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Visual rating of cortical atrophy in migraine and tension-type headache

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Abstract

Background: Studies of cortical atrophy in migraine and tension-type headache (TTH) have reported inconsistent results. Some studies have reported decreased cortical thickness or volume, while others have reported thickening in the somatosensory and visual cortices in migraine patients. The same controversy is true with respect to episodic and chronic headaches. This study evaluated and compared cortical atrophy in migraine and TTH as well as in episodic and chronic headache. *Methods:* The study included 43 (37 female) migraine and 15 (12 female) TTH patients. Demographic, clinical, and brain magnetic resonance imaging (MRI) data were evaluated. 1.5 Tesla MRI brain coronal T2 sequences were reviewed by two neurologists, and atrophy was graded according to a visual rating scale (VRS). Two neurologists jointly evaluated and scored cortical thickness on a Likert scale of 0 to 3 or 4 at the following sites bilaterally: olfactory sulcus, anterior cingulate sulcus, circular insular sulcus, anterior temporal and medial temporal lobes, and posterior cingulate and parieto-occipital sulci. The scores at all sites were then summed into a total atrophy score (TAS) for each subject. *Results:* There was no significant difference between the migraine and TTH groups regarding demographics, clinical findings, and atrophy scores in any particular region or with respect to the TAS. When we divided our study subjects into episodic and chronic headache groups, there was no significant difference between these groups in terms of demographic and clinical findings or individual and total atrophy scores.
Conclusions: These results are in line with previous studies that have reported no differences between migraine and TTH in terms of cortical atrophy.

Keywords: migraine; tension-type headache; cortical atrophy; visual rating scales

INTRODUCTION

Migraine and tension-type headache (TTH) are the two the most common primary headaches.[1] Although they have distinct clinical characteristics and pathophysiology, they also share similarities and may coexist in the same patient.[2] Since both are disabling disorders, it is crucial to understand their pathophysiology.

Although there are no typical neuroimaging findings for the diagnosis of both diseases, magnetic resonance imaging (MRI) findings have been described in both conditions.

White matter hyperintensities (WMH) are reported to be increased in migraine[3-5], and migraine is an independent risk factor for stroke[6-8], especially for posterior circulation infarctions.[9,10] Studies of cortical thickness in migraine have reported inconsistent results. Increased cortical thickness in the somatosensory cortex[11,12], visual cortex[13], frontal lobe[12], and temporo-occipital gyrus[14] have been reported in migraine patients compared to healthy controls. However, there are also studies reporting decreased cortical thickness in the frontal lobe[15] and somatosensory cortex[14,16], and one study has found no differences[17] compared to healthy controls.

Neuroimaging studies evaluating cortical thickness or morphometry in TTH patients are much fewer than in migraine patients. These studies have also shown conflicting results, some showing no difference, others showing decreased cortical thickness.[18,19]

Cortical thickness analysis and voxel-based morphometry (VBM) methods are computer-aided quantitative methods that enable the

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automated analysis of neuroimaging data. With these methods, cortical and subcortical volume and thickness measurements can be performed to investigate disease-specific atrophy patterns, especially in neurodegenerative diseases. Although these methods are very useful in research, they are not suitable for clinical practice. For this reason, visual rating scales (VRS) have been introduced to evaluate atrophy in clinical practice, especially for the diagnosis and follow-up of primary neurodegenerative diseases.

In 1992, Scheltens *et al*. was the first to develop a VRS for medial temporal lobe atrophy (MTA) in Alzheimer's disease.[20] "Disproportionate atrophy on structural MRI in medial, basal, and lateral temporal lobe, and medial parietal cortex" has been included in the diagnostic criteria for Alzheimer's disease dementia as a marker of neurodegeneration[21], MTA scoring enables the quantification and objectification of disproportionate hippocampal atrophy. In 2011 Koedam *et al*. suggested another score for evaluating posterior cortical thickness, naming it the posterior atrophy (PA) score.[22] Several other VRSs have subsequently been proposed: anterior temporal for semantic dementia; as well as orbitofrontal, anterior cingulate, and fronto-insula for behavioral variant fronto-temporal dementia.[23-27] Harper *et al.* studied the usefulness of VRS in the differential diagnosis of dementia in 184 patients in whom definitive post-mortem diagnoses were available.[28] They concluded that the VRSs "are quick and easy to learn and can be applied, in total, in less than 3 min." They added that "taken together, these results suggest that visual rating scales offer clinicians without expertise in neuroradiology a means of extracting diagnostically useful information in a time-efficient and inexpensive way that is ideally suited for integration into routine clinical practice."

