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Research Article

Could There Be a Relationship Between Paranasal Sinus and Migraine Etiology?

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Abstract

Aim: Migraine is a complex neurological disease with a neurogenic inflammatory component in which nitric oxide (NO) levels increase. Studies have shown that the NO level produced in adults is closely related to the paranasal sinus volume. The aim of this study is to investigate the differences in paranasal sinus volumes responsible for NO synthesis in migraine patients.
Material and Method: The paranasal sinuses of migraine patients (n=50) and healthy subjects (n=50) were examined using cranial T1-weighted magnetic resonance images (MRI). Right and left maxillary, sphenoid and frontal-ethmoid sinus volumes of the groups were calculated in 3D Slicer program and recorded in mm^3. Statistical analysis of the study was performed with IBM SPSS 23.0 and $p<0.05$ values were considered significant.
Results: A statistically significant difference was observed between migraine patients and healthy subjects across all sinus volumes, with the sinus volumes of migraine patients being higher than those of healthy subjects ($p<0.05$).
Conclusion: We think that the fact that the paranasal sinus volume, which is primarily responsible for NO synthesis, was found to be high in migraine patients may be related to the high NO level in migraine patients.

Keywords: Paranasal sinus, nitric oxide, migraine, pain, maxillary sinus

INTRODUCTION

Migraine is a recurring, moderate or severe headache that can occur at any age and usually lasts between 4 hours and 3 days. In migraine, problems such as headache, sensitivity to sound and light, nausea and vomiting can be seen (1). While migraine headache is among the 10 most common diseases in men, it is among the five most common diseases in female (2). Although the pathophysiology of migraine is not yet clear, it has been reported in many studies that nitric oxide (NO) production and level may play a role in migraine pathophysiological mechanisms (3-6). NO, which has different roles in many systems, is accepted as a biological regulator. NO has a vasodilatation effect on vessels, a relaxant effect on smooth muscles, and a neurotransmitter effect on the peripheral and central nervous systems (7). Although NO is synthesized in more than one anatomical region in the human body, it is known to be produced mostly by epithelial cells in the paranasal sinuses (8,9). Paranasal sinuses are located within the bones of the same name and are called maxillary, frontal, ethmoid and sphenoid sinuses (10). Many studies have reported that NO is synthesised to a large extent in migraine patients (4-6.) Studies have shown that the NO level produced in adults is closely related to the paranasal sinus volume (9,11).

Considering the aforementioned explanations, determining whether the paranasal sinus volumes, which are responsible for NO synthesis, change in migraine patients may give an idea about the etiology of migraine. Therefore, the aim of this study was to compare the paranasal sinus volumes obtained using magnetic resonance images (MRI) in migraine patients with those of healthy individuals without migraine.

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MATERIAL AND METHOD

Study Design

The study received approval from the Kayseri City Training and Research Hospital Clinical Research Ethics Committee under decision number 1017, dated December 15, 2023. The cross-sectional cohort study was conducted in a single center in accordance with the Declaration of Helsinki. Participants who met the study criteria were informed about the study and their written informed consent was obtained.

Participants

In a pilot study with 7 individuals for each of the two groups, the sample size was determined to be at least 40 participants for each group, with an effect size of 0.636 using a power of 0.80 and α=0.05. The primary outcome measure for this calculation was right maxillary sinus volume.

Migraine Group (n=50): It consists of a total of 50 migraine patients, 30 female and 20 male, diagnosed with migraine.

Control group (n=50): Consists of a total of 50 healthy individuals, 26 female and 24 male.

Although there is no specific test for the diagnosis of migraine, the criteria set by the International Headache Society for migraine in 2018 are used. Patients with migraine were evaluated according to the criteria of the International Headache Society and patients who met the criteria were included in the study. The criteria set by the International Headache Society for migraine are given in the table below (12).

