Original Article

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Serum Copeptin Levels in Adult Patients with a Migraine Attack: A Cross-Sectional Study

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Abstract

Aim: This study investigated the potential role of serum copeptin, a mediator of acute pain via sympathetic stress stimulation, as a biomarker of varying degrees of migraine-related disability. Specifically, we aimed to analyze whether the serum copeptin level can be used to differentiate migraine types (e.g., with and without aura).

Methods: The study population included 80 consecutively consenting adult patients who had migraine attacks and attended the emergency department from June 2020 through November 2020, as well as 80 age- and sex-matched healthy controls. Using the Migraine Disability Assessment Scale (MIDAS), the same medical professional assessed each patient's level of headache-related disability. Based on their MIDAS scores, the patients were separated into four groups: no disability (score 0-5; group MIDAS-I); mild disability (score 6-10; group MIDAS-II); moderate impairment (score 11-20; group MIDAS-III); and severe disability (score >20; group MIDAS-IV). There were also two categories of migraineurs: those with auras and those without auras. Upon admission, comparisons were made between the groups' serum copeptin values.

Results: In comparison to the control group, the patient group's serum copeptin levels were noticeably higher (2113.30±206.20 vs. 1383.40±488.40; p<0.001). The study of the receiving operator's characteristics showed that the cut-off copeptin level was 1898.5 pg/mL, with 90% sensitivity and 82.4% specificity for distinguishing patients from controls. There were no noticeable differences in the mean serum copeptin levels between the patient groups when compared by MIDAS score. Additionally, patients with and without aura did not differ notably in terms of mean serum copeptin levels. (2118.70±211.60 vs. 2071.10±160.40).

Conclusion: Serum copeptin levels may be used as a diagnostic aid to help anticipate migraine-related headache attacks when combined with clinical signs and symptoms.

Keywords: Copeptin, migraine, biomarker, headache

Introduction

Migraine is a primary headache disorder recognized by the International Headache Society (IHS). It is neurovascular in origin, caused by mechanisms involving neurogenic inflammation, cerebral vasomotor dysfunction, and cerebrovascular inflammation (1). Among the factors responsible for migraine are neuroinflammatory conditions, cytokines, numerous neuropeptides, and vasomotor changes. With the onset of a migraine attack, vasoactive peptides are formed as a result of trigeminal nerve stimulation, resulting in an increase in blood flow, leakage of proteins from the vessels, and neurogenic (2). However, the etiology of migraines is still not fully understood.

Unlike in other diseases, in which the identification and validation of biochemical markers have greatly improved, there are currently no accepted biochemical markers for chronic or episodic migraine attacks (3,4). The peptide arginine-vasopressin (AVP) is an important hypothalamic stress hormone released from the hypothalamus. The 39-amino-acid glycopeptide copeptin is a precursor of AVP and forms the C-terminal part of the 164 amino acid pre-provasopressin molecule (5). Copeptin is an easily measured biochemical marker of AVP released in response

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to many physiological and pathological stimuli, including pain, hypoglycemia, hypoxemia, stroke, infection, shock, and stress (6). It may thus serve as a biochemical marker of acute pain triggered by sympathetic stress stimulation (7). Nonetheless, there has been little research on the relationship between the serum copeptin level and acute migraine episodes (8). Clarification of this relationship may contribute to the prevention of unnecessary and excessive radiological examination requests in terms of the approach to diagnosis.

We hypothesized that serum copeptin levels may have predictive value in migraineurs who were admitted to the ED with complaints of headache. In this study, we investigated the correlation between the serum copeptin level and the Migraine Disability Assessment Score (MIDAS) in these patients. We also examined the predictive value of serum copeptin levels for differentiating between migraine with aura and migraine without aura (e.g., with and without aura).

Methods

Compliance with Ethical Standards

Ethical approval for this study was obtained from the Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (trial registration no. 2020/68). This study was conducted in accordance with the 1989 Declaration of Helsinki.

