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Copeptin Levels in Clinically Silent Multiple Sclerosis

Klinik Sessiz Multipl Sklerozda Kopeptin Düzeyleri

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Abstract

Objective: Hypothalamic-pituitary-adrenal (HPA) axis dysfunction is thought to be found in patients with multiple sclerosis (MS). Copeptin is a serum protein that is indicated as an indirect marker of HPA axis. The aim of this study was to evaluate the relationship between HPA axis and clinically silent MS (CSMS) by evaluating copeptin levels.

Materials and Methods: Sixty patients with CSMS which was defined as relapsing-remitting MS without attack and progression, and 60 healthy individuals were included in the study from September 2016 to September 2017. All patients were in the remission period. HPA axis dysfunction was examined by measuring serum copeptin levels in all individuals. Copeptin level was compared with clinical parameters in patients with MS.

Results: A total of 120 individuals were composed of 60 patients with CSMS and 60 healthy controls. The average ages of the patients and the control group were 37.1±8 (20-52) and 35.1±8.9 (18-54), respectively. The copeptin level was significantly lower in patients compared to the control group ($p<0.001$). In both groups, gender played no differential role in copeptin levels ($p<0.05$). No significant correlation was determined between copeptin levels, age ($r=0.121$, $p=0.188$), last Expanded Disability Status Scale score ($r=-0.035$, $p=0.790$) and disease duration ($r=0.032$, $p=0.810$).

Conclusion: These results indicate that HPA axis may also be hypoactive in remission period in patients with CSMS. According to our findings, we consider that copeptin levels can be used as a prognostic marker in patients with clinically inactive MS in the future.

Keywords: Hypothalamic pituitary adrenal axis, multiple sclerosis, copeptin

Öz

Amaç: Multipl sklerozlu (MS) hastalarda hipotalamus-hipofiz-adrenal (HPA) aksın disfonksiyonunun ortaya çıktığı düşünülmektedir. Kopeptin, HPA ekseninin dolaylı bir belirteci olarak belirtilen bir serum proteinidir. Bu çalışmanın amacı, kopeptin düzeylerini değerlendirerek HPA aksı ile klinik sessiz MS (KSMS) arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Eylül 2016-Eylül 2017 tarihleri arasında atak ve progresyon göstermeyen 60 KSMS tanılı hasta (ataksız ve progresyonsuz relapsing-remitting MS'li hastalar) ve 60 sağlıklı birey çalışmaya dahil edildi. Tüm hastalar remisyon dönemindeydi. HPA aksın disfonksiyonu serum kopeptin düzeyleri ölçülerek değerlendirildi. Kopeptin düzeyleri MS'li hastalarda klinik parametrelerle karşılaştırıldı.

Bulgular: Altmış KSMS'li hasta ve 60 sağlıklı kontrol olmak üzere toplam 133 birey çalışmaya alındı. Hastaların ve kontrol grubunun yaş ortalamaları sırasıyla 37,1±7,8 (18-60) ve 34,9±8,6 (18-54) idi. Kontrol grubuna göre hastalarda kopeptin düzeyi anlamlı olarak daha düşüktü ($p=0,001$). Her iki grupta da cinsiyet ile kopeptin düzeyleri arasında anlamlı fark yoktu ($p<0,05$). Kopeptin düzeyleri ile yaş ($r=0,255$, $p=0,064$), son Genişletilmiş Özürlülük Durum Ölçeği skoru *(Expanded Disability Status Scale)* ($r=-0,126$, $p=0,325$) ve hastalık süresi ($r=0,168$, $p=0,187$) arasında anlamlı bir ilişki saptanmadı.

Sonuç: Bu sonuçlar, KSMS'li hastalarda remisyon döneminde HPA aksının de hipoaktif olabileceğini göstermektedir. Bulgularımıza göre, kopeptin düzeylerinin klinik olarak aktivite göstermeyen MS'li hastalarda gelecekte prognostik belirteç olarak kullanılabileceğini düşünmekteyiz.

Anahtar Kelimeler: Hipotalamus-hipofiz-adrenal aks, multipl skleroz, kopeptin

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Introduction

Environmental and genetic factors are effective in the development and progression of multiple sclerosis (MS) which is an autoimmune disease. At this point, the neuroendocrine system has important functions in triggering autoreactive immunity (1,2). The neuroendocrine system, which also has an immunomodulatory role, performs these effects through hormones, by using connection pathways such as the hypothalamic-pituitary-adrenal (HPA) axis.

