

ORIGINAL ARTICLE

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Serum ischemia modified albumin level in acute migraine attacks

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Abstract

Although the pathogenesis of migraines is not yet fully known, oxidative stress is thought to play an important role in the pathogenesis of this disease. In our study, we aimed to evaluate the serum level of ischemia-modified albumin (IMA), one of the systemic markers of oxidative stress, in acute migraine attacks admitted to the emergency department. The study included a control group consisting of 40 healthy individuals and a group of 40 patients admitted to the emergency department with migraine attacks. Serum IMA levels were studied using the ELISA kit. The average age of the migraine group was 39.9 ± 8.2 and 31 were female. The average age of the control group was 42.5 ± 9.2 and 29 were women. There was no difference between groups in terms of age and gender ($p=0.18$, $p=0.79$, respectively). Mean serum IMA levels were significantly higher in the migraine group than in the control group ($p=0.001$). On receiver operating characteristic curve (ROC) analysis, use of optimal IMA cutoff level of 92.6 ng/ml was associated with 70% sensitivity and 55% specificity (AUC= 0.713, 95% CI: 0.600-0.826, $p=0.001$). In the migraine group the mean attack frequency was 2.55 ± 1.3 within three months, with an average duration of migraine 8.87 ± 4.76 years. The mean Visual Analogue Scale (VAS) was 8 ± 1.2 . A positive correlation was found between IMA levels and duration of migraine ($r=0.621$, $p=0.001$), attack frequency ($r=0.568$, $p=0.001$) and VAS ($r=0.352$, $p=0.026$). We found that serum IMA levels in acute migraine attacks were significantly higher than in the control group.

Keywords: Migraine attack, ischemia-modified albumin, oxidative stress

Introduction

Migraine is a common chronic neurological disease characterized by moderate or severe headache attacks and reversible neurological and systemic symptoms [1,2]. Headaches are often accompanied by photophobia, phonophobia, nausea and vomiting [1,3]. Although its exact physiopathology is unknown, oxidative stress is suggested to play an important role in the pathogenesis of migraines [2,4]. Oxidative stress caused by an imbalance between the production of free radicals and the antioxidant defense mechanism has been associated with the pathophysiology of neurological diseases such as chronic neurodegenerative diseases, epileptic seizures, multiple sclerosis, and dementia [2]. Ischemia modified albumin (IMA) occurs as a result of the reduced binding capacity of transition metals such as cobalt, copper and nickel in the N-terminal region of albumin in cases of ischemia, hypoxia, acidosis, oxidative stress and free iron and copper exposure [3]. IMA is used as a marker of

hypoperfusion and oxidative stress [2, 5, 6]. In studies, it has been reported that serum levels increase in many neurological diseases [7-10]. Serum IMA levels were investigated in a small number of studies in migraine patients, but different results emerged and the findings were not clear. Some studies indicated that serum IMA levels increased in migraine patients compared to the control group [2, 3] while some studies did not find any difference [4]. In our study, we planned to investigate the serum IMA level of patients who were admitted into the emergency department with an acute migraine attack.

Materials and Methods

The study was initiated after obtaining approval of the local ethics committee (11.12.2020-428920). Our study included patients over the age of 18 who were diagnosed with migraines and admitted to the emergency department for migraine attacks, according to the 3rd edition of the International Classification of Headache Disorders (ICHD-3). Those with known neurological diseases other than migraine, cardiovascular disease, diabetes mellitus, renal failure, liver failure, hypertension, psychiatric disease, acute infection, pregnancy and malignancy were excluded from the study. The control group consisted of volunteer individuals who

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did not have a known disease. Demographic data of the migraine and control group were recorded. The number of attacks within three months and the duration of the disease in the migraine group was determined. The severity of pain in emergency admissions was evaluated with the Visual Analogue Scale (VAS). The VAS was determined by the patient's marking the visual scale on a line of 10 cm, from 0 indicating no pain to 10 expressing the worst pain.

For laboratory analysis, 5 ml of blood was taken from the patient and control group and centrifuged for 6 minutes per 3000 cycles/minute. The separated serums were stored in a freezer of 80°C until testing. Serum IMA levels were studied using the Human IMA ELISA kit (Sunred Biological Technology, Shanghai, China) in accordance with the operating procedures specified in the kit catalogs. Washing-incubation of the plate was done on the CombiWash (Human Diagnostics, Wiesbaden, Germany) device and the absorbance measurement was performed on the Chromate 4300 Microplate Reader (Awareness Technology, Palm City, USA) device. IMA's minimum detection limit was 2.26 ng/mL.