Participants with a history of trauma or surgery in the neurocranium and viscerocranium bones or problems affecting the paranasal sinus volume, such as loss of molar teeth, were excluded.

Data Acquisition

MRI procedures were performed with a 3T (Tesla) Siemens Magnetom Skyra, Netherlands brand device. T1-weighted MPRAGE sequence settings were used to evaluate paranasal sinus volumes in the study; sagitial was determined as Slice Thicknes=1mm, Repetition time (TR)=2300ms, FOV=250mm, Matrix: 256x256, Echo Time (TE)=3.4ms.

Data Processing

The volume calculation of the paranasal sinuses was done in the 3D Slicer program. 3D Slicer is a free and open source software application. It is used for volume, area calculation or visualization of any anatomical structure (13,14).

The MRI data of the participants was uploaded to the 3D Slicer tool set and the “Modules” tab was navigated to the “Segment Editor” tab. The first step of volume calculation was completed with the "Segmentation" tab opened as a result of these operations. In the second step, the image was "Thresholded" using the "Threshold Range" to cover the anatomical boundaries of the paranasal sinuses to be measured. The three-dimensional raw image of the paranasal sinus measured with these procedures was accessed using the "Apply" and "Show 3D" tabs. The raw image obtained was checked from the axial, sagittal and coronal planes, and if there were overflows or deficiencies in the anatomical border of the measured paranasal sinus, it was corrected using the "Erase", "Scissors" and "Paint" tabs (Figure 1). As a result of these procedures, the paranasal sinus volumes in mm^3 were calculated and compared between the groups.

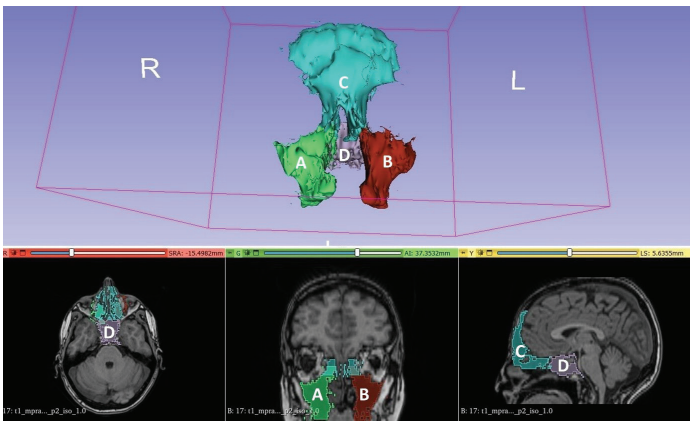

Figure 1. Three-dimensional representation of paranasal sinuses; A: The right maxillary sinus; B: The left maxillary sinus; C: The frontal-ethmoid sinuses; D: The sphenoid sinus

Statistical Analysis

Statistical analysis was performed using IBM® SPSS© 24 software (IBM SPSS Corp., Armonk, NY, USA). The normality of numerical variables was assessed using both visual methods, such as histograms and probability plots, and analytical methods, including the Kolmogorov-Smirnov test. Descriptive statistics, comprising means and standard deviations, were employed for normally distributed numerical variables, while frequencies and percentages were used for summarising categorical variables. The Independent Samples t-test was utilised to compare two independent groups with a normal distribution, and the chi-square test was employed for categorical data. A value of $p<0.05$ was considered statistically significant.

RESULTS

The demographic characteristics of individuals in the groups are presented in Table 1. No statistically significant differences were observed between the groups concerning these demographic characteristics ($p>0.05$). The volumes of the right maxillary sinus, left maxillary sinus, sphenoid sinus, and frontal-ethmoid sinus for both groups are detailed in Table 1. A statistically significant difference was observed between migraine patients and healthy subjects across all sinus volumes, with the sinus volumes of migraine patients being higher than those of healthy subjects ($p<0.05$).