The HPA axis dysfunction is reported in several studies in MS (2). One of the most important hormones in the HPA axis is arginine vasopressin (AVP). AVP, which has homeostatic, endocrinological and neurological effects, has a role in balancing the osmolality of plasma, responding to stress and adaptation (3). AVP shows its effects on three different receptors. It mediates arteriolar vasoconstriction via V1a receptor and antidiuretic effects via V2 receptor (3). V3 (also known V1b) receptor is found in the adenohypophysis and pancreas and provides adrenocorticotrophic hormone (ACTH) and insulin secretion, respectively (3). The measurement of AVP serum level is difficult because it is released in a pulsatile pattern, and is unstable due to its short half-life; moreover, it is bound to platelets at a high rate (4,5). Copeptin, which is a 39-amino acid peptide, is synthesized together with AVP from 164 amino acid polypeptide pre-provasopressin, a precursor molecule, located at the C-terminal part of the precursor molecule (6). Unlike AVP, it is a stable molecule and it is easy to measure its level in the plasma (5). Copeptin levels are indicators of AVP levels since activation of the HPA axis stimulates copeptin secretion into the circulation from the posterior pituitary gland in equimolar amounts with AVP. Therefore, copeptin levels can be used as a marker of HPA axis activity (3).

The release of copeptin is activated not only by changes in plasma osmolality and blood volume, but also endogenous stress and inflammation (7). Moreover, copeptin has been reported to be a significant diagnostic and prognostic marker in many diseases such as ischemic stroke, intracerebral and subarachnoid hemorrhages, head trauma, acute myocardial infarction, heart failure and sepsis (4,6). It is also thought that copeptin has a role in neuroimmunological diseases. Although there are data that demonstrate HPA axis dysfunction in patients with MS, there are only a limited number of studies in which copeptin levels are evaluated. In these studies, the role of copeptin in MS has not been clarified. In the present study, patients with relapsing-remitting MS (RRMS) without attack(s) and progression [clinically silent MS (CSMS)], were included for evaluating the inflammatory nature of RRMS independently of attack or progression. We aimed to investigate HPA axis dysfunction by measuring serum copeptin levels of patients with MS, and to compare them with healthy subjects.

Materials and Methods

Study Population

Sixty recently diagnosed patients with CSMS and 60 healthy individuals were included in the study from September 2016 to September 2017. Patients with RRMS were preferred because inflammation is prominent in this period, while neurodegeneration takes over in progressive MS clinical subtypes such as secondary progressive MS and primary progressive MS. Therefore, we thought that it was more accurate to measure copeptin levels to reflect HPA axis activity in patients with RRMS in which neuroinflammation is in the foreground. However, in order to assess the inflammatory nature of MS regardless of attack and progression, patients with Expanded Disability Status Scale (EDSS) scores below 5.0 and who had no attack for at least 6 months were included and they were named as patients with "clinically silent" MS. Patients were followed up whether they had an attack by monitoring their symptoms including fatigue, depressive symptoms and cognitive impairment that might be associated with in HPA axis dysfunction. In our clinic, if symptoms and neurological examination were suggestive of an attack, neuroimaging was performed. The eligibility criteria for inclusion were as follows: MS diagnosed by a neurologist, being aged between 18-59 years, no clinical and radiological attack(s) in the last six months, no progression in one year follow-up, and no corticosteroid treatment in the last six months. Patients with fluid-electrolyte imbalance, malignancy or psychiatric disease, patients with an acute inflammatory process such as sepsis and community-acquired pneumonia, patients who had an ischemic stroke, acute myocardial infarction or chronic obstructive pulmonary disease exacerbation in last three months, patients who received oral corticosteroid or pulse corticosteroid in the last six months, and patients with history of chronic diseases such as cardiovascular disease, kidney or liver failure, diabetes mellitus, diabetes insipidus and other endocrine impairments were excluded from the study. The data of age, sex, course of disease (initial symptom, MS type, disease duration, EDSS score), and treatment were recorded. According to the EDSS score, patients were scaled between 0 and 10, with higher scores indicating increased disability.

Sixty healthy volunteers who did not have neurological, psychiatric or endocrinological diseases and did not use any drugs were included. University of Health Sciences Turkey, Izmir Tepecik Training and Research Hospital Ethics Committee approved the study (approval no: 29/2016). Informed consent forms in line with the Declaration of Helsinki were obtained from all patients and healthy volunteers.

