JOURNAL OF HEALTH SCIENCES AND MEDICINE

Sağlık Bilimleri ve Tıp Dergisi

J Health Sci Med 2020; 3(1): 31-35

Research Article/Araştırma Makalesi

Serum levels of ischemia-modified albumin and prolidase in migraine subjects

Migren olgularında iskemi-modifiye albumin ve prolidaz serum düzeyleri

Bahar Say[1], Nermin Dindar Badem[2], Ufuk Ergün[1]
[1]Kırıkkale University, Faculty of Medicine, Department of Neurology, Kırıkkale, Turkey
[2]Kırıkkale University Faculty of Medicine, Department of Biochemistry, Kırıkkale, Turkey

ABSTRACT

Objective: Migraine is one of the most common neurological diseases with headache attacks. Although its pathophysiology is still unclear, it is thought to be multifactorial. Oxidative stress is one of the topics discussed in the pathophysiology of migraine. The aim of this study was to investigate ischemia-modified albumin (IMA) and prolidase levels, which are oxidative stress markers in migraine.

Material and Method: In this study, 35 migraine and 35 healthy controls were included. Serum IMA and prolidase levels were measured in serum obtained after centrifugation from venous blood samples by ELISA. Prolidase and IMA in migraine patients were compared with the control group.

Results: The mean age was 40.06±11.14 years in migraine (34 female, 1 male) and 34.31±8.26 in controls (31 female, 4 male). There was no significant difference between the groups in terms of age and gender (p=0.08, p=0.29). Interictal IMA and prolidase levels of migraine subjects were significantly higher than the control group (p=0.02, p<0.001). Prolidase was significantly higher in the attack period than the control group (p<0.001), but there was no significant difference in IMA levels (p=0.34). Prolidase and IMA levels during the attack were higher than an interictal period in migraine but there was no significant difference (p>0.05).

Conclusion: Prolidase and IMA may be an indicator of oxidative stress in migraine patients. Prolidase, one of the oxidative stress indicators, also correlates with the frequency of attacks in migraine. It is thought that these markers may lead to antioxidant agent studies in the prophylactic treatment of migraine.

Keywords: Headache, migraine, IMA, prolidase, interictal

ÖZ

Giriş: Migren başağrısı ataklarıyla seyreden sık görülen nörolojik hastalıklardan biridir. Patofizyolojisi halen net bilinmemekle birlikte multifaktöriyel olduğu düşünülmektedir. Oksidatif stres migren patofizyolojisinde üzerinde durulan konulardan biridir. Bu çalışmada migrende oksidatif stres göstergesi olarak iskemi-modifiye albumin (İMA) ve prolidaz belirteçlerinin araştırılması amaçlandı.

Gereç ve Yöntem: Bu çalışmaya 35 migren ve 35 sağlıklı kontrol alındı. Prolidaz ve İMA belirteçleri, ELİSA yöntemiyle venöz kan örneklerinin santrifüjü sonrası elde edilen serum numunelerinden bakıldı. Migren hastalarında ki İMA ve prolidaz düzeyleri kontrol grubu ile karşılaştırıldı.

Bulgular: Migren (34 kadın, 1 erkek) grubunda ortalama yaş 40,06±11,14 kontrol grubunda (31 kadın, 4 erkek) ortalama yaş 34,31±8,26'dı. Gruplar arasında yaş ve cinsiyet açısından anlamlı farklılık izlenmedi (p=0,08, p=0,29). Migren grubunun atak dışı dönem İMA ve prolidaz düzeyleri kontrol grubundan istatistiksel olarak anlamlı yüksekti (p=0,02, p<0,001). Atak döneminde prolidaz kontrol grubuna göre anlamlı yüksekti (p<0,001) ancak İMA düzeylerinde anlamlı farklılık izlenmedi (p=0,34). Migrende atak dönemindeki İMA ve prolidaz düzeyleri atak dışı döneme göre yüksekti ancak anlamlı farklılık gözlenmedi (p>0,05).

Sonuç: Prolidaz ve İMA migren hastalarında oksidatif stresin göstergesi olabilir. Oksidatif stres göstergelerinden prolidaz migrende atak sıklığı ile de korelasyon gösterebilmektedir. Bu belirteçlerin, migrenin profilaktik tedavisinde antioksidan ajan çalışmalarında da yol gösterebileceği düşünülmektedir.

