

Increased Plasma Ceruloplasmin Levels in Schizophrenia

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ÖZET:

Şizofrenide artmış plazma seruloplazmin düzeyleri

Amaç: Seruloplazmin hepatositler tarafından sentezlenen insan serumunda bulunan bir proteindir. Ayrıca karaciğer dışında beyin, akciğer, dalak ve testis gibi organlarda da gen ekspresyonları gösterilmiştir. Seruloplazmin serum bakiyorunun yaklaşık %95'ini içerir ve bakır diğer birçok dokuya taşır. Seruloplazmin büyük oranda bakır yoğunluğunu yansıtır. Seruloplazmin aynı zamanda antioksidan etkiye sahiptir ve bir akut faz reaktanıdır. Ayrıca, seruloplazmin serotonin, epinefrin ve norepinefrinin oksidasyonunda da rol almaktadır. Seruloplazmin anormallik birçok nörodegeneratif hastalıkla ilişkilendirilmiştir. Seruloplazminin şizofreni ve hastanın akut veya kronik fazda olması, hastalık süresi, hastanın tedavide olup olmaması gibi şizofreninin bazı klinik özellikleriyle de bağlantılı olduğu bildirilmiştir. Bununla beraber, seruloplazmin ve şizofreni ilişkisi hakkında hala çelişkiler vardır, çünkü şizofrenide seruloplazmin düzeyinin arttığı, azaldığı ve normal sınırlarda kaldığı ile ilgili yayınlar da bulunmaktadır. Bu çelişki, kullanılan ölçüm yönteminin farklılığından, hastaların klinik durumunun farklı olmasından ve etnobiyojik farklılıklardan kaynaklanabilir. Biz bu çalışmada Türk hastalarda plazma seruloplazmin düzeyi ile şizofreni ilişkisini araştırmayı amaçladık.

Yöntem: Çalışmaya Gaziantep Üniversitesi, Tıp Fakültesi, Psikiyatri Anabilim Dalı, Psikotik Bozukluklar Biriminde ayaktan takip edilen 116 hasta içinden DSM-IV'e göre şizofreni tanısı konulmuş ve dışlama ölçütlerini karşılamayan 60 hasta (24 erkek, 36 kadın, yaş ortalaması 31.93±9.37 yıl, yaş aralığı 19–55 yıl) alındı. Yaş ve cinsiyet olarak benzer 40 sağlıklı kişiden (17 erkek, 23 kadın, yaş ortalaması 35.53±9.86 yıl, yaş aralığı 20–58) kontrol grubu oluşturuldu. Heparinize tüplere sol ön koldan venöz kan örnekleri alındı. Kan örnekleri santrifüj edilerek plazma ayrıldı. Ferröz iyonun ferik iyon enzimatik oksidasyonu temeline dayanan Erel'in seruloplazmin ölçüm yöntemi ile seruloplazmin ölçümü yapıldı.

Bulgular: Seruloplazmin düzeyi şizofreni hastalarında sağlıklı kontrollere göre anlamlı olarak yüksekti ($p<0.001$). Ayrıca kadın hastalar erkek hastalara göre daha yüksek plazma seruloplazmin düzeyine sahipti ($p<0.001$), oysa kontrollerde kadın ve erkekler arasında fark yoktu. Seruloplazmin ile yaş, hastalık süresi, sigara kullanımı, şizofreni alt tipleri, belirtiler şiddeti ve antipsikotik tedavi arasında ilişki yoktu.

Tartışma: Bu çalışma seruloplazminin şizofreni fizyopatolojisinde rolü olabileceğini ortaya koymuştur. Ayrıca, bildiğimiz göre literatürde ilk defa olarak, plazma seruloplazmin düzeyi kadın hastalarda erkek hastalara göre daha yüksek olarak bulunmuştur. Artmış seruloplazminin düzeyinin şizofrenideki rolünün ve cinsiyet farkının öneminin açıklığa kavuşturulması için ileri çalışmalar gerekmektedir.

Anahtar sözcükler: Şizofreni, seruloplazmin, cinsiyet farklılığı

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ABSTRACT:

Increased plasma ceruloplasmin levels in schizophrenia

Objective: Ceruloplasmin is a protein in the human serum that is synthesized by hepatocytes, but extrahepatic gene expression in the brain, lung, spleen, and testis has also been reported. Ceruloplasmin contains approximately 95% of serum copper and it carries copper from liver to numerous tissues. Ceruloplasmin level reflects largely the copper concentration of the serum. However, ceruloplasmin has also an antioxidant function that is known as the acute phase reactant. Additionally, ceruloplasmin has a role in the oxidation of serotonin, epinephrine, and norepinephrine. Abnormalities in ceruloplasmin levels have been associated with several neurodegenerative diseases. Moreover, the alteration of plasma ceruloplasmin levels has been linked to schizophrenia and its some clinical characteristics including acute or chronic phase, the length of the disease or whether the patients on treatment or not. However, there exists a controversy on relationship between the plasma level of ceruloplasmin and schizophrenia. There are number of reports on the increased or decreased and/or normal level of plasma ceruloplasmin in association with schizophrenia. These differences may have been originated from the usage of different measurement methods, clinical situations, and ethnobiological differences. In the present study, we aimed to investigate the association between plasma ceruloplasmin level and schizophrenia in Turkish patients.

