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A study of the relationship between serum uric acid levels and pain in patients with migraine

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Abstract

Serum uric acid (SUA), the end product of purine metabolism acts as an antioxidant and is related to oxidative stress. It has been reported that SUA may be involved in the pathogenesis of neurodegenerative diseases including Alzheimer disease, Huntington disease, Parkinson disease, and multiple sclerosis. However, studies evaluating SUA levels in migraine are scarce. This study aimed to explore the relationship between pain characteristics and SUA levels in patients with migraine and compare SUA levels in migraine patients during a headache attack and headache-free period with those control groups. This prospective, cross-sectional study included 78 patients with migraine and 78 healthy subjects who were randomly selected from hospital personnel as the control group. Headache characteristics (duration of attack, pain intensity, and headache frequency) and sociodemographic features were recorded. The SUA level was measured once in the control group and twice in the migraine patients, during the migraine attack and headache-free periods. Although the SUA levels of the migraine group in the headache-free period were higher than those of the control group, the difference was not statistically significant. Gender was not significantly related to the change in SUA levels between the attack and headache-free period. When the correlation between age, duration of migraine, frequency, duration, and intensity of pain was evaluated; the difference between SUA levels in female migraine patients was weakly correlated with headache intensity, whereas male patients had a moderate correlation. ($P < .05$; $R > 0.250$, and $R > 0.516$, respectively). The difference in SUA level in the migraine attack period compared to the headache-free period showing a positive correlation with pain intensity suggested that SUA may have a role in migraine due to its antioxidant role.

Abbreviations: SUA = serum uric acid, TBARS = thiobarbituric acid reactive products, VAS = visual analog scale.

Keywords: antioxidant, gender, migraine, oxidative stress, pain, uric acid, visual analog scale (VAS)

1. Introduction

Migraine is one of the most common neurological disorders in developed countries. Its incidence is similar between countries (10–12%), and it is seen 2 to 3 times more in women than in men. It most commonly occurs between the ages of 20 to 40.[1] It is typically defined as unilateral, throbbing headache attacks accompanied by symptoms such as nausea, vomiting, photo-phonophobia, and the complaints last for 4 to 72 hours.[2]

According to the accepted neurological inflammation theory in the pathogenesis of migraine, sterile inflammation occurs in the dura mater surrounding the brain due to neuropeptide release from the perivascular trigeminal nerve endings and sensitization develops in the sensory nerves.[3] As a result, the blood vessels in the structures sensitive to pain become dilated, and extravasation develops, which causes more sensitization in the trigeminal nerve.

Oxidative stress is defined as the deterioration of the oxidative balance as a result of the increase of reactive oxygen species such as hydroxyl radical, superoxide radical, and hydrogen peroxide formed during cellular metabolism and the deficiency of antioxidants that detoxify them. Disruption of this balance causes oxidative damage in the body and plays a role in the etiopathogenesis of many diseases (atherosclerosis, cancer, diabetes, ischemia/reperfusion injury, etc.).[4,5] Uric acid is known to act as a powerful endogenous antioxidant and cleanser in the body. It is thought to have a 2-way neuroprotective and damaging effect on the central nervous system.[6] Studies have shown that increased serum uric acid (SUA) level is associated with decreased central nervous system inflammation and decreased tissue damage, while

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the opposite effect has been shown in patients with acute ischemic stroke.[7–11] This suggests that uric acid can increase antioxidant and inflammatory processes at normal doses, but uric acid contributes to increased oxidative stress levels at high serum levels.

A strong link between oxidative alterations and migraine has been identified in certain research, but some have not found a significant correlation.[12–15] In our study, considering the possible role of oxidative stress in the pathophysiology of migraine, we aimed to measure the SUA level in patients with migraine during headache-free and attack periods, to compare it with a healthy control group, and to investigate the relationship between SUA level and migraine features such as duration, severity, and frequency.

2. Materials and methods

This prospective, cross-sectional study was approved by the ethics committee of the University of Health Sciences, Bakirkoy Prof Dr Mazhar Osman Psychiatric and Neurological Diseases Education and Research Hospital, Istanbul, Turkey, (Study Protocol Number: 2018-10-01) and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. Consecutive patients with migraine who were admitted to the neurology clinic for 12 months from June 2019 to June 2020 were enrolled in the study. Diagnosis of migraine was made according to International Classification of Headache Disorders-3 diagnostic criteria.[16] Demographic features, chronic diseases, and blood parameters of both patient and control groups were recorded.

