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ORIGINAL ARTICLE

Olfactory bulb atrophy in migraine patients

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Abstract

Objective Osmophobia and headache triggered by odors are commonly seen in migraine, and these are symptoms that differentiate migraine from other primary headaches. Since these odor-related symptoms are disease-specific, we aimed to measure the volume of olfactory bulb and depth of olfactory sulcus in migraine patients.

Patients and method A total of 93 subjects, consisting of 62 episodic migraine (32 with osmophobia, 30 without osmophobia) patients and 31 healthy controls, were included in this study. Diagnosis and classification of migraine were performed according to the beta version criteria of International Classification of Headache Disorders (ICHD-3 Beta version). Beck depression and beck anxiety inventory were applied to the patients, and the measurement of bilateral olfactory bulb volume (OBV) and olfactory sulcus depth (OSD) was performed manually in the brain magnetic resonance imaging (MRI).

Results More significantly in the left OBV, low OBV has been determined in migraine patients compared to the control group ($p < 0.001$, $p = 0.020$). When migraine patients with or without osmophobia were compared to the control group; OBV was determined to be the lowest in migraine group with osmophobia, and left-weighted bilateral OBV was determined to be low ($p < 0.001$, $p = 0.046$). No statistically significant difference was determined between groups in OSD measurements ($p = 0.646$, $p = 0.490$).

Conclusion Left-weighted bilateral OBV atrophy determined in migraine patients may be guiding for the clarification of migraine pathophysiology and enlightening of the relation between migraine and odor.

Keywords Migraine · Olfactory bulb atrophy · Osmophobia · Neurodegeneration

İntroduction

Osmophobia is defined as aggravation of pain with smells during migraine attacks and it is a specific symptom differentiating migraine from other primary headaches [1, 2]. It has been stated that osmophobia has a diagnostic and prognostic role in people with primary headaches [3]. In the diagnosis of migraine, the sensitivity of osmophobia has been determined as 53.1%, and specificity as 87.5% [4]. Its prevalence was reported to be up to 95% [5]. It has also been suggested that headache triggered by odors is specific for migraine and that it is a factor that may be used in the differential diagnosis of other headaches [6]. It has been claimed that osmophobia and crisis triggered by odors and their reason might be similar, and they may be based on common neurological pathways [5]. On the other hand, it has been shown that there is a relation between odors and trigemino-nociceptive pathway in the pathophysiology of migraine [7]. In migraine patients, olfactory system-related specific symptoms are found and these symptoms have a role in the differential diagnosis of other

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headaches; therefore, in this study, we aimed to measure the volume of olfactory bulb and depth of olfactory sulcus.

Material and methods

Sixty-two migraine (32 with osmophobia, 30 without osmophobia) patients aged between 18 and 50 who have been diagnosed with episodic migraine and applied to Neurology Clinic between August 2017 and January 2018 and 31 healthy controls have been included in this prospective and cross-sectional design study. Migraine diagnosis and classification were made according to the 2013 beta version of International Headache Classification [8].

People who experienced head trauma, have allergic rhinitis and sinonasal infection, pregnant women, lactating women, smokers, people using any drugs including for migraine prophylaxis, and have any neurological, psychiatric, and systemic disease other than migraine have been excluded from the study.

Detailed history of migraine patients was taken. Systemic physical examinations and neurological examinations were performed. All patients were examined when they did not have a headache. The duration, frequency, and severity of migraine episode and disease period were recorded. Visual analog scale (VAS) was used to measure the severity of headache: 1–3: mild; 4–6: moderate; 7–8: severe; 9–10: extremely severe [9]. Migraine headache attack frequency was recorded monthly. Headache episode duration was determined in hours, and disease period was determined in years. Aura, photophobia, and phonophobia were investigated. By recording height and weight measurements and calculating body mass index, body mass index was classified as per World Health Organization [10]. Beck depression and anxiety scale were used due to the fact that the olfactory bulb volume is decreased in depression and osmophobia is associated with anxiety symptoms [11, 12].

The presence of osmophobia was evaluated by asking whether odors aggravate the pain or avoid smells during headache attack. Also, the presence of headache triggered by odors was evaluated by asking patients "Could any odor triggers your pain in the absence of headache?"

Bozok University School of Medicine Ethics Committee approved the study protocol (protocol number: 2017-KAEK-189_2017.06.21_03) and all the participants provided written informed consent.