In this study, we aimed to evaluate the presence of cortical atrophy in migraine and TTH patients using VRS.

METHODS

Participants

According to a protocol approved by the Local Ethics Committee of Bagcilar Training and Research Hospital, all participants provided written informed consent, as per the Declaration of Helsinki. The study included 43 migraine and 15 TTH patients diagnosed according to the International Headache Society (IHS) classification system in the neurology and algology outpatient clinics of Bagcilar Training and Research Hospital.[29] Demographic data, including age, sex, educational level, occupation, monthly income (in Turkish Liras), marital status and comorbidities, and clinical data including duration of disease, frequency of attacks per month, and days with headache per month were collected. Afterwards, all patients were divided into two groups as episodic and chronic headache according to the IHS 2018 diagnostic criteria.[29]

MRI data obtained with a 1.5 Tesla MRI device in the radiology unit of Bagcilar Training and Research Hospital were analyzed retrospectively. Although T1-weighted MRI sequences have been recommended for VRS evaluation in the literature, we evaluated coronal T2-weighted sequences because coronal T1-weighted MRI was not performed in our hospital.

The VRS of each participant was determined jointly by two neurologists (ZY and TE). For each participant, the olfactory sulcus (OS) for the orbitofrontal cortex, the anterior cingulate sulcus (ACS) for the anterior cingulate cortex, the circular insular sulcus (Ins) for the fronto-insular cortex, the anterior temporal lobe (ATL), medial temporal lobe (MTA), as well as the posterior cingulate sulcus (PCS) with the parietooccipital sulcus (POS) for posterior atrophy (PA) were evaluated bilaterally. OS, ACS, Ins, and PA were scored Likert-type between 0-3 (0: no atrophy, 3: severe atrophy), ATL and MTA were scored Likert-type between 0-4 (0: no atrophy, 4: severe atrophy). These scores were then summed for a total atrophy score (TAS) for each participant.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 25.0 (Armonk, NY: IBM Corp.).[30] Normality of variables was analyzed with the Shapiro–Wilk test. Homogeneity of group variances was assessed by Levene's test. The Mann-Whitney U test was used to compare continuous data that did not show a normal distribution. Pearson chi-square and Fisher's exact tests were used to compare categorical data. An index was calculated by multiplying the disease duration by headache frequency and named the headache burden index (HBI). Simple linear regression was performed with HBI as the independent and TAS as the dependent variable, first in the whole group and then in the migraine and TTH groups separately. Analysis results were

presented as the number of observations (n), percentage, mean and standard deviation (Sd). A p-value <0.05 was considered as statistically significant.

RESULTS

The mean age was 35.4±11.9 and 37.3±9.6 years in the migraine and TTH groups respectively, and a female predominance was evident in both groups. There was no significant difference between the groups with respect to age, sex, educational level, occupation, monthly income, marital status, co-morbidities, duration of disease, frequency of headache in one month or HBI scores (Table 1). The number of days with headache in a month was significantly higher in the TTH group ($p = 0.028$). The proportion of chronic daily headache (headache occurring on 15 days/month on average for >3 months) was higher in TTH patients than in migraine patients.

25.6% (n = 11) of the migraine patients were diagnosed with episodic migraine with aura, 30.2% (n = 13) with episodic migraine without aura, and 44.2% (n = 19) with chronic migraine. On the other hand, 26.7% (n = 4) of TTH patients were diagnosed with episodic TTH and 73.3% (n = 11) were diagnosed with chronic TTH.

Maximum ratings of atrophy scores in all examined sulci and anatomical regions did not exceed 1. There was no difference between the two groups in terms of atrophy scores in any area. There was no significant difference between the two groups in terms of the TAS obtained by summing the scores of all domains (Table 2).

On classifying the study population into episodic and chronic headaches, the mean ages of the two groups were 36.1±9.6 and 35.7±12.9 years respectively. There was no significant difference between the groups with respect to age, sex, educational level, occupation, monthly income, marital status, co-morbidities, and disease duration (Table 1). As expected, the frequency of headache ($p<0.001$), the number of days with headache in one month ($p<0.001$), and HBI scores ($p = 0.021$) were significantly higher in chronic headache patients. There were also no significant difference between these two groups in terms of individual atrophy scores and TAS (Table 2).