Statistical Package for the Social Sciences (SPSS v.22, Chicago, IL, USA) package program was used for statistical analysis. Before making a comparison between the groups, it was checked with the Kolmogorov-Smirnov test whether the data distribution was normal or not. Chi-square test for non-measurement parameters, Student's t-test for comparison of parameters between groups, Mann Whitney U test for comparison of non-parametric groups, and Pearson correlation test for examining the relationship between parameters in groups were performed. $P < 0.05$ values were accepted as the lowest significance level. Sample size was calculated using sample size calculating software G*Power version 3.1.9.2 (Germany). With power of 90%, 0.05 level of statistical significance and effect size of 0.8, sample size for each group was calculated to be 34.

Results

The study included 40 migraine attack patients and 40 volunteer control groups. The average age of the migraine group was 39.9 ± 8.2 and 31 were female. The average age of the control group was 42.5 ± 9.2 and 29 were women. There was no difference between groups in terms of age and gender ($p=0.18$, $p=0.79$, respectively).

The mean duration of the disease in the migraine group was 8.87 ± 4.76 years and within three months the average attack frequency was 2.55 ± 1.3 . The mean VAS was 8 ± 1.2 . In the migraine group, 77.5% ($n=31$) had nausea, 62.5% ($n=25$) vomiting, 60% ($n=24$) photophobia, and 52.5% ($n=21$) phonophobia accompanied headache. Table 1 shows the demographics of the groups and the clinical characteristics of the migraine group.

Mean serum IMA levels were significantly higher in the migraine group (117.5 ± 31.4 ng/mL) than in the control group (94.4 ± 27.3 ng/mL) ($p=0.001$) (Figure 1). In the ROC analysis, use of optimal IMA cutoff level of 92.6 ng/ml was associated with 70% sensitivity and 55% specificity (AUC = 0.713, 95% CI: 0.600-0.826, $p=0.001$) (Figure 2). A positive correlation was found between IMA levels and duration of migraine ($r=0.621$, $p=0.001$), attack frequency ($r=0.568$, $p=0.001$) and VAS ($r=0.352$, $p=0.026$).

Table 1. Demographic and clinical characteristics of a migraine attack and control group

	Migraine Attack	Control	P-value
Age (year)	39.9 ± 8.2	42.5 ± 9.2	0.18
Gender (female/male)	31/9	29/11	0.79
Nausea n (%)	31 (77.5)	-	-
Vomiting n (%)	25 (62.5)	-	-
Photophobia n (%)	24 (60)	-	-
Phonophobia n (%)	21 (52.5)	-	-
Aura n (%)	8 (20)	-	-
Mean VAS	8 ± 1.2	-	-
Migraine duration (year)	8.87 ± 4.76	-	-
Attack frequency / 3 months	2.55 ± 1.3	-	-

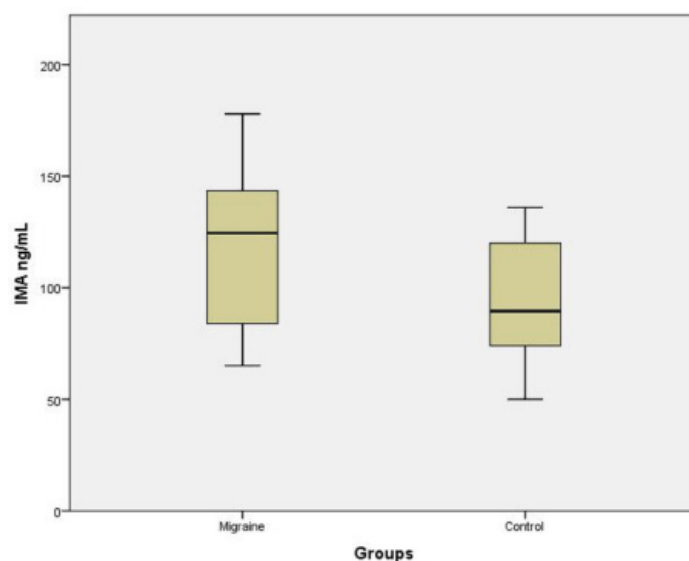


Figure 1. Comparison of ischemia modified albumin levels between a migraine attack and control group