Methods: 60 patients (36 women and 24 men, mean of age 31.93±9.37 years, range 19-55) that were diagnosed as schizophrenia according to DSM-IV were included for this study at the Psychotic Disorders Unit, Department of Psychiatry, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey. The control group consisted of 40 healthy subjects in similar age and gender (23 women, 17 men). Venous blood samples were collected from the left forearm into heparinized tubes. The blood samples were centrifuged and the plasma was removed. Erel's ceruloplasmin measurement method that is based on the enzymatic oxidation of ferrous ions to ferric ions was used. SPSS Windows program 13.0 was applied for statistical analysis.

Results: Plasma ceruloplasmin levels of schizophrenic patients were significantly higher than the healthy controls ($p<0.001$). In addition, female patients had higher ceruloplasmin levels than male patients ($p<0.001$), while there was no statistically significant difference between women and men in the control group. There was no association between the ceruloplasmin levels and the age, the duration of illness, smoking, schizophrenia subtypes, symptom severity, and antipsychotic therapy.

Conclusions: The study suggests that ceruloplasmin may play a role in pathophysiology of schizophrenia. Moreover, female patients having a higher level of ceruloplasmin than those of male patients that is first time reported in the literature. However, further studies are needed to clarify the higher level of ceruloplasmin in schizophrenia and to reveal the importance of the gender differences in ceruloplasmin levels in schizophrenia.

Key words: Schizophrenia, ceruloplasmin, gender difference

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INTRODUCTION

Ceruloplasmin is a protein of the α_2 -globulin fraction of human blood serum. Plasma ceruloplasmin is largely synthesized by the hepatocytes, but extrahepatic gene expression has been documented in the brain, lung, spleen, and testis. Ceruloplasmin is also expressed in astroglial cells, the cerebral microvascular network, and in

neurons of the central nervous system (1). Ceruloplasmin proteins are the carrier of copper ion from liver to numerous tissues and constitute 95% of serum copper content. Ceruloplasmin is also an iron oxidase; for this capacity, it is known as ferroxidase I. On the other hand, the ceruloplasmin is an acute phase reactant, whose concentration mostly as an antioxidant increases in inflammation, infection, trauma, etc.

Ceruloplasmin has other functions including the oxidation of serotonin, epinephrine, and norepinephrine (1). Alterations in ceruloplasmin level are currently regarded as one of the mechanisms underlying the development of a number of neurodegenerative disorders (1).

Several studies have reported association between ceruloplasmin levels and schizophrenia (2-13). In most studies ceruloplasmin levels were increased (2-7,9). The nature of relationship between increased levels of ceruloplasmin and schizophrenia has not been clarified yet. Studies have generally focused on association of copper content in relation to ceruloplasmin level. Because, it has been demonstrated very definitely that ceruloplasmin levels largely determine the copper concentration and as a result copper content in plasma (14,15). Thus, one strategy to study the copper content is the measurement of ceruloplasmin, since approximately 95% of the copper in blood is bound to ceruloplasmin (13). An increase in ceruloplasmin level would be expected to correlate with the increase in serum copper content. Increased copper and ceruloplasmin levels have been found in patients with schizophrenia (13).

The importance of dopamine has been largely studied and well known in schizophrenia. Copper has a role in synthesis and metabolism of dopamine. For example, the copper-dependent enzyme tyrosine hydroxylase shunts tyrosine away from DOPA production, copper inhibits dopa-decarboxylase thereby inhibiting dopamine production, the copper-dependent enzyme dopamine-hydroxylase catalyzes the breakdown of dopamine into norepinephrine, and the copper-dependent enzyme monoamine oxidase (MAO) catalyzes the breakdown of dopamine into other metabolites (16). Therefore, chronic copper exposure to certain areas of the brain may lead to dopamine deficiency. Dopamine deficiency may cause hypersensitization of post-synaptic dopaminergic receptors resulting in psychotic symptoms (13,16). A similar explanation has been suggested for schizophrenic symptoms of Wilson's disease, in which there is copper deposition in liver, cornea, and brain due to lack of ceruloplasmin, which leads over-exposure brain to copper (1). In addition, psychotic symptoms can occur in some cases of chronic copper poisoning (1).