Patient Population

Eighty consecutive adult patients (61 females and 19 males, aged 18-56 years) who attended our emergency department with a migraine episode in the ictal phase were included in this cross-sectional study. The flowchart of the study is shown in Figure 1. The control group consisted of 80 age- and sex-matched, healthy volunteers. After their vital functions were measured, the patients were monitored in an isolated area in the ED, and they or their authorized representatives provided signed informed consent. Prior to their involvement in the study, all of the healthy participants were told about the protocol and provided with signed consent.

The third edition criteria of the Headache Classification Committee of the IHS and the patient's medical history were used to diagnose migraine (1). A migraine is characterized as having at least five headache attacks with a duration of 4 to 72 hours (untreated or inadequately treated) and at least two of the following symptoms: One of the following conditions must be present: unilateral location, pulsing quality, moderate or severe pain intensity, or exacerbation brought on by or resulting in the avoidance of regular physical activity (such as walking or ascending stairs). The same medical professional used the MIDAS to evaluate patients entering the emergency department for headache-related impairment. The questionnaire's score was derived to assess how a migraine headache affected the patient's capacity for functioning at work, in the house, and in everyday life (9). The following data were recorded for each patient: age, sex, symptoms, comorbidities [e.g., hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and coronary artery disease (CAD)], accompanying aura (e.g., visual, sensory, speech and/or language, motor, brainstem, retinal), duration of symptoms, MIDAS score, and serum copeptin level at admission. The people who had migraines were then separated into four groups depending on their MIDAS scores. There are four categories of disability: none (score 0-5; MIDAS-I group MIDAS-I), mild (score 6-10; group MIDAS-II), moderate (score 11-20; group MIDAS-III), and severe (score >20; group MIDAS-IV). In addition, migraineurs were divided into two subgroups, with and without aura. Serum copeptin levels on admission were compared between the groups.

Blood Sampling

Patients' venous blood samples (5 mL) were taken from the antecubital vein at the time of admission without the administration of any drugs, serum infusions, or imaging procedures that would have influenced the serum copeptin level. Blood samples were drawn into heparinized tubes and put right away in a freezer at 4 °C. Before usage, plasma was separated by centrifugation at 4,000 rpm for 5 min. It was then kept at 40 °C. Prior to analysis, the temperature of each serum sample was raised to room temperature.

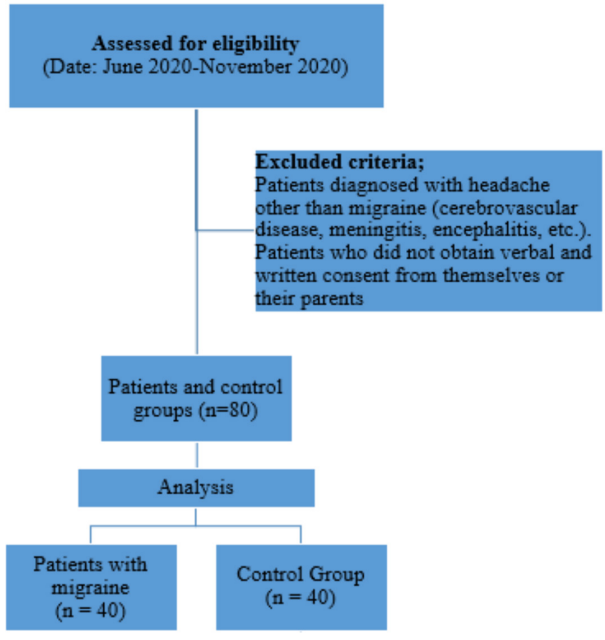

Figure 1. Flowchart of study

Measurement of Serum Copeptin

Using a human copeptin antibody, an enzyme-linked immunosorbent assay was used to determine the levels of serum copeptin (Catalogue No. YLA 1139HU; Shanghai YL Biotech Co.).

Calculation of the MIDAS Score

The MIDAS is used to determine how seriously a migraine affects the patient's quality of life. The MIDAS score has been related to clinical trials determining the need for medical care and has been demonstrated to have moderate test-retest reliability for headache patients (9).