2.1. Participants

Seventy-eight patients with migraine over 18 years of age and 78 healthy individuals who were perfectly compatible with this group in terms of age and sex were included. All patients with migraine did not receive any prophylactic migraine treatment.

Participants were included in both groups after exclusion of structural lesions, magnesium-containing drug intake, pregnancy, alcoholism, renal or gastrointestinal tract problems, history of vascular disease (diagnosed hypertension, obesity, metabolic syndrome, previous stroke, angina, myocardial infarction, and peripheral artery disease), active infection, neoplasia, diabetes, prediabetes, gout disease, thyroid dysfunction, chronic obstructive pulmonary disease, chronic inflammatory bowel disease, use of steroids, acetylsalicylic acid, thiazide diuretics, use of colchicine and allopurinol, etc.

Patients' data were recorded in a database that included information about clinical and demographical characteristics, and follow-up.

2.2. Collection of samples and obtaining SUA

For serum, potassium ethylenediaminetetraacetic acid tubes were utilized, while separator gel tubes were used for blood counts. To separate serum, separator gel tubes were centrifuged for 10 minutes at 5000 rpm after being left for 20 minutes. Biochemical tests were investigated using a closed spectrophotometric measuring system with a Cobas 8000 series c702 modular analyzer (Roche Diagnostics). The blood counts (hemogram) were gathered from the XN-1000 findings that were acquired at our lab. Uric acid measurement was made in venous blood samples twice in the patient group during the attack and headache-free period in the morning, and once in the control group.

2.3. Statistical analysis

In the analysis of the data, Statistical Package for the Social Sciences version 22.0 (IBM) was used. Descriptive statistical analyzes (percentage, minimum-maximum, mean, standard deviation, and frequency) were used when evaluating the data obtained from the patient and control groups, and the chi-square test was used to compare the qualitative data. Independent Student *t* test was used to compare the means of parametric variables with normal distribution. A nonparametric Wilcoxon test was used where parametric assumptions were not met. Spearman correlation analysis was used to examine the correlations of the variables with each other. A P value <.05 was considered to be statistically significant. Multivariable linear regression model was used to determine which pain intensity was designed as the response variable.

3. Results

In accordance with the incidence of migraine in both genders, 52 (66.7%) women and 26 (33.3%) men, and similar characteristics of a total of 78 control cases were included in the current study. The mean age of migraine patients was 34.13 ± 10.61, and the mean age of the control group was 34.64 ± 9.66. The mean age was 34.75 ± 10.48 in women with migraine and 31.18 ± 11.28 in men. In the control group, the mean age of women was 35.15 ± 9.53 and the mean age of men was 32.45 ± 10.36, respectively. There was no significant age difference between the groups (P > .05). Table 1 demonstrates the clinical characteristics of migraine-type headaches.

The migraine patient group was compared with the healthy control group according to the uric acid results in the attack and headache-free periods. The mean SUA level of the migraine group in the headache-free period was 4.29 ± 1.16; the mean uric acid level during the attack period was 4.12 ± 1.32. The mean SUA level of the control group was found to be 3.94 ± 1.15. Although the uric acid levels of the migraine group were higher than the control group, being more prominent in the headache-free period, it was not statistically significant (P = .102).

The mean headache-free period SUA level of female migraineurs was 3.93 ± 0.83 and the mean uric acid level during the migraine attack was 3.79 ± 0.84. In male migraineurs, the SUA level during the non-attack period was 5.96 ± 1.03, and the attack period was 5.60 ± 1.15. In the control female group, the mean uric acid level was 3.65 ± 1.01 and 5.15 ± 0.95 in males. When the mean uric acid levels of men and women in the non-attack and exacerbation period were examined, the mean SUA level in the headache-free period was higher than in the attack, but no statistical significance was found. When the male and female subgroups of migraine patients were evaluated separately, the mean uric acid level was significantly higher in the non-attack period compared

Table 1

Clinical characteristics of migraine.