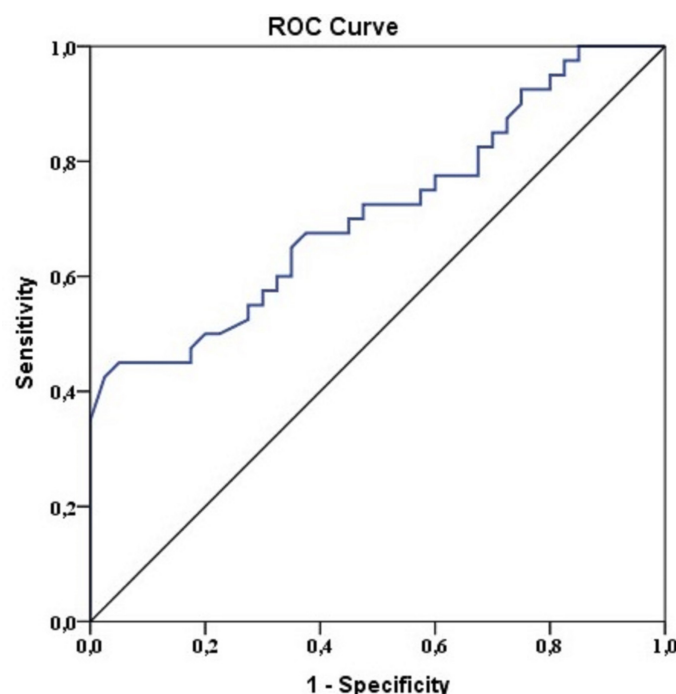


Figure 2. ROC analysis showing serum Ischemia modified albumin levels in a migraine attack

Eight patients had an aura. Serum IMA levels were higher in the aura migraine group than in the aura-free group (138.7 ± 16.6 ng/mL, 112.2 ± 32.2 ng/mL, $p=0.03$ respectively).

Discussion

In this study, we found that serum IMA level, which is an indicator of oxidative stress, was significantly higher in patients who were admitted to the emergency department with migraine attacks compared to the control group. The serum IMA level showed a positive correlation with VAS showing duration of the disease, frequency of attacks and pain intensity. The sensitivity of the serum IMA level in the diagnosis of a migraine was 70% and the specificity was 55%.

Reactive oxygen derivatives increased by ischemia and ischemic damage contributes to the formation of IMA. It has been reported in studies that IMA is a sensitive marker for the diagnosis of myocardial ischemia [6, 11, 12]. IMA is a nonspecific marker of tissue ischemia, and it has been shown that IMA levels increase in ischemic conditions such as ischemic stroke [7, 10, 13], pulmonary embolism [14], mesenteric ischemia [15], in addition to myocardial ischemia. IMA production during ischemic events is thought to be related to oxidative stress caused by free radicals during ischemia and/or reperfusion [6, 16].

In migraine, it is thought that the activity of some antioxidant enzymes decrease and, consequently, free radicals increase, resulting in oxidative stress [2, 4]. Oxidative stress can damage cell membranes, lipids, nucleic acids, and proteins [4]. It is thought there to be a link between migraine and vascular disease [3] and has been proposed as a risk factor for ischemic stroke [17, 18]. In a meta-analysis of 21 studies involving 622,381 patients conducted by Spector et al., Migraine was associated with a 2-fold increased risk of ischemic stroke [17]. Oligemia associated with cortical spreading depression (CSD), constriction of intracerebral great arteries and hypercoagulation associated with the endothelium, medications and inflammatory factors may cause cerebral ischemia in migraine patients [16, 18, 19].

Several studies have shown that serum IMA levels in migraine patients are higher than in the control group [2, 3, 16, 20]. Ersoy et al. found that the IMA level was higher than in the control group in 121 migraine patients they examined during the interictal period. White matter lesions were detected in 62 of these migraine patients. White matter lesions, a variant of small vascular disease, are thought to be caused by chronic ischemia due to perfusion deficiency. Serum IMA levels were found to be higher in migraine patients with white matter lesions than in those who did not. Increased serum IMA levels in migraine patients are thought to indicate the role of ischemia/hypoxia [3]. In their study, Say et al. compared 35 migraine patients with a healthy control group and showed that IMA and prolidase levels were significantly higher in migraine patients than in the control group as an indicator of oxidative stress [2]. Michalak et al. also compared 50 migraine patients and 25 healthy control groups in the interictal period and found that IMA was suddenly high in the migraine group [16]. In our study, we found that serum IMA level VAS was significantly higher than the healthy control group, supporting the above studies.

In addition to studies showing that serum IMA levels increase in

migraine patients, there are also studies in the opposite direction. In their study on 30 migraine patients without aura, Cakina et al examined IMA together with paraoxonase, arylesterase activities, thiols levels, the total oxidant status, total antioxidant status, and oxidative stress index levels. While they found that the levels of paraoxonase and arylesterase activities, which play an antioxidant role, were significantly lower in the migraine group compared to the control group, they could not find a significant difference between the other markers. They reported that the techniques used, patient subgroups and analyzed biological samples may be effective in these results, which contradict with other studies [4].

In our study, the serum IMA level was higher in the aura patient group than in the aura-free group. Michalak et al. [16] found the serum IMA level higher in the migraine group with aura than in the intermittent migraine group, similar to our study; while Say et al. [2] could not find a significant difference between the two groups.