Statistical Analysis

SPSS statistical software (version 15.0 for Windows; IBM Corp., NY, USA) was used to analyze the data. Categorical variables (such as sex and age) are reported as numbers (n) and a percentage (%); numerical data (such as copeptin values) are expressed as the mean (standard deviation), minimum, maximum, and median. The Mann-Whitney U test was used for non-normally distributed data, and chi-squared and Student's t-tests were used for intergroup comparisons (controls vs. patients). To calculate the cut-off copeptin level, predictive factors were identified using logistic regression analysis using the forward approach. Correlations between copeptin values and age, symptom duration, and MIDAS score were evaluated based on Spearman's rank correlation coefficient (rho) tests. The significance level was set at $p \leq 0.05$.

Results

The mean age of the 80 patients included in this study was 36.70±9.80 years (range: 18-56 years), and 61 were female (76.20%). The average age of the 80 healthy volunteers was 38.60±10.60 years (range: 19-57 years), and 61 were female (76.20%). Age and sex between patients and controls did not significantly differ from each other. Although the mean serum copeptin level was much higher in patients than in controls (1383.40±488.44 vs. 213.30±206.20) (Figure 2), it was not statistically significant. Comparing the patient and control groups in terms of demographics and serum copeptin levels is shown in Table 1.

A cut-off copeptin level of 1898.50 pg/mL was determined by receiver operating characteristic (ROC) analysis to be 90% sensitive and 82.4% specific for differentiating patients from controls [area under the curve (AUC) 0.923; 95% confidence interval (CI), 0.877-0.969] (Table 2 and Figure 3).

Using the MIDAS score, patients were categorized based on the degree of migraine-related disability; most of them participated in the MIDAS-II (n=31, 38.75%) and MIDAS-III (n=31, 38.75%) groups. Eleven patients (13.75%) were in the MIDAS-I group and seven (8.75%) in the MIDAS-IV group. Nine patients (11.3%) had auras, and 70 (88.7%) had none. The most common aura in patients was photophobia, which occurred in 55 patients (68.8%), followed by nausea (58.8%) in 47 patients, phonophobia in 42 patients (52.5%), anorexia in 13 patients (16.3%), vomiting in 6 patients (7.5%), and diarrhea in 3 patients (3.8%). The mean duration of symptoms according to the patients was 9.90±5.90 h. The minimum duration of symptoms was 2 h, and the maximum was 36 h.

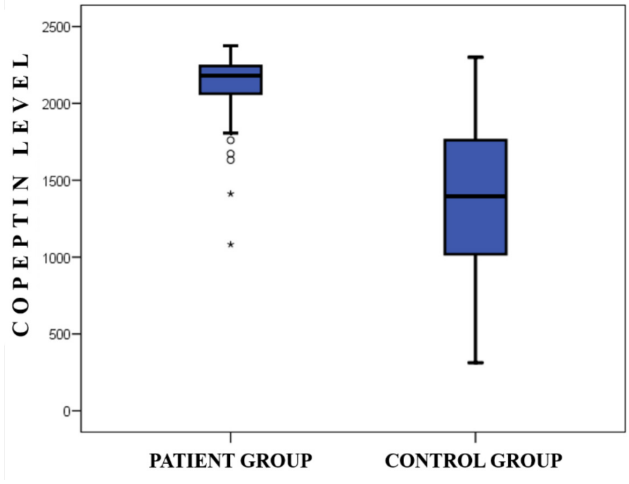

Figure 2. Serum copeptin levels (pg/mL) in patients and control groups

Table 1. Demographic data (age and gender) and plasma measures of 80 adult patients with migraine-related headache and 80 healthy controls

		Patients	Controls	
Characteristics		**% (n)**	**% (n)**	**p-value***
Gender	**Male** **Female**	23.8 (19) 76.2 (61)	23.8 (19) 76.2 (61)	0.189
		Mean±SD	Mean±SD	
Age		36.70±9.80	38.60±10.60	0.851
Copeptin (pg/mL)		2,113.30±206.20	1383.40±488.44	<0.001

Data are expressed as numbers (n), percentages (%), mean ± standard deviation (SD). *Intergroup comparisons (controls versus patients) were conducted using the chi-square, independent samples t-test, and Mann-Whitney U tests where appropriate

Table 2. Specificity and sensitivity ratios for serum copeptin levels to predict the patient with migrain-related headache in ROC curve analysis