MR imaging was performed by using 1.5 Tesla system and standard quadrature head coil (Initial Ingenia model no: 7813–72; Philips Medical Systems, Netherlands, Tilburg). As described before, olfactory bulb anatomy was detected in a tangent plane to the posterior of the eyeballs [13]. Coronal sections were placed perpendicular to a virtual midline between nasal septum and cerebral falx. Coronal T2-weighted sections were obtained by using the following parameters: 1000/100 ms (TR/TE); section thickness, 5 mm; matrix, 384 × 239; FOV, 230 × 184 mm; and in-plane pixel resolution, 0.5 × 0.5 mm. Olfactory bulb (OB) was observed as a hypointense structure surrounded by hyperintense cerebrospinal fluid. OB was imaged manually by using T2 weighted coronal sections. Volumes were presented in cubic centimeters by calculating the plane area and structure thickness [14]. Olfactory sulcus depth measurements were performed for all cases in a selected section of coronal images. For this measurement, a coronal section tangential to the posterior of the eyeballs was used in order to confirm the same section positions. Also, there was no definitive lesion or structural abnormality in the brain MRI of the patient and control group.

Statistical analysis

The findings of this study were analyzed with "The Statistical Package for Social Sciences for Windows" (SPSS v18) software. The conformity of continuous variables to normal distribution was tested with Kolmogorov–Smirnov test. The descriptive statistics of continuous variables were expressed as mean ± SD or median (min-max). Categorical variables were expressed in positive/negative values and compared using chi-square analyses, and Fishers's exact test was applied when required. Statistical difference between the groups in terms of continuous variables was examined with ANOVA for parametric variables and Kruskall–Wallis test for nonparametric variables. Post-hoc testing was performed where the overall significance of the ANOVA or Kruskall–Wallis test was significant ($p < 0.05$). The presence of a correlation between the groups was determined by Pearson and Spearman rho tests. $p < 0.05$ was considered as the threshold of statistical significance for all tests.

Results

Demographic and clinical features of the migraine patients with and without osmophobia, and healthy controls are summarized in Table 1. No significant difference was found between the groups with respect to age, sex, BMI, beck depression, and anxiety scores ($p > 0.05$). Headache characteristics, including attack severity, frequency and duration, disease duration and aura, photophobia, osmophobia, crisis triggered by odors, and results were similar between migraine with osmophobia or without osmophobia ($p > 0.05$). It was determined that osmophobia and phonophobia demonstrated statistically significant correlation upon comparing migraine groups with or without osmophobia ($p = 0.016$).

Bilateral OBV was decreased in migraine patients compared to the control group, more significantly in the left OBV. When three groups, consisting of migraine patients with or without osmophobia and control group, were compared,

Table 1 Demographic and clinical data of controls and migraine patients with and without osmophobia

Characteristics	Control group ($n = 31$)	With osmophobia ($n = 32$)	Without osmophobia ($n = 30$)	p
Age (years)	33.29 ± 5.78	36.28 ± 8.37	33.40 ± 7.59	0.192
Gender (male/female)	6/25	6/26	6/24	0.99
BMI (kg/m^2)	23.83 ± 3.68	26.23 ± 6.05	24.49 ± 3.46	0.111
Nausea		27/5	24/6	0.65
Photophobia		32/0	29/1	0.29
Phonophobia		32/0	25/5	*0.016**
Attack frequency		3.18 ± 2.02	4.46 ± 2.25	0.06
Attack duration (hour)		37.12 ± 22.57	37.7 ± 20.39	0.22
VAS		8(5–10)	7(5–10)	0.152
Disease duration (years)		9.9 ± 5.24	8.56 ± 8.28	0.12
Aura		9/23	4/26	0.153
Crisis triggered by odors		18/14	12/18	0.20
Beck depression inventory	5(0–12)	6(0–27)	5.5(0–29)	0.232
Beck anxiety inventory	4.7 ± 3.4 (0–14)	6.2 ± 2.87 (1–13)	7.00 ± 4.82(0–17)	0.064

BMI, body mass index; *VAS*, visual analog scale

*All comparison were considered statistically significant at $p < 0.05$

bilateral OBV was determined to be low more significantly on the left ($p < 0.001$ and $p = 0.046$) No significant difference was determined between groups in olfactory sulcus measurements (Table 2).

When migraine patients with or without osmophobia and the control group were correlated, it was determined that the right and left olfactory bulb volume was the lowest in the migraine group with osmophobia (Fig. 1).

No significant correlation was determined between the left olfactory bulb volume, which was affected more significantly in patients with migraine and osmophobia, and disease duration, frequency-severity of episodes, aura, nausea, photophobia, phonophobia, osmophobia, and crisis triggered by odors (Table 3).