Pain characteristics	Mean ± SD	Median value	Minimum-maximum range
Duration of headache (yr)	11.13 ± 8.71	10	1–35
Frequency of headache	6.27 ± 4.86	5	1–20
Duration of migraine attack (h)	23.84 ± 20.82	16	2–72
VAS score	5.38 ± 2.22	5	2–10

SD = standard deviation, VAS = visual analog scale.

to the control group. However, this difference was not statistically significant (P = .064). Table 2 shows the mean uric acid levels according to gender distribution in the migraine group.

No correlation was found between the headache-free period and attack period uric acid levels of all migraine patients and age, migraine age, frequency of attacks, duration of pain, and visual analog scale (VAS) (R < 0.25). There was no correlation between the headache-free and attack periods of uric acid levels of female migraineurs and age, migraine age, duration of pain, frequency, and VAS scores (R < 0.25). However, there was a negative correlation between initial uric acid level and age (r: –0.301), and a weak correlation with VAS scores (r: 0.420) among male migraineurs.

Duration of migraine and level of serum UA levels during the attack period showed a negatively weak correlation (r: –0.487); however, a moderate negative correlation (r: –0.533) was shown between the duration of pain and the level of serum UA levels during the migraine attack period.

The correlation between the uric acid level difference in the non-attack and exacerbation period (numerical difference between the uric acid level in the non-attack period and the uric acid level in the attack period; initial UA-attack UA) with age, migraine age, frequency, duration of pain, and VAS score were evaluated. It was found that the difference between uric acid levels in female migraine patients had a positive and weak correlation with VAS scores (P < .05; R > 0.250). In male patients, this correlation was found to be moderate (r: 0.516). Evaluation of the relationship between headache-free and attack period uric acid difference and pain intensity in migraine patients was demonstrated in Table 3.

Multivariable linear regression model in which pain intensity was designed as the response variable (n = 121) was performed to adjust for confounders of SUA (Table 4). However, no significant variable was detected.

Table 2

The mean serum uric acid levels according to gender distribution in the migraine group.

Gender	Headache-free period	Attack period	*P* value
Female	3.93 ± 0.83	3.79 ± 0.84	.064
Male	5.96 ± 1.03	5.60 ± 1.15	.202

Table 3

Evaluation of the relationship between headache-free and attack period uric acid difference and pain intensity in migraine patients.

Correlation between SUA levels and VAS score		
	R value	*P* value
Female	0.295	.034
Male	0.516	.104

SUA = serum uric acid, VAS = visual analog scale.

4. Discussion

The purpose of this study was to evaluate SUA levels in migraine patients during a headache attack and a headache-free period, as well as in control groups, and to investigate the association between the clinical features and SUA levels in patients with migraine. In our study, no significant difference was found between the SUA levels of the patient versus the control group and migraine attack versus headache-free period. The difference in uric acid levels in the headache-attack period compared to the headache-free period showed a positive correlation with pain severity. Despite the fact that the other pain characteristics of the patients did not show a relationship with SUA levels, lower levels of serum UA were associated with a longer duration of migraine-type headache.

Migraine is defined as a common and multifactorial neurovascular headache disorder including various symptoms. The relationship between migraine and oxidative stress has been shown in many studies.[17–20] In a meta-analysis conducted in 2014, thiobarbituric acid reactive products (TBARS) were found to be significantly higher and superoxide dismutase activity was found to be lower in patients with migraine in terms of oxidative stress levels.[21]

In a study by Erdal et al, 27 migraine patients and 27 age- and gender-matched control groups were evaluated. Substances reacting with TBARS, indicators of lipid peroxidation, SUA, and albumin levels were measured during the attack and headache-free periods and compared with the control group.[20] The level of TBARS was found to be higher in the headache patient group compared to the healthy individuals, and it was observed that this elevation was more pronounced during the attack period. Uric acid attack levels were found to be significantly lower compared to the headache-free period and control group.[22] Although the number of samples was lesser than in our study, similar to our findings, the authors found that there was no significant difference between the SUA levels of the headache-free period and control group. These results were interpreted as the fact that oxidative stress might have a role in migraine pathophysiology and the deterioration of the oxidant balance in migraine in the direction of lipid peroxidation.[20] Exploring the oxidative stress status of migraine may play a key role to understand the pathophysiology mechanism of migraine. Findings from this study contribute to the existing knowledge on how the levels of SUA change during a migraine attack and headache-free period.

