ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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SERUM COPEPTIN LEVEL AS A BIOMARKER FOR DETECTING TRANSIENT ISCHEMIC ATTACK IN THE EMERGENCY ROOM: A PROSPECTIVE CASE-CONTROL STUDY

ACİL SERVİSTE GEÇİCİ İSKEMİK ATAK TESPİTİNDE BİYOBELİRTEÇ OLARAK SERUM KOPEPTİN DÜZEYİ: PROSPEKTİF BİR VAKA KONTROL ÇALIŞMASI

Hamit Hakan ARMAĞAN[1], Kıvanç KARAMAN[2], Derya YALÇIN YILMAZ[3], Vedat Ali YÜREKLİ[4], Özgür ÖNAL[5], Abdurrahman ŞİMŞEK[6], Fevziye Burcu ŞİRİN[7], Nesrin Gökben BECEREN[1], Önder TOMRUK[1]

[1] Suleyman Demirel University, Faculty of Medicine, Emergency Medicine Department, ISPARTA
[2] Muğla Sıtkı Koçman University, Faculty of Medicine, Emergency Medicine Department, MUĞLA
[3] Isparta State Hospital, Emergency Department, ISPARTA
[4] Suleyman Demirel University, Faculty of Medicine, Department of Neurology, ISPARTA
[5] Suleyman Demirel University, Faculty of Medicine, Department of Public Health, ISPARTA
[6] Ağrı Training and Research Hospital, Emergency Department, AĞRI
[7] Suleyman Demirel University, Faculty of Medicine, Department of Biochemistry, ISPARTA

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Öz

Amaç
Acil Servise (AS) başvuran TİA (Geçici iskemik atak) tanısı almış hastaların plazma kopeptin düzeylerini sağlıklı kontrollerle karşılaştırarak TİA saptamak için kopeptin'in tanısal doğruluğunu araştırmayı amaçladık.

Gereç ve Yöntem
Acil servise nörolojik bir semptomla başvuran hastalar arasında ileriye dönük bir vaka kontrol çalışması yaptık. Nörolog tarafından TİA tanısı konan hastalar dahil edildi. 38 hastanın elektrokardiyografi, manyetik rezonans görüntüleme ve karotis doppler ultrasonografi tetkik sonuçları; Acil servis sonuçları (hastaneye yatış, taburculuk), risk grubu dağılımı (ABCD2 puanlarına göre) ve bir yıllık tekrar olay insidansına ilişkin değişkenler karşılaştırıldı. Ayrıca hastaların serum kopeptin düzeyleri sağlıklı kontrollerle karşılaştırıldı.

Bulgular
Ortalama kopeptin düzeyi hasta grubunda 435.80 ± 316.45 pg/ml iken kontrol grubunda 770.20 ± 912.53 pg/ml idi. TİA'lı hastaların ortalama kopeptin düzeyi anlamlı olarak daha düşüktü (p = 0.018). TİA tanısında tüm katılımcılarda kopeptin 386.28 pg/ml cut-off değerinde %60.53 duyarlılık ve %68.42 özgüllüğe sahipti. Ayrıca 60 yaş üstü katılımcılarda kopeptin 460.37 pg/ml cut-off değerinde %75.86 duyarlılık ve %72.41 özgüllüğe sahipti.

Sonuç
Bildiğimiz kadarıyla bu, bir serum biyobelirteçlerinin TİA tanısında yüksek etkinliğini gösteren ilk çalışmadır. Klinik şüphesi düşük ve kopeptin değeri düşük olan hastalarda acil hekimleri alternatif tanıları araştırmalıdır.

Anahtar Kelimeler: Arginin-vazopressin, Kopeptin, Acil, Nöroloji, Geçici İskemik Atak'.

İletişim kurulacak yazar/Corresponding author: hhakan2002@yahoo.com
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ORCID IDs of the authors: H.H.A: 0000-0002-5749-3753; K.K: 0000-0002-4105-2785; D.Y.Y: 0000-0002-5553-155X; V.A.Y: 0000-0002-2042-4463; Ö.Ö: 0000-0001-6514-2120; A.Ş: 0000-0003-1280-3292; F.B.Ş: 0000-0001-5304-1007; N.G.B: 0000-0001-7902-1477; Ö.T: 0000-0003-2997-1938

Abstract

Objective
We aimed to investigate the diagnostic accuracy of copeptin to detect transient ischemic attack (TIA) by comparing the plasma copeptin levels of patients diagnosed with TIA who were admitted to the Emergency Department (ED) with those of healthy controls.