Table 1. Analysis of data between control and migraine groups

		Control group (n=50)	Migraine group (n=50)	
		X±SD	X±SD	Sig. (p)
Age (years)		23.34±3.32	23.02±3.50	0.869
BMI (kg/m²)		23.88±2.87	24.11±2.49	0.414
		n (%)	n (%)	
Gender	M	24 (48.0)	20 (40.0)	0.567
	F	26 (52.0)	30 (60.0)	
Right maxillary sinus (mm³)		22541.66±3004.94	25617.34±3409.25	0.027*
Left maxillary sinus (mm³)		21830.03±3119.25	25254.53±3382.97	0.030*
Sphenoid sinus (mm³)		18154.20±2746.16	20794.68±3063.32	0.019*
Frontal-ethmoid sinuses (mm³)		38067.60±3004.92	41411.07±2958.96	0.022*

X: mean, SD: standard deviation, *p<0.05, BMI: body mass index, M: male, F: female

DISCUSSION

Although the etiopathogenesis of migraine remains unclear, it has been suggested that high levels of NO synthesis may play a role (15). In the present study, it was determined that the volume of the paranasal sinuses, which are responsible for synthesizing high amounts of NO, was significantly different in migraine patients compared to healthy individuals.

Migraine is a complex neurological disease with a neurogenic inflammatory component in which NO levels increase (16). It has been assumed that paranasal sinus-derived NO spread in the nasal mucosa is the primary molecule that initiates migraine, and this situation is called the sinus hypoxic nitric oxide theory. According to this theory, NO originating from the paranasal sinus spreads to the nasal mucosa, causing repetitive or intermittent stimulation of the trigeminal nerve. It has been suggested that this situation causes vasodilation in the blood vessels in the nasal mucosa and in the extracranial blood vessels that initiate the migraine attack, respectively (15).

In the presented study, all paranasal sinus volumes, especially the sinus maxillaris, were found to be higher in migraine patients than in healthy individuals. High paranasal sinus volume also affects NO synthesis. We believe that the high volume of the paranasal sinus, which is primarily responsible for NO synthesis in the body, in migraine patients may explain the high levels of NO observed in migraine patients. It has been reported that the NO content of air absorbed from the paranasal sinuses of migraine patients during an acute attack is 132.5 parts per billion (ppb) and 154 ppb on the left and right sides, respectively, while in controls it is 36 ppb and 34.5 ppb, respectively. This study further reports that NO levels are not only elevated in migraine patients compared to healthy individuals but also demonstrate asymmetry between the right and left side nasal air (17). In the present study, the volume of the right sinus maxillaris in migraine patients was found to be higher than the volume of the left sinus maxillaris, which may be an explanation for the high level of NO in the right side airway of the nose.

Mechanical suction of paranasal air is used to reduce NO production and NO stagnation in the nasal and paranasal cavities (18). In migraine patients, mechanical suction of paranasal air has been proven to neutralise nasal NO and reduce migraine attacks and severity (19). In the study, the fact that migraine patients have larger paranasal sinuses than healthy individuals may have increased the stored NO level and caused the formation of very high concentrations of NO. In humans, NO has been reported to be produced by epithelial cells in the paranasal sinuses (8). The number of epithelial cells in the paranasal sinuses is directly related to the surface area and, therefore, the volume of the paranasal sinuses. A larger volume means more epithelial cells and more NO.

Although it is known that NO synthesis is closely related to paranasal sinus volume, NO level could not be evaluated in migraine patients in this study. In addition, the study was conducted in a single center. In some individuals, it is very difficult to determine the exact boundary between the frontal sinus and ethmoid sinus. Therefore, frontal and ethmoid sinus volumes were measured together in this study. These processes related to the study can be seen as a limitation of the study.

CONCLUSION

The etiology and pathogenesis of migraine remain mysterious despite dozens of studies. Although certain topics are emphasized in the studies, it is seen that the increase in NO level is effective on the etiology of migraine. In the present study, we think that the fact that the paranasal sinus volume, which is primarily responsible for NO synthesis, was found to be high in migraine patients may be related to the high NO level in migraine patients. We believe that this study will contribute to the elucidation of the high NO level in migraine.