Some authors have suggested that the relationship between ceruloplasmin and schizophrenia is based on the immunology-inflammatory hypothesis of schizophrenia, which claims ceruloplasmin increases as an acute phase reactant and as an antioxidant (4,12,17). Some in-vitro studies have demonstrated that ceruloplasmin is a potent antioxidant, even more potent than albumin and superoxide dismutase (SOD) (18).

Although, majority of studies found increased levels of ceruloplasmin in schizophrenia (2-7,9), some studies reported lower levels (7,8), while others demonstrated no difference in ceruloplasmin levels between patients and healthy controls (11). It has been suggested that these differences may have been originated from the use of different methods, clinical features, and ethnobiological differences of the patients (12). Therefore, we aimed to investigate the association between serum ceruloplasmin levels and the schizophrenia in relation to the clinical features of the patients in a Turkish sample. To our knowledge, this study was the first study of ceruloplasmin in Turkish schizophrenic patients.

METHODS

Patients and control group

This cross-sectional case control study included 60 outpatients who were diagnosed with schizophrenia according to the 4th edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV), age between 18-65 and do not met exclusion criteria out 116 patients that applied to Psychotic Disorders Unit, at the Gaziantep University Hospital, Gaziantep, Turkey. A DSM-IV diagnosis of schizophrenia was based on independent clinical interviews by a certified senior psychiatrist (OV). The control group consisted of 40 healthy subjects, comparable to patients in age and gender distribution. The controls were chosen among volunteers from hospital staff and none had any personal or family history of any psychiatric disorder.

Psychiatric Assessment Scales

The severity of symptoms of schizophrenia was evaluated by the Brief Psychiatric Rating Scale (BPRS)

(19), the Positive and Negative Syndrome Scale (PANSS) (20), and Clinical Global Impressions-severity ratings (CGI-severity) (21).

BPRS: It is used to assess psychotic and depressive symptom severity in schizophrenia and other psychotic disorders. It consists of 18 items. Each item is evaluated between 0-6 points and total score is calculated after addition of all points. The scores between 5 and 30 indicate minor syndrome and scores equal to 30 and higher indicate major syndrome.

PANSS: It consists of 30 items and 7 items measure positive symptoms, 7 measure negative symptoms and 16 items reflect general psychopathology. The symptom severity is scored between 1-7 points on each item.

CGI: It assesses a general evaluation of illness severity and the response to the treatment. We used only the part of symptom severity in this study.

Exclusion criteria

In addition to psychiatric examination, physical and neurological examinations were performed for the patients and controls. Liver and kidney function tests were performed. Exclusion criteria were designated as follows: Presence of any Axis I psychiatric disorder other than schizophrenia, mental retardation, epilepsy, neurodegenerative disorders (i.e. Parkinson's, Huntington's, and Alzheimer disease), presence of severe organic condition (i.e. Wilson's disease, Down syndrome, malnutrition, pregnancy, diabetes mellitus, chronic renal failure, cancers, liver cirrhosis, or thyroid diseases), treatment with glucocorticoids, oral contraceptives, or any antioxidant agents (i.e. vitamin C or E), xanthine oxidase inhibitors (i.e. allopurinol, folic acid), and non-steroidal anti-inflammatory drugs (NSAIDs), presence of infectious disease, and excessive obesity.

After the detailed description of the study to the subjects, all subjects or guardians gave informed written consent, which was in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board.

Blood samples and ceruloplasmin measurement

Venous blood samples withdrawn from the left

forearm were collected into heparinized tubes between 07.00 and 08.00 hours after overnight fasting. The blood samples were centrifuged at 3000 rpm for 10 min at 4 °C to remove plasma. The buffy coat on the erythrocyte sediment was separated carefully. Plasma samples were stored ≥ 80 °C until analysis.

Erel's ceruloplasmin measurement method was used. It is based on the enzymatic oxidation of ferrous ion to ferric ion (22). This method is automated, colorimetric, and based on the enzymatic oxidation of ferrous ion to ferric ion. The results were expressed in milligrams per deciliter, and the precision of this assay is higher than 97%. Interested readers may refer to Erel's articles for details (22,23). A Cecil 3000 spectrophotometer with a temperature controlled cuvette holder (Cecil) and an Aeroset automated analyzer (Abbott) were used (23).