It is reported that uric acid has a neuroprotective and damaging 2-way effect on the central nervous system.[6] Studies have shown that uric acid has antioxidant effects at normal doses, but prooxidant and inflammatory effects at high serum levels on the central nervous system.[7–9] It is also known that uric acid reduces the release and bioavailability of nitric oxide, which has an important role in the pathophysiology of migraine.[23,24] In our study, although the mean SUA level of the control group was lower than the migraine patients, there was no statistically significant difference between the mean values. When we compared the uric acid levels of migraine patients during the attack and headache-free period, SUA levels during the attack were found to be lower than in the headache-free period. However, it was not statistically significant. The number of studies comparing SUA levels in migraine

Table 4

Multivariable linear regression model in which VAS was designed as the response variable (n = 121).

Variable	Estimate	SE	Stand. estimate	95% CI		*P*
				Lower	Upper	
Intercept	5.92	0.91				**<.001**
Δ Uric acid	0.99	0.37	0.33	0.09	0.57	**.009**
Age	–0.02	0.03	0.03	–0.34	0.143	.416

A P value less than .05 is deemed to be statistically significant.

Δ = overall change, CI = confidence interval, SE = standard error, Stand. = standardized, VAS = visual analog scale.

patients during attack and non-attack periods is limited. Further studies are needed to confirm these preliminary findings.

In a study by Yazar et al, the researchers aimed to identify the serum UA levels according to migraine subtypes such as aura, without aura, and episodic, chronic migraine. They found that the SUA, ferritin, and urea levels in patient groups were significantly low compared to the healthy control group. However, they did not detect any statistically significant differences between SUA levels between aura/without aura and episodic/chronic migraine subtypes. In their study, the participants were evaluated during their attendance at the neurology clinic. Our approach to researching the oxidative stress in migraine by detecting SUA levels differs from this study. We explored if there is a significant difference in SUA levels during a migraine attack and a headache-free period in the same patient. Although we detected a slight change during an attack, it was not statistically significant. The non-significant result could be due to the small sample size in our study. Larger sample sizes may give more reliable results and provide more accurate results. Nonetheless, we think that our research is a decisive study exploring the mean levels of SUA in patients with migraine during the attack and headache-free periods; moreover, it can shed light on future studies.

It is believed that oxidative stress and/or antioxidant defense contribute to the pathophysiology of migraines and the development of the chronic form of headache.[25] Chronification of migraine leads to worse subjective well-being and lower quality of life. Although it is not part of the objective of this paper, it can be speculated that the detection of the SUA levels and determining its effects on oxidative stress can be useful as a predictor biomarker for evaluating the presence of the chronification of migraine.

Our study has several strengths. First, to our knowledge, this is the first sample to assess the difference of mean SUA levels during a migraine attack and headache-free period on the same migraineur. Second, we further compared the SUA levels with healthy control levels. There were also some limitations. We did not investigate the levels of UA among migraine subtypes namely episodic and chronic migraine groups. In addition, contrary to expectations, SUA levels did not differ significantly in migraine and control groups. This study still cannot demonstrate anything with great certainty; however, it can be considered a pilot study to conduct further investigations.

In conclusion, it is yet unknown whether uric acid has a critical protective capacity against autoimmune and neurological illnesses as well as blood-borne infections. Despite the negative results of this study, the authors encourage other researchers to repeat a similar investigation with larger samples. Considering its antioxidant role, it is possible that the uric acid level may be affected during a headache attack due to proinflammatory processes. In our study, the difference in uric acid levels in the attack period compared to the headache-free period showed a positive correlation with the severity of pain. This may be suggestive of more comprehensive studies in terms of the lack of research on this subject in the current literature. We believe that besides giving an insight into the pathophysiology of migraine, assessing the importance of SUA on migraine pathophysiology will contribute to the clinical follow-up, attack severity, and treatment approaches of patients with migraine.

Author contributions

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