Materials and Methods
We conducted a prospective case-control study among patients admitted to the ED with a neurological symptom. The patients diagnosed with TIA by the neurologist were included. The results of electrocardiography, magnetic resonance imaging, and carotid doppler ultrasonography investigations of 38 patients; the ED outcomes (hospitalization, discharge), the risk group distribution (according to ABCD2 scores), and the variables regarding one-year re-event incidence were compared. Additionally, the serum copeptin levels of the patients were compared to those of healthy controls.

Results
The mean copeptin level was 435.80 ± 316.45 pg/ml in the patient group, whereas it was 770.20 ± 912.53 pg/ml in the control group. The mean copeptin level of patients with TIA was significantly lower (p = 0.018). In the diagnosis of TIA, copeptin had 60.53% sensitivity and 68.42% specificity at a cut-off value of 386.28 pg/ml, in all the participants. In addition, in participants above 60 years old, copeptin had 75.86% sensitivity and 72.41% specificity at a cut-off value of 460.37 pg/ml.

Conclusion
To the best of our knowledge, this is the first study demonstrating the high efficacy of a serum biomarker in the diagnosis of TIA. Emergency physicians should search for alternative diagnoses in patients with a low degree of clinical suspicion and a lower copeptin value.

Keywords: Arginine-vasopressin, Copeptin, Emergency, Neurology, Transient Ischemic Attack.

Introduction

Transient ischemic attack (TIA) is described as a short-term period of neurological dysfunction (lasting <24 hours) that develops because of focal cerebral ischemia with no evidence of permanent cerebral infarction (1). Since the definition of TIA, which is the most significant precursor of stroke, is related to subjective criteria, the diagnosis and management of patients with TIA is a clinically difficult challenge for emergency medicine specialists, particularly in an Emergency Department (ED) where magnetic resonance imaging (MRI) is unavailable. It is also reported that 30% to 50% of classically defined TIAs show brain injury on diffusion-weighted MRI (1). Several clinical management models have been proposed to solve this challenge (1, 2). The most commonly used model in clinical practice is the ABCD2 scoring system, and adding various imaging methods and laboratory tests to this system has been reported to be beneficial in recent years (3, 4). However, most of these studies were related to the evaluation of stroke risk, and the number of studies that have evaluated how TIA is diagnosed in the ED is insufficient.

One of the first physiological responses in stroke is the activation of the hypothalamic-pituitary-adrenal axis (5). Besides, various studies have reported a significant relationship between the arginine-vasopressin level and the severity of stroke (6). However, arginine-vasopressin is challenging to use in clinical practice because of its very short half-life in plasma, its instability in a plasma sample even at -20°C, and its high binding ratio to platelets (7, 8). In recent years, copeptin, which is known to be present in plasma in an amount equal to arginine-vasopressin and more stable and easier to measure, has been investigated as a diagnostic and prognostic marker since it has revealed physiological stress in numerous clinical pathologies (9-11). Thus, we believe that copeptin might be a significant parameter for diagnosing TIA, which is considered a precursor of stroke.

The primary aim of this study was to investigate the utility of copeptin as a potential diagnostic marker for TIA by comparing the plasma copeptin levels of patients with TIA admitted to the ED with the healthy control group. The secondary aim of the study was to evaluate the findings in electrocardiography (ECG), hospital admission MRI, the recurrent cerebrovascular event (re-event) ratio in one year, and the carotid Doppler ultrasonography (US) in patients with TIA group and then to investigate the relationship between these variables and plasma copeptin level.

Materials and Methods

Study Population

This is a prospective single-center study conducted in the ED of Suleyman Demirel University hospital, Emergency Medicine Department. As of 01.03.2020, patients who admitted to the ED with a symptom of functional neurological disorder lasting less than 1 hour in the last 24 hours were examined by a neurologist (VAY) who is one of the authors of the study. All adult patients (above 18 years old) diagnosed with TIA by the neurologist were included in this study. Following the written consent of the patients, blood samples were taken. Also, patients' ECG, MRI, carotid Doppler US findings, and ED outcomes were recorded when available. Every patient was re-evaluated by phone or outpatient clinic control one year after his/her first admission date to examine re-event. Patients were excluded if they met any of the following criteria: had any other acute or chronic illnesses or any drug use, a history of trauma within the last week, a history of alcohol or corticosteroid use within the last week, any underlying morbidity that could have caused neurologic dysfunction, and pregnancy.