Anahtar Kelimeler: Baş ağrısı, migren, İMA, prolidaz, interiktal

Corresponding Author: Bahar Say, Kırıkkale Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, Ankara Yolu 7.Km., Kırıkkale Üniversitesi Kampüsü, 71450, Yenişehir, Yahşihan, Kırıkkale, Türkiye
E-mail: drbaharsay@gmail.com
Received: 25.10.2019 **Accepted:** 14.11.2019 **Doi:** 10.32322/jhsm.638466

Cite this article as: Say B, Dindar Badem N, Ergün U. Serum levels of ischemia-modified albumin and prolidase in migraine subjects. J Health Sci Med 2020; 3(1): 31-35.

INTRODUCTION

Migraine is a common chronic neurological disease that is characterized by episodes of headache. It is believed to be multifactorial, and although the exact physiopathology remains unknown, oxidative stress is one factor that has been considered in its physiopathology.

Oxidative stress is caused by an imbalance between the production of free radicals and the antioxidant defense mechanism, and results from the overproduction of oxidant radicals, decreased antioxidants or both. This may cause cell membrane damage through lipid peroxidation, damage to the enzymes that play a critical role in intermediate metabolism and other proteins, and DNA strand breaks (1). Oxidative stress is an important process affecting the central nervous system and has been linked to the pathophysiology of chronic neurodegenerative diseases, epileptic seizures, multiple sclerosis, dementia and other conditions (2,3).

During migraine episodes, in other words, in the interictal period, peroxides and oxidant products are elevated in the subject's plasma, urine, and platelets. Although the reason for the increase in these products in the interictal period is unknown, it has been suggested that it could be associated with a decrease in the activity of certain antioxidant enzymes and/or increased activity of such vasoconstrictors as angiotensin, endothelin-1 or urotensin. In addition, it is thought that the increased cortical hyperexcitability associated with migraine can result in the overproduction of oxidant products through an increase in metabolic activity (4).

Ischemia-modified albumin (IMA) and prolidase are systemic markers of oxidative stress. The binding capacity of albumin-cobalt decreases as a result of chemical changes in albumin caused by free oxygen radicals during ischemia, and the resulting albumin molecule is called IMA. It has been reported previously that this molecule can also increase in inflammatory conditions (5,6). Prolidase is an exopeptidase that detaches proline or hydroxyproline from the carboxyl terminal position of dipeptides, and is found in the plasma as well as in such organs as the brain, heart, uterus, and thymus (7). It plays an important role in such processes as wound healing, inflammation, carcinogenesis, angiogenesis, cell migration, and differentiation (8,9). Proline is found in the central nervous system, and reports have suggested that it plays a neuromodulator role in synaptic transmission (10,11). It is also considered to be a neurotransmitter, with increased levels of proline having been linked to increases in prolidase levels. Proline is believed to potentialize the effects of glutamine which is known to play a role in migraine episodes (12). The role of oxidative stress in migraine is one of the subjects that have been the focus of research to light the way for new therapies (diet regulation, use of antioxidants, etc.). The present study is designed to investigate IMA and prolidase that could be a marker of oxidative stress in migraine.

MATERIAL AND METHOD

In this study, the participants consisted of migraine subjects admitted to tertiary health center neurology outpatient clinic and healthy volunteers with sociodemographic characteristics similar to migraine subjects. Serum IMA level and prolidase activity in migraine cases were compared with the control group.

Ethical Declaration

Informed consent form for the study was obtained from all migraine subjects and healthy controls. The local ethics committee has approved this study (20.03.2018-06/05).

Participants

The migraine subjects diagnosed according to the most current version of the International Classification of Headache Disorders (ICHD-3) of the IHS (International Headache Society) were enrolled for this study (13).

Renal, hepatic and thyroid diseases, presence of anemia, malignancy, cardiac disease, hypertension, epilepsy, presence of any other headache, regular and/or frequent drug use (including vitamin and antioxidant use), smoking, alcohol use, obesity (body mass index> 30 kg/m^2), pathological findings on previous brain imaging (tomography and/or magnetic resonance imaging) and diagnosed as psychiatric disease in migraine subjects were excluded.

Cigarette/alcohol use and regular/frequent drug use were excluded in the control group.

Ischemic Modified Albumin and Prolidase Analyses

Venous blood samples were taken from migraine subjects and controls. In migraine subjects, blood samples were taken in both interictal and exacerbation periods in migraine subjects.

The samples were centrifuged for 10 minutes at 2000 g for half an hour immediately after being taken into a preservative-free biochemistry tube and stored at-80 °C until analysis. Serum IMA and prolidase levels were measured by ELISA with a commercial kit in serum.