Simple linear regression was used to test if HBI scores significantly predicted TAS. The regression analysis was not statistically significant in the whole group which included migraine and TTH ($R^2 = 0.027$, adjusted $R^2 = 0.009$ $F(1, 56) = 1.545$, $p = 0.219$). When the prediction of HBI scores on TAS was analyzed in the migraine and TTH groups separately, no significant results were obtained neither the migraine ($R^2 = 0.008$, adjusted $R^2 = -0.017$ $F(1, 41) = 0.318$, $p = 0.576$) nor the TTH group ($R^2 = 0.150$, adjusted $R^2 = 0.085$ $F(1, 13) = 2.3$, $p = 0.153$).

DISCUSSION

Our study found no difference in cortical atrophy scores derived using VRS between migraine and TTH patients. To the best of our knowledge, this is the first study assessing cortical atrophy with VRS in these two conditions. Only quantitative methods such as VBM and cortical thickness analyses have been used to date. Quantitative techniques are not practical in clinical settings because of special hardware requirements, long processing times, and the need for specific acquisition software. Conversely, VRSs are designed to quickly assess focal and general cerebral atrophy in neurodegenerative disorders. The optimal cut-off for all six VRSs to distinguish AD cases from normal controls has been reported as 1.5.[31]

In our study, the maximum scores of the patients did not exceed 1 for each VRS. Considering the 1.5 cut-off that discriminates healthy individuals from patients with AD dementia, this score can be regarded as being within normal limits. In our study, an important point is that VRSs were evaluated on coronal T2 sequences instead of T1 sequences as recommended. The use of T2 sequences may cause an overestimation of sulcus depth and width, and which therefore may lead to an exaggeration of atrophy grading resulting in false positive rather than false negative rates for atrophy. Our study found no atrophy despite using T2 rather than T1 sequences.

VBM and cortical thickness studies conducted in migraine patients have shown inconsistent results. Several studies have reported higher cortical thickness or cortical volume in migraine patients compared to healthy controls in the somatosensory cortex[11,32,33], left middle frontal sulcus, and left temporo-occipital sulcus[14], lateral occipital-temporal cortex[34], as well as the left occipital lobe.[35]. Increased gray matter density in the caudate nucleus has also been reported.[36] A lower cortical thickness or cortical volume in the left superior frontal sulcus and left precentral sulcus[14], left middle frontal gyrus[12,37], bilateral central sulcus, right occipitotemporal area, left visual cortex[37], bilateral postcentral gyri[12], left anterior midcingulate gyrus[38], insula[34,39], superior temporal gyrus, inferior frontal gyrus, precentral

Table 1: Demographics and clinical data of both groups and of episodic and chronic headache groups