A control group was formed from healthy volunteers who had similar gender distribution with the patient group. All exclusion criteria determined for the patient group are also valid for the control group. Written consent was obtained from all the volunteers. All the participants underwent a detailed neurological examination, which was done by the neurologist. Since the mean age of the patient group was high, we encountered difficulty in finding healthy controls who were advanced in age. As a result, the mean ages of the patient and the healthy control groups were not similar. However, we tried to overcome this difficulty by equalizing the number of patients and controls aged over 60 years.

Ethics

The study was approved by the local ethics committee of Suleyman Demirel University, Faculty of Medicine Clinical Research Ethics Committee (protocol code: 2020/64). The study was also performed following the principles of the Declaration of Helsinki.

Sample Collection And Measurement Of Serum Copeptin Levels

Peripheral venous blood samples were collected in a gel containing tubes and centrifuged at 3000 rpm for 10 minutes. Then separated serum samples were stored at -80°C until the study day. Serum copeptin levels were measured with the enzyme-linked immunosorbent assay (ELISA) method. According to the manufacturer's instructions of a commercial ELISA kit (Human Copeptin ELISA Kit, E-EL-H0851, Elabscience, Wuhan, China), a calibration curve was generated by measuring the standard concentrations, and the copeptin concentrations of each sample were calculated from the calibration curve. The detection limit of the ELISA kit was 18.75 pg/ml.

Statistical Analyses

The data were analyzed with SPSS 20.0 (IBM Inc., Chicago, IL, USA). Descriptive statistics are presented as the mean ± SD for numerical variables and frequency (percentage) for categorical variables.). Several statistical tests were conducted. To evaluate whether continuous variables conform to the normal distribution curve, the Shapiro-Wilk W test was used. When the result of this test was negative, Kruskal-Wallis and Mann-Whitney U tests were used to compare the independent samples. As for categorical variables, a chi-square analysis was performed. We investigated the diagnostic performance of copeptin regarding TIA with a Receiver Operating Characteristic (ROC) curve. The relevant statistical measures (i.e., positive or negative predictive values, sensitivity, and specificity) were estimated relying on the thresholds taken from the curve. We specified the size of the sample based on a power analysis using GPower 3.1.0 (Universitat Kiel). The analysis indicated that to be able to achieve a power of 80% combined with 5% false positive and 0.5 effect size, the least number of patients needed to be 38 and that of the controls needed to be 76. The level of significance was determined to be less than 0.05.

Results

The results of ECG, MRI, and carotid Doppler US of 38 patients with TIA, the ED outcome (hospitalization, discharge), risk group distribution (according to ABCD2 scoring), together with the variables regarding one-year re-event incidence and the detailed comparison of serum copeptin levels according to these variables are shown in Table 1. Among all these clinical features, copeptin had a statistical difference only in the re-event parameter. Patients with re-event within 1 year had statistically significantly higher copeptin levels.

The mean serum copeptin level was 435.80 ± 316.45 pg/ml in the patient group, whereas it was 770.20 ± 912.53 pg/ml in the control group (Figure 1). The mean serum copeptin level of patients with TIA was significantly lower (p = 0.018). There was no statistical difference between the two groups regarding gender distribution, whereas the mean age of the patients

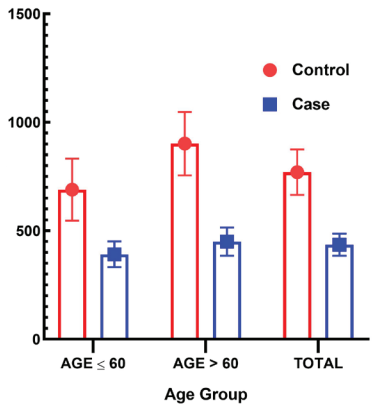


Figure 1
Comparisons of copeptin levels

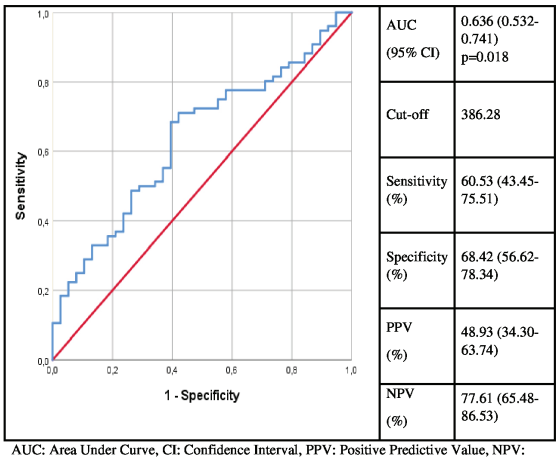
with TIA was significantly higher compared to the control group ($p < 0.001$) (Table 2). Thus, serum copeptin values of the patient and control groups were compared again considering 60 years of age (the 25th percentile within the patient age range) as the criterion, serving as a factor for the ABCD2 score. While no difference regarding serum copeptin level was found between the patients and the controls aged 60 years and below, it was determined that the patient group aged over 60 years had a statistically significantly lower serum copeptin level than the controls (Table 3) (Figure 1). A detailed comparison clinical features of patients according to 60 years was also given in the table 4.