Data Acquisition

Demographic data (age, gender) and education level were recorded in the study group. Disease duration, frequency of attacks (within 3 months), presence of aura were questioned in migraine subjects. Data records and examination of migraine and control subjects were done by the same neurologist.

Statistical Analyses

SPSS 21.0 statistical package program was used for data analysis. The results were taken as mean ± standard deviation for the variables with normal distribution, median and

minimum-maximum values for the variables with anormal distribution. The value of p<0.05 was considered statistically significant. Chi-square test in categorical variables, t-test according to whether the distribution was normal or Mann-Whitney U test was used to evaluate the differences between the data obtained from the groups. Spearman Correlation test was used to analyze the correlation between categorical (sequential) and continuous variables.

RESULTS

The demographic characteristics of migraine subjects and the control group in the study are shown in **Table 1.**

Table 1. Demographic characteristics of the study group

Data	Migraine (n=35)	Control (n=35)	p value
Age (mean±SD)	40.06±11.14	34.31±8.26	0.08
Gender, n (%)			0.29
Female	34 (97.1)	31 (88.6)	
Male	1 (2.9)	4 (11.4)	
Education, year (mean±SD)	7.40±2.95	8.71±3.97	0.66

The disease duration of migraine subjects was 20.57 ± 9.9 years. The frequency of attack was 6 (min-max: 1-18) days within three months. A total of 5 (14.3%) subjects had migraine with aura and 30 (85.7%) subjects had migraine without aura.

Prolidase and IMA serum levels of the migraine and control groups are given in **Table 2.**

Table 2. Levels of IMA and prolidase in both groups

Oxidative stress marker	Migraine		Control
	Attack	Interictal	
IMA, ng/mL			
Mean±SD	34.77±88.04	22.96±59.5	19.19±11.97
Median (min-max)	14.5 (3.6-509)	9.9 (1.7-359)	19.78 (0.5-50.4)
Prolidase, U/L			
Mean±SD	24.4±26.22	14.6±9.86	5.8±4.92
Median (min-max)	10.4 (2.1-153.4)	10.08 (2.4-49.7)	4.1 (0.17-20.8)

IMA; Ischemia-modified albumin

There was no significant difference between the migraine attack and the interictal period in IMA and prolidase levels (p=0.130, p=0.902). The IMA and prolidase levels were significantly higher in the migraine group compared to the control (p = 0.02, p <0.001). There was no significant difference between IMA levels of a control group and during the migraine attack (p = 0.34). Prolidase levels were significantly different (p<0.001).

Ischemia-modified albumin level was 23.6 ± 23.8, (min-max:11.4-70.06) ng/mL prolidase was 8.8 (min-max:2.1-32) U/L in attack period of migraine subjects with aura. In attack period of migraine without aura, IMA was 35.79 ± 94.87, median:14.36 min-max: 3.6-509 ng/mL and prolidase was 10.48, min-max:2.8-153.4 U/L. There was no significant difference migraine with aura and without aura (p=0.202, p=0.345).

When the interictal period is evaluated there was no significant difference between IMA (16.84±13.90, median:13.99 min-max:4.7-40.6 ng/mL) in migraine with aura and IMA (23.91±64.21, median:9.47 min-max:1.7-359 ng/mL) in migraine without aura (p=0.524). In also prolidase level, there was no significant difference between migraine with aura (22.43±18.21, median:21.19 min-max:2.4-49.7 U/L) and migraine without aura (13.39±7.50, median:10.67 min-max:2.4-29.3 U/L) (p=0.311).

While the attack and interictal IMA levels did not show a significant correlation with the frequency of attacks (p>0.05). The prolidase level in the attack was correlated with the attack frequency (rs=0.333, p=0.04).

DISCUSSION

The present study investigates the potential of IMA and prolidase levels in migraine subjects as an indicator of oxidative stress. Prolidase levels were found to be significantly higher in migraine subjects than in the control group during a migraine episode and in the interictal period, while IMA was significantly higher when compared to the control group only in the interictal period.