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Conflict of interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *The Kayseri City Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (15.12.2023/number: 1017).*

REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33:629-808.
2. Saylor D, Steiner TJ. The global burden of headache. Semin Neurol. 2018;38:182-90.
3. Blau JN. Migraine: theories of pathogenesis. Lancet. 1992;339:1202-7.
4. Neri M, Frustaci A, Milic M, et al. A meta-analysis of biomarkers related to oxidative stress and nitric oxide pathway in migraine. Cephalalgia. 2015;35:931-7.
5. Buckley MS, Agarwal SK, Garcia-Orr R, et al. Comparison of fixed-dose inhaled epoprostenol and inhaled nitric oxide for acute respiratory distress syndrome in critically Ill adults. J Intensive Care Med. 2021;36:466-76.
6. Rathnasiri Bandara SM. Paranasal sinus nitric oxide and migraine: a new hypothesis on the sino rhinogenic theory. Med Hypotheses. 2013;80:329-40.
7. Tassorelli C, Greco R, Morocutti A, et al. Nitric oxide-induced neuronal activation in the central nervous system as an animal model of migraine: mechanisms and mediators. Funct Neurol. 2001;16:69-76.
8. Lundberg JO, Farkas-Szallasi T, Weitzberg E, et al. High nitric oxide production in human paranasal sinuses. Nat Med. 1995;1:370-3.
9. Lundberg JO. Nitric oxide and the paranasal sinuses. Anat Rec (Hoboken). 2008;291:1479-84.
10. Lee S, Fernandez J, Mirjalili SA, Kirkpatrick J. Pediatric paranasal sinuses-development, growth, pathology, & functional endoscopic sinus surgery. Clin Anat. 2022;35:745-61.
11. Abouzid M, Roshdy Y, Daniel JM, et al. The beneficial use of nitric oxide during cardiopulmonary bypass on postoperative outcomes in children and adult patients: a systematic review and meta-analysis of 2897 patients. Eur J Clin Pharmacol. 2023;79:1425-42.
12. Tinsley A, Rothrock JF. What are we missing in the diagnostic criteria for migraine?. Curr Pain Headache Rep. 2018;22:84.
13. Gering DT, Nabavi A, Kikinis R, et al. An integrated visualization system for surgical planning and guidance using image fusion and an open MR. J Magn Reson Imaging. 2001;13:967-75.
14. Payas A, Batın S. The role of paranasal sinuses in the mysterious etiopathogenesis of idiopathic scoliosis. Ann Med Res. 2024;31:71-6.
15. Rathnasiri Bandara SM. Migraine and psychiatric disorders co-morbidity explained by sinus hypoxic nitric oxide theory - a new hypothesis on the Sino rhinogenic theory. Med Hypotheses. 2014;82:257-65.
16. de O S Mansur T, Gonçalves FM, Martins-Oliveira A, et al. Inducible nitric oxide synthase haplotype associated with migraine and aura. Mol Cell Biochem. 2012;364:303-8.
17. Bandara SMR, Samita S, Kiridana AM, Herath HMMTB. Elevated nitric oxide and carbon monoxide concentration in nasal-paranasal sinus air as a diagnostic tool of migraine: a case - control study. BMC Neurol. 2021;21:407.
18. Bandara SMR, Samita S, Kiridana AM, et al. Paranasal sinus air suction for immediate pain relief of acute migraine - a randomized, double blind pilot study. BMC Neurol. 2019;19:248.
19. van der Kuy PH, Merkus FW, Lohman JJ, et al. Hydroxocobalamin, a nitric oxide scavenger, in the prophylaxis of migraine: an open, pilot study. Cephalalgia. 2002;22:513-9.