Gunduztepe et al. [20] showed that there is a relationship between serum IMA level and the frequency of attacks and pain intensity. Michalak et al. [16] found that IMA had a positive correlation with VAS. In our study, supporting these studies, we found a positive correlation between serum IMA level and the frequency of attacks and VAS.

In our study, the serum IMA level was evaluated only during a migraine attack. The serum IMA levels of these patients in the interictal period were not measured. This is the limitation of our study.

In conclusion, we found that serum IMA levels in migraine attacks admitted to the emergency department were significantly higher than the healthy control group. We think that this increase in serum IMA level supports the oxidative stress resulting from hypoxia, which is suggested to play a role in the pathogenesis of migraine.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

All authors declare no financial support.

Ethical approval

Obtained approval of the local ethics committee (No: 97132852/050.01.04).

References

1. Dodick DW. Migraine. Lancet 2018;391:1315-30.
2. Say B, Badem ND, Ergun U. Serum levels of ischemia-modified albumin and prolidase in migraine subjects. J Health Sci Med. 2020;3:31-5.
3. Ersoy A, Yasar H, Mertoglu C, et al. Is ischemia associated with the formation of White matter lesions in migraine? Clin Neurol Neurosurg. 2020;193:105770.
4. Cakina S, Yücel S, Polat CC, et al. Oxidative stress parameters in patients with migraine without aura. Namık Kemal Tıp Dergisi. 2020;8:31-5.
5. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia a preliminary report. Emerg Med J. 2000;19:311-5.
6. Askin L, Sercelek A, Tanriverdi O, et al. A novel systemic indicator of cardiovascular ischemic events: Ischemia modified albumin levels. MN Kardioloji. 2019;26:198-202.
7. Menon B, Ramalingam K, Krishna V. Study of ischemia modified albumin as a biomarker in acute ischaemic stroke. Ann Neurosci. 2018;25:187-90.

8. Aydin O, Ellidag HY, Eren E, et al. Ischemia modified albumin is an indicator of oxidative stress in multiple sclerosis. *Biochemia Medica*. 2014;24:383-9.
9. Tunc S, Atagun MI, Neselioglu S et al. Ischemia-modified albumin: a unique marker of global metabolic risk in schizophrenia and mood disorders. *Psychiatry and Clinical Psychopharmacology*. 2019;29:123-9.
10. Gunduz A, Turedi S, Mentese A, et al. Ischemia-modified albumin levels in cerebrovascular accidents. *Am J Emerg Med*. 2008;26:874-8.
11. Talwalkar SS, Bon-Homme M, Miller JJ, et al. Ischemia modified albumin, a marker of acute ischemic events: A pilot study. *Ann Clin Lab Sci*. 2008;38:132-7.
12. Anwaruddin S, Januzzi Jr JL, Baggish AL, et al. Ischemia-modified albumin improves the usefulness of standard cardiac biomarkers for the diagnosis of myocardial ischemia in the emergency department setting. *Am J Clin Pathol*. 2005;123:140-5.
13. Senes M, Kazan N, Coskun O, et al. Oxidative and nitrosative stress in acute ischaemic stroke. *Ann Clin Biochem*. 2007;44:43-7.
14. Turedi S, Gunduz A, Mentese A, et al. The value of ischemia-modified albumin compared with d-dimer in the diagnosis of pulmonary embolism. *Respir Res*. 2008;9:49.
15. Gunduz A, Turkmen S, Turedi S, et al. Time-dependent variations in ischemia-modified albumin levels in mesenteric ischemia. *Acad Emerg Med*. 2009;16:539-43.
16. Michalak S, Osztynowicz K, Płóciniczak A, et al. Ischemia-modified albumin in patients during interictal period. *Journal of Medical Science*. 2016;85:231-7.
17. Spector JT, Kahn SR, Jones MR, et al. Migraine headache and ischemic stroke risk: an updated meta-analysis. *The American Journal of Medicine*. 2010;123:612-24.
18. Zhang Y, Parikh A, Qian S. Migraine and stroke. *Stroke and Vascular Neurology*. 2017;2:e000077.
19. Gryglas A, Smigiel R. Migraine and stroke: what's the link? what to do? *Curr Neurol Neurosci Rep*. 2017;17:22.
20. Gunduztepe Y, Setenay Mit S, Gecicioglu E, et al. The impact of acupuncture treatment on dynamic thiol-disulphide homeostasis and ischemia-modified albumin levels to assess the oxidative stress in migraine patients. *Acupuncture & Electro-Therapeutics Research*. 2020;44:229-40.