The diagnostic performance of copeptin in TIA was evaluated by a receiver operating curve analysis either in all participants or in participants above 60 years old. Copeptin had a sensitivity of 60.53% and specificity of 68.42% at a cut-off value of 386.28 pg/ml in all participants and sensitivity of 75.86% and specificity of 72.41% at a cut-off value of 460.37 pg/ml in participants above 60 years old. More detailed information is provided in Figures 2 and 3.

Table 1 Comparison of copeptin levels according to the clinical features of the patients

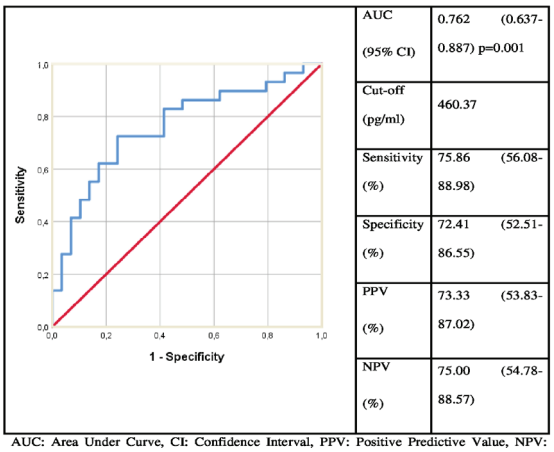
		n (%)	Copeptin level (pg/ml)	P value
ECG findings	Sinus rhythm	29 (76.3)	463.37 ±354.94	0.499
	Atrial fibrillation	9 (23.7)	346.98 ±102.78	
Outcome in the ED	Hospitalized	30 (78.9)	445.20 ±345.46	1.000
	Discharged	8 (21.1)	400.56 ±181.81	
Risk group according to ABCD2 score	Low (0-3)	8 (21.1)	376.94 ±126.04	0.929
	Moderate (4-5)	22 (57.8)	475.55 ±395.74	
	High (6-7)	8 (21.1)	385.36 ±178.15	
Re-event	Exist	7 (18.4)	487.04 ±138.62	**0.049**
	Absent	31 (81.6)	424.23 ±344.83	
Acute cerebral infarction in MRI	Exist	14 (36.8)	575.17 ±481.11	0.120
	Absent	24 (63.2)	354.51 ±107.44	
Stenosis in Carotis Doppler US (n:26)	No stenosis	6 (23.2)	366.15 ±88.23	0.943
	<%50	14 (53.8)	519.45 ±494.43	
	%50-70	3 (11.5)	398.38 ±169.94	
	>%70	3 (11.5)	412.60 ±98.83	

ECG: Electrocardiography, MRI: Magnetic Resonance Imaging, US: Ultrasonography, ED: Emergency Department.



AUC: Area Under Curve, CI: Confidence Interval, PPV: Positive Predictive Value, NPV: Negative Predictive Value

Figure 2
Receiver operating characteristic curve and performance of copeptin in all patients with TIA



AUC: Area Under Curve, CI: Confidence Interval, PPV: Positive Predictive Value, NPV: Negative Predictive Value

Figure 3
Receiver operating characteristic curve and performance of copeptin in patients above 60 years

Table 2 Comparison of patients with TIA and control group according to copeptin level and demographic features

	Patient	Control	P value
Age (mean ±SD)	70.37 ±14.05	53.72 ±20.28	**<0.001**
Gender (m/f)	23/15	35/41	0.145

SD: Standart Deviation, M: Male, F: Female

Table 3 Comparison of copeptin levels among patients and controls

		Copeptin (mean±SD- mean rank)	P value
Participants <60 y	Patients (n:9)	391.46 ±176.62 -24.44	0.145
	Controls (n:47)	689.18 ±980.95 -29.28	
Participants ≥60 y	Patients (n:29)	449.57 ±350.12 -21.90	**0.001**
	Controls (n:29)	901.52 ±787.85 -37.10	
All Participants	Patients (n:38)	435.80 ±316.45 -47.13	**0.018**
	Controls (n:76)	770.20 ±912.53 -62.68	