Copeptin (pg/mL)		
Equal or higher value	Sensitivity	Specificity
1,756.50	0.950	0.750
1,764	0.938	0.750
1,783	0.938	0,.65
1,802	0.938	0.779
1,817.5	0.925	0.779
1,841.5	0.925	0.794
1,874	0.900	0.794
1,898.5	**0.900**	**0.824**
1,915.5	0.863	0.824
1,936.5	0.863	0.838
1,950	0.863	0.853
1,968	0.850	0.853
1,994.5	0.850	0.897
ROC: Receiver operating characteristic		

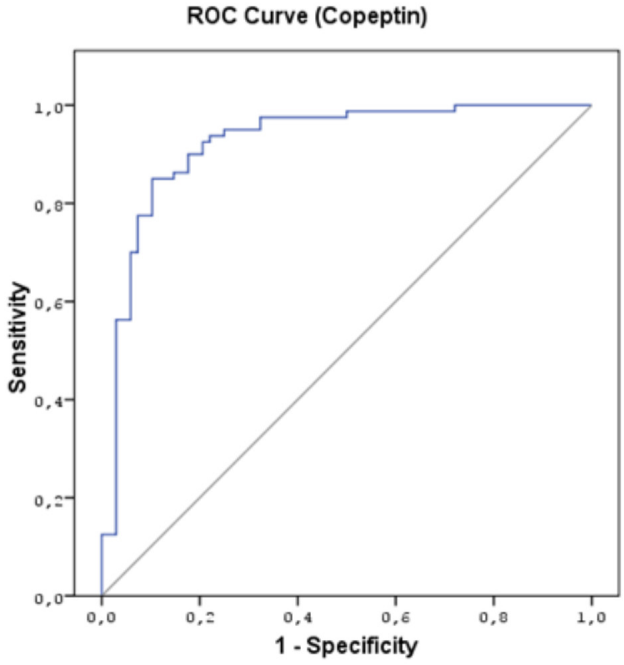

Figure 3. Specificity and sensitivity of the serum copeptin level for distinguishing patients with migrain attack from the controls using receiver operating characteristics curves (AUC 0.923; 95% CI 0.877-0.969)

AUC: Area under the curve, CI: Confidence interval, ROC: Receiver operating characteristics

Comorbidities were reported by 41.2% (n=33) of the patients and included HT (8.7%, n=7), DM (7.5%, n=6), CAD (5%, n=4), COPD (2.5%, n=2), and others (gastroesophageal reflux disease, hypothyroidism, anemia, asthma, and multiple sclerosis; 17.5%, n=14).

There was no statistically significant difference in the mean serum copeptin levels of the four MIDAS groups, nor was there a significant correlation (rho=-0.017 and p=0.883) between the serum copeptin level and the MIDAS score. Male and female patients also did not significantly differ in terms of the mean serum copeptin level. Although migraine patients without aura had greater mean serum copeptin levels than those with aura, the difference was not statistically significant (2,118.70±211.60 vs. 2,071.01±160.04) (Table 3).

Discussion

Migraines can occur at any age, including during childhood but especially during adolescence (10), and are approximately three times more common in women than in men (11). With increasing age, the number of early migraine attacks decreases. Migraines without aura are more frequent than migraines with aura (12). Consistent with those studies (10-12), in the present study, the prevalence of migraine varied according to age and sex. The mean age of the patients was 36.70 (±9.80, range 18-56) years, corresponding to middle age, and 76.2% were female, whereas 23.8% were male, a three-fold difference.

In the study of Yılmaz et al. (8), based on 52 migraineurs and 51 healthy individuals, the mean copeptin level in the patient group during the attack and non-attack periods was 689.28 pg/mL and 576.68 pg/mL, respectively, compared with 608.68 pg/mL in the control group. The difference in the mean copeptin level during the attack and attack-free periods was significant (p=0.026). The copeptin cut-off level was 388.67 pg/mL, which had 58.8% sensitivity and 60.7% specificity. In the study by Yılmaz et al. (8),

Table 3. Distrubution of serum copeptin levels according to gender, aura symptoms, and MIDAS score groups