Copeptin Level Analysis

Copeptin level measurement was preferred in our study due to the fact that copeptin levels were reported to be superior to cortisol levels in measuring stress levels, and that cortisol level is influenced by strong circadian rhythms, and that it was challenging to measure it as a free molecule (8). Blood samples were collected in EDTA tubes from both patient and control groups between 08.00-08.30 a.m., following an 8-hour fasting time. Venous blood samples were immediately stored at 4 °C for 15 minutes, centrifuged at 4000 rpm for 10 minutes, and extracted plasma was stored at -86 °C. Serum levels of copeptin were detected by using ELISA commercial kits (Phoenix Pharmaceuticals, inc., EK-065-32) in the immunology laboratory. Assay sensitivity was 0.12 ng/ml, range was 0-100 ng/ml and the inter-assay and intra-assay coefficients of variations were 5-10% and <15%, respectively.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) v.20.0 (IBM Corp. Armonk, NY: USA., Released 2011) package program. Standard deviation,

mean-minimum-maximum values and frequency values were used as descriptive statistics. In the analysis of categorical variables, X^2 test was used. In independent samples, qualitative analysis was made with a t-test. The potential linear relationship between copeptin levels and disease was assessed with the Pearson correlation analysis. P<0.05 was considered statistically significant.

Results

A total of 120 subjects consisting of 60 patients with CSMS (65% of them were females) and 60 healthy controls (68% of them were females) were included in the study. The mean ages of the patients and the healthy subjects were 37.1±8 (20-52), 35.1±8.9 (18-54), respectively. There was no age difference between the two groups (p=0.189). Disease duration was 12.3±6.5 years and EDSS score was between 0 and 4 (2±0.8). Initial symptoms were sensory in 16 patients (26.7%), pyramidal in 14 (23.3%), optic in 12 (20%), brainstem in 12 (20%), cerebellar in 3 (5%), cerebellar and sensory in 2 (3.3%), and spinal in 1 (1.7%) patient. Ten patients (16.7%) did not receive either immunomodulatory or immunosuppressive treatments. Table 1 shows the demographic and clinical characteristics of the patients.

The mean values of copeptin level were 0.23±0.18 ng/ml (0.01-0.64) in patients with MS and 0.43±0.31 ng/ml (0.1-1.5 ng/ml) in the control group (p<0.001) (Figure 1). In both groups, no difference was found between copeptin levels and gender (p=0.699). No significant correlation was determined between copeptin levels and age (r=0.121, p=0.188), EDSS score (r=-0.035, p=0.790), or disease duration (r=0.032, p=0.810) (Table 2). There was no significant difference in copeptin levels between those in the patient group with treatment and those not receiving any treatment (p=0.914). No relation was identified between the initial symptoms and copeptin levels in the patient group (p>0.05).

Discussion

The potential mechanisms of HPA dysfunction are damage to the hypothalamus or a secondary effect of a global stress response to the disease (9). Although there are studies showing that the low reactivity of the HPA axis increases the susceptibility to experimental allergic encephalomyelitis, which is the animal experimental model for MS, HPA axis has also been reported to be hyperactive in several clinical studies (10,11,12,13). Enlargement in adrenal glands and an increase in the number of neurons co-expressing corticotrophin-releasing hormone and AVP (CRH/AVP neurons) were reported in postmortem studies (14,15,16). The observation of HPA axis hyperactivity in MS was further supported by an increased cortisol level in cerebrospinal fluid (17). Against

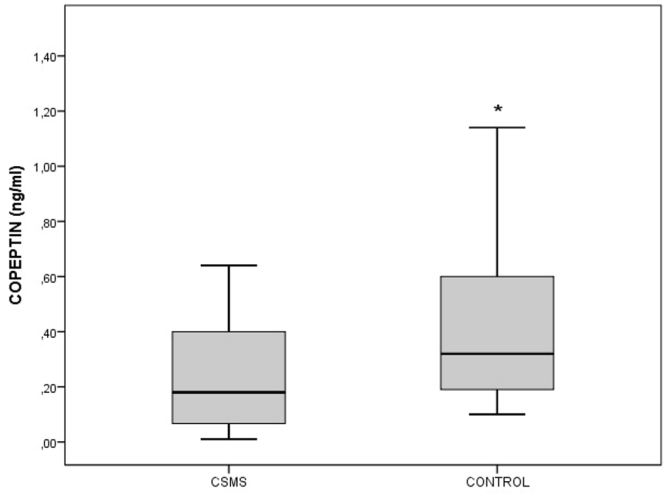

Figure 1. Copeptin levels of patients with CSMS and control group
CSMS: Clinically silent multiple sclerosis