Discussion

The most important result of our study is the determination of bilateral OB atrophy, which is more significant in the left OB, in migraine patients with or without osmophobia.

While the majority of neurogenesis is completed in embryonic period, neurogenesis of OB ceases in the second year of life. As it is known, OB is one of the first elements affected by neurodegenerative diseases [15]. OB atrophy has been shown in neurogenerative diseases such as Alzheimer's disease and Parkinson's disease [16, 17], multiple sclerosis (MS) [18], neuromyelitis optica (NMO) [19], REM sleep behavior disorder [20], and normal pressure hydrocephalus [21]. It was attempted to explain olfactory involvement in neurodegenerative diseases with neuropathological markers, neurotransmitter dysfunction, and environmental exposure (viruses and xenobiotics) [15].

Microglia in olfactory bulb were suggested to be sensors and modulators of brain inflammation [22] and olfactory dysfunction was considered as an early sign of neuroinflammation in the central nervous system [23]. Olfactory dysfunction has been observed in autoimmune diseases such as MS, systemic lupus erythematosus, autoimmune encephalitis, and NMO [24, 25]. Sorbo et al. have demonstrated that high levels of aquaporin P-4 antibody are expressed in the synaptic unit in OB [26]. It was also determined to play a role in neuroinflammation in studies performed on neuroinflammatory diseases.

Table 2 Measurement of olfactory bulb and depth of olfactory sulcus in control, migraine patient with and without osmophobia

	Control group ($n = 31$)	Migraine patient with osmophobia ($N = 32$)	Migraine patient without osmophobia ($N = 30$)	p
R olfactory bulb V	60.89 ± 13.67	51.87 ± 12.97	55.14 ± 16.20	**0.046***
L olfactory bulb V	64.34 ± 11.19	51.24 ± 12.56	55.92 ± 13.79	**< 0.001***
R depth of olfactory sulcus (mm)	8.36(7.61–9.51)	8.34(7.02–9.32)	8.09(7.28–9.95)	0.646
L depth of olfactory sulcus (mm)	8.37 ± 0.58	8.22 ± 0.55	8.21 ± 0.56	0.490