N = 58	Migraine	TTH	P	Episodic HA	Chronic HA	P
Age (years), *mean (Sd)*	35.4 (11.9)	37.3 (9.6)	0.715	36.1 (9.6)	35.7 (12.9)	0.827*
Monthly Income (TL), *mean (Sd)*	2365.1 (1995.3)	2006.7 (1882.8)	0.520	2282.1 (1639.6)	2263.3 (2241.4)	0.874*
Disease Duration (months), *mean (Sd)*	118.7 (124.1)	81.7 (82.4)	0.443	125.6 (121.4)	94.1 (109.2)	0.254*
Frequency (months), *mean (Sd)*	13.4 (9.2)	19.5 (10.9)	0.083	7.2 (4.6)	22.3 (7.8)	<0.001*
HBI scores, *mean (Sd)*	1421.1 (1717.3)	1541 (1949.3)	0.79	865.5 (939.7)	1999.6 (2155.6)	0.021*
Gender, *N (%)*			0.682			1.000**
Female	37 (86)	12 (80)		24 (85.7)	25 (83.3)	
Male	6 (14)	3 (20)		4 (14.3)		
Occupation, *N (%)*			0.945			0.481***
Regular worker	18 (41.9)	7 (46.7)		10 (35.7)	15 (50)	
Temporarily unemployed	12 (27.9)	4 (26.7)		8 (28.6)	8 (26.7)	
Unemployed	13 (30.2)	4 (26.7)		10 (35.7)	7 (23.3)	
Educational Level, *N (%)*			0.902			0.311***
Illiterate	2 (4.7)	0		2 (7.1)	0	
Primary school	16 (37.2)	6 (40)		13 (46.4)	9 (30)	
Secondary school	7 (16.3)	2 (13.3)		4 (14.3)	5 (16.7)	
High school	14 (32.6)	6 (40)		7 (25)	13 (43.3)	
University	4 (9.3)	1 (6.7)		2 (7.1)	2 (10)	
Marital Status, *N (%)*			0.197			0.372***
Single	16 (37.2)	4 (26.7)		8 (28.6)	12 (40)	
Married	27 (62.8)	10 (66.7)		20 (71.4)	17 (56.7)	
Divorced	0	1 (6.7)		0	1 (3.3)	
Comorbidities, *N (%)*			1.000			0.589***
DM	0	0		0	0	
Hypertension	1 (2.3)	0		0	1 (3.3)	
Thyroid disease	4 (9.3)	1 (6.7)		2 (7.1)	3 (10)	
Heart disease	2 (4.7)	1 (6.7)		2 (7.1)	1 (3.3)	
Asthma	6 (14)	1 (6.7)		2 (7.1)	5 (16.7)	
COPD	2 (4.7)	0		2 (7.1)	0	
Other	9 (20.9)	1 (6.7)		5 (17.9)	5 (16.7)	
Number of days with headache (monthly), *N (%)*			0.028			<0.001***
Everyday	12 (27.9)	9 (60)		0	20 (66.7)	
15-30 days	9 (20.9)	0		0	5 (16.7)	
10-15 days	5 (11.6)	4 (26.7)		7 (25)	5 (16.7)	
5-10 days	10 (23.3)	0		11 (39.3)	0	
< 5 days	7 (16.3)	2 (13.3)		10 (35.7)	0	

N: number; Sd: standard deviation; TTH: tension-type headache; HA: headache; TL: Turkish Liras (1$ = 14 TL); HBI: headache burden index; DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease

*: Mann-Whitney U test

**: Fisher's Exact test

***: Pearson Chi-square test

Table 2: Atrophy scales in both diagnostic groups and in episodic and chronic headache groups

N = 58	Migraine	TTH	*P*	Episodic HA	Chronic HA	*P*
Right olfactory sulcus, *N (%)*			1.000			0.369*
0	38 (88.4)	14 (93.3)		26 (92.9)	26 (86.7)	
1	5 (11.6)	1 (6.7)		2 (7.1)	4 (13.3)	
Left olfactory sulcus, *N (%)*			1.000			0.354*
0	39 (90.7)	14 (93.3)		27 (96.4)	26 (86.7)	
1	4 (9.3)	1 (6.7)		1 (3.6)	4 (13.3)	
Right anterior cingulate sulcus, *N (%)*			1.000			0.425*
0	38 (88.4)	13 (86.7)		26 (92.9)	25 (83.3)	
1	5 (11.6)	2 (13.3)		2 (7.1)	5 (16.7)	
Left anterior cingulate sulcus, *N (%)*			0.103			0.354*
0	41 (95.3)	12 (80)		27 (96.4)	26 (86.7)	
1	2 (4.7)	3 (20)		1 (3.6)	4 (13.3)	
Right insular sulcus, *N (%)*			1.000			0.665*
0	39 (90.7)	14 (93.3)		25 (89.3)	28 (93.3)	
1	4 (9.3)	1 (6.7)		3 (10.7)	2 (6.7)	
Left insular sulcus, *N (%)*			1.000			1.000*
0	38 (88.4)	14 (93.3)		25 (89.3)	27 (90)	
1	5 (11.6)	1 (6.7)		3 (10.7)	3 (10)	
Right anterior temporal lobe, *N (%)*			0.313			1.000*
0	38 (88.4)	15 (100)		26 (92.9)	27 (90)	
1	5 (11.6)	0		2 (7.1)	3 (10)	
Left anterior temporal lobe, *N (%)*			0.682			0.147*
0	37 (86)	12 (80)		26 (92.9)	23 (76.7)	
1	6 (14)	3 (20)		2 (7.1)	7 (23.3)	
Right medial temporal lobe, *N (%)*			1.000			1.000*
0	40 (93)	14 (93.3)		26 (92.9)	28 (93.3)	
1	3 (7)	1 (6.7)		2 (7.1)	2 (6.7)	
Left medial temporal lobe, *N (%)*			0.064			1.000*
0	43 (100)	13 (86.7)		27 (96.4)	29 (96.7)	
1	0	2 (13.3)		1 (3.6)	1 (3.3)	
Right posterior atrophy, *N (%)*			0.767			0.441*
0	23 (53.3)	9 (60)		17 (60.7)	15 (50)	
1	20 (46.5)	6 (40)		11 (39.3)	15 (50)	
Left posterior atrophy, *N (%)*			1.000			0.192*
0	25 (58.1)	9 (60)		19 (67.9)	15 (50)	
1	18 (41.9)	6 (40)		9 (32.1)	15 (50)	
TAS, *mean (Sd)*	1.8 (2.2)	1.8 (2)	0.829	1.39 (2)	2.2 (2.3)	0.102**