To the best of our knowledge, based on a literature search, the present study is the first to evaluate prolidase levels in migraine subjects as an indicator of oxidative stress. Prolidase plays a role in proline and hydroxyproline metabolism, and a significant linear relationship has been noted between prolidase and proline levels. A previous study involving rats showed that proline induces oxidative stress in the cerebral cortex (14). Another study demonstrated favorable outcomes with antioxidant therapy in proline-induced damage (15). The findings of decreased serum catalase levels in migraine subjects in the interictal period and the associated difficulty in hydrogen peroxide detoxification, the decreased activity of superoxide dismutase and glutathione peroxidase in erythrocytes and platelets, and the decreased glutathione peroxidase activity in the erythrocytes all support the oxidative stress hypothesis in disease pathogenesis (16-18). The present study identified increased prolidase levels in migraine subjects, both during episodes and in the interictal period, and this finding is deemed to support the oxidative stress hypothesis.

The relationship between proline and glutamate is one of the reasons for the selection of prolidase as an indicator in the present study. It has been suggested in previous studies that endogenous extracellular proline increases the effect of glutamate in the synaptic cleft (19). Glutamate plays an important role in the pathogenesis of migraine, and increased glutamatergic activity triggers cortical hyperexcitability in the pathogenesis (20). Studies evaluating glutamate levels identified increased levels of glutamate in the plasma, cerebrospinal fluid, and saliva in the interictal period

(21), while in the present study it is a striking finding that the frequency of episodes correlates with prolidase levels. This correlation may be linked to the relationship between prolidase and glutamate.

The presence of oxidative stress due to the decreased activity of certain antioxidant enzymes in migraine and the associated increase in free radicals, as well as in lipid peroxides in the interictal period, have gained popularity as research topics in recent studies (22-25). In the present study, IMA and prolidase levels were found to be significantly higher in migraine subjects in the interictal period than in the controls. A study comparing oxidative stress in subjects with migraine headaches, subjects with tension-type headache (TTH) and a control group found oxidative stress to be significantly higher in migraine subjects than in subjects with TTH and the control subjects, and this is sustained in the interictal period (26). In migraine subjects, IMA and prolidase levels during episodes were higher than in the interictal period, although the difference was not significant, and this was attributed to considerably higher IMA values in the subjects than in the control subjects. Such extreme IMA values may be a result of undiagnosed accompanying depression, despite the application of strict exclusion criteria. Recently, IMA levels have been shown to be higher in depressive subjects than in healthy controls (27).

In this study, migraine without aura was significantly more than migraine without aura. IMA and prolidase levels did not differ significantly between migraine with aura and migraine without aura. If the number of subjects was sufficient in the groups, it was considered whether the result could be different or not. Furthermore, migraine subjects with aura could not be compared with the control group in terms of IMA and prolidase levels because of their small number. Previous studies in the literature investigating the association between migraine with aura and oxidative stress have produced different results. In a study investigating malondialdehyde (MDA) levels as an indicator of oxidative stress, Yılmaz et al. found no significant difference between the MDA levels of migraine subjects with aura and those of the control subjects (28). In a study by Tuncel et al., oxidative stress was found higher levels of oxidative stress in migraine subjects in the control subjects, and the difference was even more remarkable in subjects with migraine with aura (29).

Among the indicators of oxidative stress, IMA and prolidase levels are higher in migraine subjects than in healthy controls, and prolidase has also been correlated with the frequency of episodes. It is suggested in the present study that these indicators could serve as a guide for antioxidant agent studies into prophylactic therapy in migraine subjects.

Financial support: This work was supported by the Scientific Research Projects Coordination Unit of University to dipeptidase kits