R, right; L, left; V, volume. Volumes are in cubic millimeters

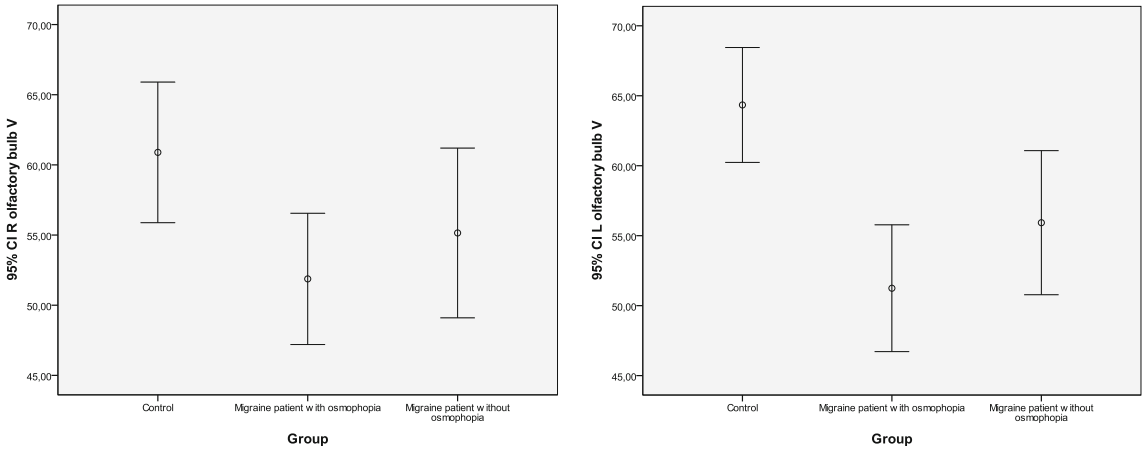

Fig. 1 Distribution of the L and R olfactory bulb volume the among groups

The role of olfactory bulb is not known in the pathogenesis of migraine. While its cause is not clear, structural changes may be seen in the brain such as lesions similar to silent infarcts in posterior circulation and volume changes in gray and white matter, mostly in white matter hyperintensities [27]. Voxel-based morphometry (VBM) analysis of the brain determined a diffuse decrease in gray matter volume in migraine patients, particularly in the frontal cortex and cingulate gyrus [28]. Palm-Meinders et al. have shown decreased gray matter in some visual areas of the right occipital cortex, and decreased volume in bilateral occipital white matter [29]. Mehnert and May have demonstrated that cerebellum has an effect on pain, and that there are structural changes in posterior cerebellum in migraine patients [30]. Recently, a study investigating migraine with transcranial sonography reported changes in basal ganglia such as substantia nigra, lentiform nucleus, and caudate nucleus [31]. In addition to structural changes in migraine described above, we have determined bilateral olfactory bulb atrophy in our study. Some authors have suggested that cortical and subcortical areas related to pain processing show antinociceptive reorganization even in interictal period in migraine patients [32]. Olfactory bulb atrophy may be a result of antinociceptive reorganization. In a study investigating olfactory evoked potentials with H2S stimulation, the amplitude of olfactory evoked potential was determined to be lower than the control group [33]. The data from this study supports the result of our study. In a study performed with OCT in migraine patients, retinal nerve fiber layer was determined to be significantly thinner [34]. Retinal nerve fiber thinning and OB atrophy may have developed with similar etiological mechanisms. Szabó et al. have suggested degenerative and maladaptive plasticity in migraine by showing microstructural changes in white matter in interictal period [35]. Described degenerative and maladaptive changes may have caused olfactory bulb atrophy.

Table 3 The correlation analysis of the left olfactory bulb volume in patients with migraine

Variables ($N = 62$)	r	p
Disease duration (years)	− 0.062	0.63
Attack frequency	− 0.033	0.79
Nausea	− 0.035	0.788
Photophobia	0.081	0.52
Phonophobia	0.057	0.65
Osmophobia	0.178	0.167
Crisis triggered by odors	− 0.047	0.717
Visual analog scale	− 0.196	0.127
Aura	0.030	0.817

All parameters were determined as not significant (Pearson's correlation)

In our study, the OB volume was the lowest in migraine patients with osmophobia. The right and left OBV are symmetrical in most people. Morphometric assessment of OBV is a sign of general olfactory functions and it is also correlated with olfactory functions [36]. If osmophobia is considered an olfactory dysfunction, the presence of osmophobia may contribute in volume decrease due to migraine. The reason for the effect of migraine and osmophobia being higher on the left OB than the right OB is not known. Royet et al. have reported that the right hemisphere is associated with memory and the left hemisphere is associated with emotional processes in olfactory lateralization [37]. In the PET study of Demarquay et al. on episodic migraine patients, they have observed increased cerebral blood flow in the left piriform cortex and anterior-superior temporal gyrus at interictal period in migraine patients compared to that in the control group. Also, increased activity was observed in the left temporal pole during smell simulation in this study [38]. Temporal pole is considered to be multisensorial association cortex which perceives and integrates various senses such as smell, hearing, sight, and taste with recognized significance for migraine. The left temporal pole is commonly implicated in perceptual decoding, semantic processing, and conceptualization [39]. The fact that the left OB was affected more

significantly may be due to functional characteristics and anatomic connections of the left temporal pole. The role of the left olfactory bulb in osmophobia and pain pathophysiology might be clearer with future studies. Another important finding of our study is the fact that no difference was observed between patient and control groups with regard to OS depth, even though the OB volume is decreased in migraine patients. The OB volume and OS depth are correlated with olfactory functions [13]. In studies performed on Parkinson's patients and MS patients, OB atrophy and decrease of OS depth have been determined to be correlated [14, 40]. It was indicated that neurodegeneration may be present in the common pathogenesis of multiple sclerosis and Parkinson's patients. As stated by Szabó et al., as microstructural and degenerative changes are in micro levels in migraine patients, they may not be detected in olfactory sulcus measurement, which is a macroscopic assessment. The limitations of our study are the small number of male patients and the examination of only episodic migraine patients. The effects of gender on smell function may be different, and the evaluation of olfactory bulb in chronic migraine patients may lead to different information, considering that osmophobia is more common in chronic migraine patients. Furthermore, OB has been determined to be a structure with high plasticity in MRI studies [41]. Prospective studies involving a large, more men patients and chronic migraineurs will be enlighten in the future.

As a result, bilateral OB atrophy (more significant on the left) has been added in recognized structural changes in migraine. The consideration of this result in next studies may be guiding in the explanation of migraine pathophysiology and development of new treatment modalities. Prospective studies involving a large population, more male patients, and chronic migraineurs will contribute to the literature in the future.

Compliance with ethical standards

Bozok University School of Medicine Ethics Committee approved the study protocol (protocol number: 2017-KAEK-189_2017.06.21_03) and all the participants provided written informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

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