Table 1. Demographic and clinic features of patients with CSMS and healthy controls

	CSMS	Control	*p
n	60	60	
Age	37.17±8.00	35.12±8.95	0.189
Sex (female/male)	39/21	41/19	0.699
Duration of follow-up/year (mean ± SD)	6.52±5.28	-	-
Duration of disease/year (mean ± SD)	12.37±6.58	-	-
First EDSS score (min-max)	2.22±0.81 (1-4)	-	-
Last EDSS score (min-max)	2.07±0.89 (0-4)	-	-
Duration between first two attacks (year)	2.20±2.23 (0.1-11)	-	-
Treatment (%)		-	
Interferon	29 (48.3)	-	-
Glatiramer asetat	10 (16.7)	-	-
Fingolimod	10 (16.7)	-	-
Natalizumab	2 (3.3)	-	-
Not treated	10 (16.7)	-	-
Copeptin (ng/ml)	0.235±0.186	0.435±0.31	<0.001

* t-test was evaluated for independent examples. n: Number, CSMS: Clinically silent multiple sclerosis, EDSS: Expanded Disability Status Scale, SD: Standard deviation, min: Minimum, max: Maximum

Table 2. Correlation analysis of clinical parameters and copeptin levels in patients with CSMS

	Age	First EDSS score	Last EDSS score	Duration between first two attacks	Duration of disease
*Copeptin	r=0.121 p=0.188	r=0.116 p=0.378	r=-0.035 p=0.790	r=-0.032 p=0.810	r=0.143 p=0.276

*Pearson correlation was used. CSMS: Clinically silent multiple sclerosis, EDSS: Expanded Disability Status Scale

these data, Limone et al. (18) found normal HPA axis functions in patients with MS. These controversial results may be due to the difficulty of quantifying HPA axis activity (9). Many studies use cortisol level to measure HPA axis activity, but cortisol levels are often unreliable and difficult to standardize (9). Copeptin is an easy to measure stable marker.

The relationship between MS and copeptin was evaluated in only three studies. In the first study, Baranowska-Bik et al. (19) measured copeptin levels in the relapse period of 40 patients with newly diagnosed clinically defined RRMS that consisted of lean, over-weight and obese subjects, who were not receiving treatment during the study period. Unlike our study, all patients were symptomatic due to disease relapse. They found plasma copeptin levels to be significantly higher in the MS group, especially in overweight and obese patients (19). Prokopova et al. (20) measured copeptin levels in 19 patients with newly-diagnosed MS who were in remission period and without treatment, and 19 healthy volunteers. Copeptin level was lower in patients compared to controls, similar to our study, and authors noted that the difference was at the border of statistical significance. Also, regardless of the diagnosis, men had higher copeptin levels than women. Consequently, they suggested that HPA axis hyperactivity might not yet develop in the early stages of MS (20). Recently, Koseoglu et al. (21) investigated plasma copeptin levels in patients with RRMS and healthy controls. They divided patients with MS into three groups as patients without a prior attack in 12 months, patients with a clinical acute attack, and patients who received attack treatment one month ago. They called these groups as MS control, MS relapse, and MS remission, respectively. In contrast to our study, they found copeptin levels higher in all patients with RRMS than healthy controls and they did not find any significant correlation between copeptin levels and patients' age, disease duration and EDSS score, as in our study. In addition, the copeptin level was significantly lower in the MS relapse group compared to the MS remission group. They also found copeptin levels higher in the MS control group than the MS relapse group, but this finding did not reach statistical significance. Therefore, they suggested that copeptin levels might decrease in an acute attack. These incompatible results with our study may be due to study design and patient selection criteria. We did not include patients with acute attack and defined the absence of an attack in the last six months as "clinically silent" MS.