Discussion

Our study revealed that copeptin could be used reliably to diagnose TIA in the ED. Determining the diagnosis of patients who present to the ED with the complaint of transient neurological dysfunction has always been challenging for emergency physicians. Prabhakaran et al., in their study, reported that the final follow-up diagnosis was different in 60 out of 100 patients diagnosed with TIA in the ED (12). The primary reason for encountering such a diagnostic difficulty is the absence of an objective diagnostic criterion or, more importantly, a diagnostic test. The effectiveness of numerous serum biomarkers has been investigated, but no satisfactory result has been reported until now (13). To the best of our knowledge, this is the first study demonstrating the high efficacy of a serum biomarker in the diagnosis of TIA.

Studies evaluating TIA patients have revealed some information about imaging results. We found two small population studies have systematically assessed perfusion-weighted MRI in the evaluation of TIA patients. In both of these series, perfusion abnormalities were found in approximately one third of patients (14, 15). In another study designed by Widjaja et al, 7.5% of patients showed greater than 50% stenosis on screening with carotid Doppler ultrasound (16). In our study, similarly with literature, 36% of patients have positive MRI findings. However, the number of patients with greater than 50% stenosis on screening with carotid Doppler ultrasound is higher than literature. We think that the reason for this discrepancy is the low number of patients. Nevertheless, we believe that the results of our study are suitable for generalization, especially considering the MRI findings, which are compatible with the literature.

It has been shown that copeptin, a neuropeptide released from the pituitary gland, could be used as a diagnostic and prognostic marker in many neurologic disorders (17). However, studies conducted on copeptin in patients with TIA have focused more on its prognostic value rather than its diagnostic efficacy (18). The most comprehensive study on this topic was conducted by De Marchis et al., and it was reported that the serum copeptin level was significantly high in patients diagnosed with stroke in a three-month period (19). Also, in that study, it was stated that higher copeptin levels improved the prognostic value of the ABCD2 score for the prediction of stroke after TIA (18). Purroy and Katan reported similar results in their studies (20, 21). Even though differences regarding the sample size and methodology were present between the mentioned studies and ours, our results were consistent with the literature. We also determined that the serum copeptin level was significantly high in patients that re-event was occured within the one-year period. Based on these findings, we believe that serum copeptin levels would be useful for the prediction of re-event in addition to its diagnostic success in patients with TIA. In the studies mentioned above, the three-month re-event incidence was between 6.0% and 9.3% (18-20). On the other hand, the re-event incidence in our study (18.4%) seemed to be higher than those reported in the literature, but its primary cause was that the follow-up period was as long as one year.

It is well-known that the incidence of cerebrovascular disorder increases with advancing age. Such an increase is also present in patients with TIA; thus, one of the parameters of ABCD2 scoring, which is the most commonly used risk score in clinical practice, is 60 years of age. In our study, it was also determined that most of the patients (76.3%) were over 60 years of age. When we evaluated the patients and controls aged over and under 60 years among themselves, we determined that the sensitivity was 75%, while the specificity was 72% in patients over 60 years of age. Based on this result, we suggest that in patients aged over 60 years with a serum copeptin level above 460 pg/ml, clinicians should focus on pathologies other than TIA, and further tests for TIA would be unnecessary. We also determined that the serum copeptin level was lower in patients with TIA compared to the controls in the group with participants below 60 years. However, such a reduction was not statistically significant. Considering that the high misdiagnosis rate in patients with TIA had been reported to be associated with young age in some studies (22), we suggest that the serum copeptin level is not a reliable parameter particularly among young patients. On the other hand, we believe that a small number of patients aged under 60 years has an effect on that result.

Our study had various limitations. The most important limitation was being single-centered. Besides, even though the number of patients was determined through power analysis, it might be suggested that the number of patients would be relatively small when divided into sub-groups. Since the mean age of the patient group was high, we encountered difficulty in finding healthy controls who were advanced in age. As a result, the mean ages of the patient and the healthy control groups were not similar. However, we tried to overcome this difficulty by equalizing the number of patients and controls aged over 60 years.

Conclusion

In conclusion, our study revealed that the diagnosis of TIA could be reliably made in patients with a serum copeptin level over 386.28 pg/ml. We suggest that emergency physicians should search for alternative diagnoses rather than performing further investigations in patients with a low-degree clinical suspicion together with a smaller serum copeptin value. However, further studies are still required on this subject.

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

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