Conflict of interest: None

REFERENCES

1. Paraje MG. Oxidative Stress in Biofilms: Causes, Role in Diseases and Biological Effects. İn: Croft C, ed. Oxidative stress causes, role in diseases and biological effects. 978-1-63117-579-4 (eBook). New York. Nova Science Publishers, 2014, 61-93.
2. Halliwell B. Free radicals, proteins and DNA: oxidative damage versus redox regulation. Biochem Soc Trans 1996; 24: 1023-7.
3. Reznick, A.Z, Packer, L, 1993. Free radicals and antioxidants in muscular neurological diseases and disorders. In: Poli, G, Albano, E, Dianzani, M.U. (Eds.), Free Radicals: From Basic Science to Medicine. Birkhäuser Verlag, Basel, pp. 425–37.
4. Borkum JM. The Migraine Attack as a Homeostatic, Neuroprotective Response to Brain Oxidative Stress: Preliminary Evidence for a Theory. Headache 2018; 58: 118-35.
5. Çevik M. U, Yücel Y, Arıkanoğlu A, et al. Multipl sklerozlu hastalarda serum prolidaz ve iskemi modifiye albümin düzeyleri. Journal of Clinical and Experimental Investigations. 2012; 3: 518-20.
6. Marta MMF, Duarte A, João BT, et al. Association between ischemia-modified albumin, lipids and inflammation biomarkers in patients with hypercholesterolemia. Clin Biochem 2009; 42: 666-71.
7. Zanaboni G, Dyne KM, Rossi A, Monafo V, Cetta G. Prolidase deficiency: biochemical study of erythrocyte and skin fibroblast prolidase activity in Italian patients. Haematologica 1994; 79: 13-8.
8. Palka JA, Phang JM. Prolidase activity in fibroblasts is regulated by interaction of extracellular matrix with cell surface integrin receptors. J Cell Biochem 1997; 67: 166-75.
9. McRae PA, Porter BE. The perineuronal net component of the extracellular matrix in plasticity and epilepsy. Neurochem Int 2012; 61: 963-72.
10. Hauptmann M, Wilson DF, Erecinska M. High affinity proline uptake in rat brain synaptosomes. FEBS Lett 1983; 161: 301-5.
11. Crump FT, Fremeau RT, Craig AM. Localization of the brain-specific high-affinity I-proline transporter in cultured hippocampal neurons:molecular heterogenetiy of synaptic terminals. Mol Cell Neurosci 1999; 13: 2539.
12. Cohen S, Nadler J. Proline-induced potentiation of glutamate transmission. Brain Research 1997; 761: 271282.
13. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (ICHD-3). Cephalalgia 2018; 38: 1–211.
14. Delwing D, Bavaresco CS, Wannmacher CM, Wajner M, Dutra-Filho CS, Wyse AT. Proline induces oxidative stress in cerebral cortex of rats. Int J Dev Neurosci 2003; 21: 105-10.
15. Delwing D, Chiarani F, Bavaresco CS, et al. Protective effect of antioxidants on brain oxidative damage caused by proline administration. Neurosci Res 2005;52: 69-74.
16. Shukla R, Barthwal MK, Srivastava N, et al. Neutrophil-free radical generation and enzymatic antioxidants in migraine patients. Cephalalgia 2004; 24: 37-43.
17. Bolayir E, Celik K, Kugu N, Yilmaz A, Topaktas S, Bakir S. Intraerythrocyte antioxidant enzyme activities in migraine and tension-type headaches. J Chin Med Assoc 2004; 67: 263-7.
18. Shimomura T, Kowa H, Nahano T, et al. Platelet superoxide dismutase in migraine and tension type headache. Cephalalgia 1994; 14: 215-8.
19. Cohen SM, Nadler JV. Proline-induced potentiation of glutamate transmission. Brain Res 1997; 761: 271-82.
20. Nam JH, Lee HS, Kim J, Kim J, Chu MK. Salivary glutamate is elevated in individuals with chronic migraine. Cephalalgia. 2018; 38: 1485-92.
21. Zielman R, Wijnen JP, Webb A, et al. Cortical glutamate in migraine. Brain. 2017;140(7):1859-1871.
22. Eren Y, Dirik E, Neselioglu S, Erel O. Oxidative stress and decreased thiol level in patients with migraine: Cross-sectional study. Acta Neurol Belg. 2015;115:643-649.
23. Neri M, Frustaci A, Milic M, et al. A metaanalysis of biomarkers related to oxidative stress and nitric oxide pathway in migraine.

Cephalalgia 2015; 35: 931-7.
24. Aytac¸ B, Coskun O, Alioğlu B, et al. Decreased antioxidant status in migraine patients with brain white matter hyperintensities. Neurol Sci 2014; 35: 1925-9.
25. Borkum JM. The migraine attack as a homeostatic, neuroprotective response to brain oxidative stress: preliminary evidence for a theory. Headache 2018; 58: 118-35.
26. Gupta R, Pathak R, Bhatia MS, Banerjee BD. Comparison of oxidative stress among migraineurs, tension-type headache subjects, and a control group. Ann Indian Acad Neurol 2009; 12: 167-72.
27. Karaaslan Ö, Hacımusalar Y, Amuk ÖC. Bal C. Evaluation of ischemia modified albumin levels in major depression patients. J Surg Med 2019; 3: 557-60.
28. Yılmaz G, Sürer H, Üçler S, İnan L, Yücel D. Auralı ve aurasız migrende plazma malondialdehit düzeyleri. Turkiye Klinikleri J Med Sci 2004; 24: 309-15.
29. Tuncel D, Tolun FI, Gokce M, Imrek S, Ekerbiçer H. Oxidative stress in migraine with and without aura. Biol Trace Elem Res 2008; 126: 92-7.