N: number; Sd: standard deviation; TTH: tension-type headache; HA: headache; TAS: total atrophy score
*: Fisher's Exact Test
**: Mann-Whitney U Test

gyrus, anterior cingulate cortex, amygdala, parietal operculum, middle and inferior frontal gyrus and bilateral insula[11] have been reported in migraine patients compared to healthy controls. There are also studies that report no differences in cortical thickness between migraines and healthy controls.[16,40] Cortical thickness abnormalities have been associated with age, gender, disease duration, attack frequency, pain intensity, aura, and photosensitivity.[32,35,41]

Sheng *et al*. conducted a meta-analysis including 16 studies that compared cortical thickness between migraine patients and healthy controls, and they reported no statistically significant cortical thickness alterations in migraine.[41]

Amaral *et al*. reported that cortical thickness of visual cortices and pain processing areas in migraine patients differed from that of controls. In their study population, changes in the left posterior cingulate cortex correlated with headache frequency and intensity.[42]

Studies with TTH are quite limited. Chen *et al*. reported no significant difference in gray matter density between TTH patients and healthy controls.[18] Schmidt-Wilcke *et al*. compared chronic TTH patients with medication overuse headache patients and healthy controls. They reported lower gray matter volume in the dorsal rostral and ventral pons, bilateral anterior and posterior insulae, bilateral orbitofrontal cortex and parahippocampus, pregenual and mid anterior cingulate cortex, right posterior cingulate cortex, right posterior temporal lobe, and right cerebellum in TTH patients. They claimed that the region showing volume loss in the brainstem corresponded to periaqueductal gray, which may be specific to chronic TTH.[19]

A population-based study including relatively older participants showed no difference in cortical thickness and volume in people aged 50-66 years with headache compared to healthy subjects.[43]

Chen *et al*. compared the cortical volume of TTH and migraine patients with healthy controls through VBM. TTH patients had a higher volume in the anterior cingulate cortex, supramarginal gyrus, temporal pole, lateral occipital cortex, and caudate nucleus, and migraine patients had a lower volume in the orbitofrontal cortex than the healthy controls. Between the two patient groups, patients with migraine had lower volume in the superior and middle frontal gyrus, cerebellum, dorsal striatum, and precuneus than the TTH patients. The volumes of the left superior frontal gyrus and right cerebellum combined were able to discriminate TTH and migraine with good accuracy. When they compared episodic and chronic headache groups, the latter had a lower gray matter volume in the bilateral insula and anterior cingulate cortex.[2] In our study, however, atrophy scores did not show a significant difference between episodic and chronic headache groups, nor was there a significant relationship between TAS and the headache burden index, which we obtained by multiplying headache frequency by headache duration.

Migraine with aura patients had no difference in cerebral and cerebellar volume compared to patients with a headache due to rhinosinusitis and TTH.[44]

As one can see, there are very varying results in the literature. Our study evaluated cortical atrophy by VRS in migraine and TTH patients. We did not find any significant atrophy in both groups, or any differences between the groups. The fact that no difference was observed between the two headache groups in this study is consistent with some studies in the literature, but there are some limitations of our research. The major ones to be mentioned are the absence of a healthy control group, the small number of participants, and the fact that VRS was evaluated on coronal T2 sequences instead of T1 sequences.

Further studies with an objective analysis with the FreeSurfer program for changes in cortical thickness that cannot be detected by visual evaluation and comparing the two methods, including the patients over 50 years of age, may contribute to the present findings.

DISCLOSURE

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