		Copeptin (pg/mL)			
Characteristics		**Mean±SD**	**Minimum-Maximum**	**Median**	**p-value***
Gender	Male	2,128.30±117.09	1,854-2,307	2,180	0.532
	Female	2,108.70±227.40	1,082-2,375	2,180	
Aura	No	2,118.70±211.60	1,082-2,375	2,180	0.160
	Yes	2,071.01±160.04	1,806-2,307	2,121	
MIDAS	I	2,118.60±164.00	1,760-2,307	2,180	0.972
	II	2,097.80±256.30	1,082-2,375	2,180	
	III	2,127,30±177.90	1,412-2,307	2,180	
	IV	2,111.70±161.50	1,806-2,307	2,180	

Data are expressed as numbers (n), percentages (%), mean±standard deviation, median, or minimum and maximum values. *Mann-Whitney U test, MIDAS score: No disability (MIDAS; score 0-5 MIDAS-I group), mild disability (MIDAS; score: 6-10; MIDAS-II group), moderate disability (MIDAS score: 11-20; MIDAS-III group), severe disability (MIDAS: >20; MIDAS-IV group)
MIDAS: Migraine Disability Assessment Scale, SD: Standard deviation

although serum copeptin levels were not of diagnostic value, their use in the management of migraineurs in the ED was proposed.

Kazanasmaz et al. (13) measured copeptin in the plasma samples of 61 migraine patients and 60 paired healthy controls to determine the value of copeptin in predicting migraines in the young. Copeptin's level (mean 298.25 pg/mL) in the patients was significantly higher than that in the controls (194.35 pg/mL). The threshold was 249.5 pg/dL, which in the diagnosis of migraine had a sensitivity of 64% and a specificity of 67%.

Blum et al. (14) evaluated 391 patients who presented to the ED with headaches: 219 (56%) had primary headaches and 172 (44%) had secondary headaches. Among the latter, 75 (19%) were considered serious. The copeptin level in the group with a severe headache was significantly higher than that in the group with a milder headache (6.44 pmol/L vs. 3.89 pmol/L; p<0.0001). In addition to the underlying disease in secondary headache and the associated stress, the pain itself may have contributed to an increase in the copeptin level, which would explain the very high copeptin values in some patients with migraine.

Similar to that, in the current investigation, patients' mean serum copeptin levels were considerably greater than those of the controls. (1,383.40±488.44 pg/mL vs. 213.30±206.20 pg/mL). ROC analysis identified a copeptin cut-off level of 1898.50 pg/mL with 90% sensitivity and 82.4% specificity (AUC 0.923; 95% CI, 0.877-0.969) for distinguishing the two groups. However, there was no statistically significant difference in the mean serum copeptin levels between the groups as measured by the MIDAS score (p=0.972), nor was there a significant correlation between the serum copeptin level and the MIDAS value (rho=-0.017; p=0.883).

Study Limitations

There were several limitations to this study. First, it was conducted at a single center. Second, when patients first arrived at the emergency department, migraine-related pain severity was not assessed for each patient using a visual analogue scale (VAS). This made it impossible to compare changes in serum copeptin levels in patients with migraine based on the intensity of their pain as measured by the VAS score. Third, copeptin may have an impact on long-term results; however, the levels were not examined at a time when the patients were not experiencing headaches after being hospitalized. Future research should consider these factors. Despite these limitations, this is the first clinical study that, to our knowledge, has investigated the relationship between the level of serum copeptin and the severity of migraine-related disability as measured by the MIDAS score.

Conclusion

Serum copeptin levels in patients diagnosed with migraine attacks are not useful in predicting the degree of migraine-related disability as assessed by the MIDAS score. However, it may be useful in predicting headaches associated with a migraine attack in conjunction with clinical signs and symptoms. More clinical trials with larger samples are required to confirm these results.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (trial registration no. 2020/68).

Informed Consent: Written informed consent was obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: O.D.S., O.K., S.C., Design: I.E., O.D.S., O.K., Data Collection or Processing: I.E., O.D.S., O.K., Analysis or Interpretation: O.K., S.C., O.S., Literature Search: I.E., O.D.S., H.E., Writing: I.E., O.D.S., O.K., O.S.

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

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