Copeptin levels were reported to be higher in males compared with females in healthy subjects (22). Some authors found a correlation between age and copeptin levels, whereas some did not (6,23). In our study, significant correlation of copeptin levels with neither age nor gender was shown. In the present study, we found different results than previous studies which evaluated the correlation of MS and copeptin levels, due to different study designs. Sample size was larger and duration of disease in patients with RRMS was longer in our study than the two studies and also patients were receiving different treatments in our study (19,20). In most studies where copeptin levels were determined to be high, measurements were performed in the acute phase of the disease. In the acute phase of critical diseases, it is known that vasopressin and other stress hormones are released abruptly and massively (7). It was observed that copeptin levels increased on the first days of myocardial infarction, subarachnoid hemorrhage, and brain trauma, after which they gradually decreased (23,24). In patients with MS, copeptin levels were found to be higher in the relapse period (19). HPA axis hyperactivity during acute relapse in patients with MS is thought to be secondary to an active inflammatory response (25,26). This hyperactivity is thought to be a protective mechanism against excessive immune response (25). Some studies have examined cortisol and ACTH level measurements, and dexametasone/CRH test to demonstrate HPA activity (13,25,27). In addition, the presence of gadolinium enhancing lesions in the brain as an indicator of disease activity was also considered to be associated with HPA axis dysfunctions (27). Patients with MS in remission period were included in our study in order to minimize the activating effect of acute inflammation on the HPA axis function, therefore, we thought that copeptin levels were lower in the patient group due to the remission period.

Some studies have suggested that HPA dysfunction is also associated with clinical features of MS. HPA axis activity was found to be associated with fatigue, depressive symptoms, cognitive impairment, clinical type, and disease progression in several studies (12,25,28,29,30). The relation between disability which is detected with EDSS score and HPA axis hyperactivity is contradictory. While some authors noted a correlation between increased HPA axis activity and neurological disability measured with EDSS score, others did not determine such a correlation (12,27). Then Bergh et al. (12) found no significant correlation between indicators of HPA axis activation and disease duration. In the present study, no significant correlation was identified in patients with MS between copeptin levels and initial symptoms, EDSS score, and disease duration.

Kümpfel et al. (31) suggested that more adrenal activation compatible with adrenal sensitization occurred due to chronic HPA axis activity in patients with untreated MS. Therefore, they concluded that HPA axis regulation remained more stable in patients receiving disease modifying treatment such as interferon beta, glatiramer acetate, azathioprine and monthly intravenous methylprednisolone (31). However, Limone et al. (18) showed that HPA axis functions were not affected by interferon beta treatment. In our study, no difference in copeptin levels was found in those with and without treatment or among different treatments. In addition to being in a remission period, the majority of patients' being treated may explain the absence of an increase in the level of copeptin.

Study Limitations

Our study had several limitations. Firstly, the sample size was quite reasonable but not enough to evaluate treatment effect on HPA axis. Secondly, levels of other hormones such as cortisol and ACTH were not measured and dexamethasone/CRH test

was not performed, all of which were associated with the HPA axis. Thirdly, neuroimaging was performed if the symptoms and neurological examination of the patients were suggestive of an attack. Otherwise, we did not routinely perform MRI for silent radiological activities which might lead to underestimation of clinically silent but radiologically active patients. Fourthly, we did not include patients with MS in a relapse period, which might be useful to better understand the relationship between copeptin levels and different stages of disease. Fifthly, because of the cross-sectional design of the study, we did not evaluate copeptin levels in the relapse period of the same patient group. However, the aim of this study was to compare copeptin levels in patients with CSMS with healthy controls. Future prospective studies are needed to clarify the role of copeptin in patients with MS.

Conclusion

Copeptin levels are lower in patients with CSMS in our study. Low copeptin levels may indicate hypoactivity of the HPA axis when the disease is inactive. New studies are required to evaluate the relationship between low copeptin values and predisposition to MS and its clinical importance.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Izmir Tepecik Training and Research Hospital Ethics Committee approved the study (approval no: 29/2016).

Informed Consent: Informed consent forms in line with the Declaration of Helsinki were obtained from all patients and healthy volunteers.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: İ.İ., U.Ş., Ş.K., Y.Z., Design: İ.İ., U.Ş., Ş.K., Y.Z., L.Ö., Data Collection or Processing: İ.İ., L.Ö., U.Ş., A.S., F.T., Analysis or Interpretation: L.Ö., İ.İ., Literature Search: L.Ö., İ.İ., U.Ş., F.T., Y.Z., Writing: İ.İ., L.Ö., U.Ş.

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