperintensities in our study.

Although the pathogenesis of WMLs in migraines is unclear, ischemia and inflammatory mechanisms have been implicated. An increased incidence of endothelial dysfunction, hypercoagulability, and atrial fibrillation has been found in migraine patients. In addition, a decrease in cerebral perfusion pressure has been detected during a migraine attack, which ultimately affects the clearance of embolic particles and the development of occlusive thrombus (27). Migraine-associated hyperintensities are frequently detected in deep subcortical anatomical regions, and these lesions are considered border zone ischemia due to cerebral hypoperfusion (28). Also, various proinflammatory cytokines are generated during a migraine attack, promoting neuroinflammation and microvascular damage. Another mechanism implicated in the formation of white matter hyperintensities is cortical spreading depression (CSD), which is used to explain the migraine aura. CSD is a slowly spreading wave of abnormal brain activity characterized by significant changes in neuronal, glial, and vascular function (19). CSD, in particular, is responsible for the cumulative development of neuronal damage during migraine attacks by causing recurrent episodes of cerebral hypoperfusion and neuroinflammation (14). CSD, which is the electrophysiological event that is responsible for the development of migraine attacks, can cause cumulative, repetitive neuronal structural damage over time. This mechanism could identify the positive correlation between deep WML scores and disease duration, discovered in our study and the literature (23).

There has not been any evidence of a link between migraine and dementia or cognitive decline in many longitudinal and cross-sectional studies (8,11). On the other hand, three longitudinal studies found that individuals with migraine experienced a lesser cognitive decline during the follow-up period (8,24). However, it has been reported that executive functions such as working memory, processing speed, visual-spatial functions, and verbal fluency are temporarily affected in objective neuropsychological evaluations performed on individuals with subjective cognitive complaints during migraine attacks (11,29). In addition, increased activity has been reported in cortical and subcortical structures such as the cingulate cortex, insula, prefrontal cortex, and temporal poles during functional imaging studies performed during a migraine attack. Given the evidence, similar neurochemical pathways appear to be responsible for the development of WMLs and cognitive decline during migraine attacks.

Study Limitations

Our study was subject to the following limitations: (1) a limited number of cases; (2) evaluation of MRI retrospectively; (3) using a subjective evaluation form instead of objective cognitive assessments during a migraine attack; (4) a lack of prospective monitoring of neuroimaging and cognitive functions of participants.

Conclusion

Our study may be the first to research the relationship between white matter changes in migraines and cognitive impairment during a migraine attack. It is possible that neurochemical and vascular changes that occur during a migraine attack may be connected to both attack-related cognitive impairment and white matter changes. We believe that it is critical to evaluate pain modalities and cognitive characteristics when evaluating migraine attacks and that future studies investigating the relationship with microstructural changes will shed light on an important area in the pathogenesis of migraine.

Ethics

Ethics Committee Approval: The study was approved by the Ankara City Hospital No: 1 Clinical Research Ethics Committee (date: 02.17.2021, decision no: E1/1476/2021).

Informed Consent: Retrospective cross-sectional study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.E.B., Ö.Ö.T., Design: Ö.E.B., Ö.Ö.T., Data Collection and Processing: Ö.E.B., Ö.Ö.T., Analysis or Interpretation: Ö.E.B., Ö.Ö.T., Literature Search: Ö.E.B., Ö.Ö.T., Writing: Ö.E.B., Ö.Ö.T.

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