Statistical Analysis

SPSS for Windows V 13.0 was used for statistical data analysis. Chi square test was used to evaluate statistically significant differences between case and control group for nominal variables. Continuous variables compared with student t test between two groups and Spearman coefficient was used to show correlation between the score of psychiatric tests and plasma ceruloplasmin levels. Statistical significance level set at $p < 0.05$.

RESULTS

The age characteristics and gender ratio were similar between the patient and control groups, 36/24 versus to 23/17 (Table 1). The mean ages of patients were 31.93 ± 9.37 years (range, 19–55) and mean ages

Table 1: Gender, age and smoking characteristics of patients and controls

	Patients	Controls	P values
Gender			
Men	n=24 (40%)	n=17 (42.5%)	>0.05
Women	n=36 (60%)	n=23 (57.5%)	>0.05
Age (Mean \pm SD)	31.93 \pm 9.37 (range:19-55)	35.53 \pm 9.86 (range:20-58)	>0.05
Smoking			
Smoker	n=32 (53.3%)	n=18 (45.0%)	>0.05
Non-smoker	n=28 (46.7%)	n=22 (55.0%)	>0.05

of controls were 35.53 ± 9.86 years (range, 20–58) (Table 1). According to the clinical characteristics of the patients; numbers of paranoid, disorganized, and catatonic patients were 41, 16, and 3 respectively. The mean duration of illness was 9.72 ± 7.27 years (range: 1–34 years). The mean number of hospitalization was 1.78 ± 1.84 (range: 0–8). Among patients 21 were on typical antipsychotic, 24 were on atypical antipsychotic, and 15 patients were on a combined antipsychotic regimen. In addition to antipsychotics 5, 4, and 20 patients were receiving antidepressant, anticonvulsant, and anxiolytic drugs, respectively.

The mean psychiatric measurement scale revealed that BPRS total and the psychosis subscale and the depression subscale scores were 22.18 ± 11.49 , 14.58 ± 8.56 and 7.58 ± 6.33 respectively. Similarly, the mean PANSS total and the positive, the negative, and the general psychopathology subscale scores were 63.22 ± 21.38 , 17.38 ± 6.96 , 14.23 ± 6.88 and 31.78 ± 12.15 , respectively. The mean CGI-severity score was 4.07 ± 1.28 .

The ceruloplasmin levels of the patients and controls are shown in Table 2. The plasma ceruloplasmin levels of schizophrenia patients were significantly higher than the healthy controls (Table 2). Additionally, the female patients had higher ceruloplasmin levels than male patients (Table 2), while there was no difference between women and men plasma ceruloplasmin levels in the control group (Table 2). There was no difference between male and female patients according to age and smoking ($p > 0.05$).

There was no significant difference between schizophrenia subtypes in patients for ceruloplasmin levels. We did not find any significant correlation between psychiatric measurement scale (BPRS, PANNS, and CGI-severity) scores and the ceruloplasmin levels. Plasma ceruloplasmin levels did not show any

significant difference between smokers and non-smokers in patients, and between the patients who use typical, atypical or combined antipsychotic medications. The age and the duration of illness in schizophrenia did not correlate with the ceruloplasmin levels. There were no differences between two genders in terms of duration of illness or psychiatric measures such as BPRS total or subscale scores or PANNS total or subscale scores, and the CGI-symptom severity scores.

DISCUSSION

In the present study, we demonstrated that plasma ceruloplasmin levels in patients with schizophrenia were significantly higher than the levels of healthy controls. Our result supports the previous findings about the elevation of plasma ceruloplasmin levels in schizophrenia (2–7,9).

Studies of plasma ceruloplasmin level in schizophrenia show heterogenic results. Alias et al. reported that elevations of ceruloplasmin were found only in acute exacerbations, not in chronic patients and healthy controls (5). Also, Giner et al. suggested that the increase in ceruloplasmin levels might be a marker of the clinical improvement since they found that ceruloplasmin was increasing during acute phase of illness and elevation of ceruloplasmin was decreased after acute phase (6). Puzynski demonstrated that ceruloplasmin blood levels positively correlated with the length of the disease (4). Morera et al. reported that increased ceruloplasmin was positively correlated only with PANNS negative subscale scores, but not associated with the other features of schizophrenia (12). Chugh et al. studied the treated and untreated schizophrenic patients and found that the increase in ceruloplasmin levels were limited to the untreated group, while ceruloplasmin levels were decreased in the treated group (7). Recently, Wolf et al. looked the plasma ceruloplasmin, copper, iron levels and ferroxidase activities in schizophrenia, and they found that levels of plasma ceruloplasmin and copper were significantly higher than controls. They emphasized that the ceruloplasmin elevation in schizophrenia is specific, not simply the result of elevation of plasma copper-

Table 2: Ceruloplasmin levels of patients and controls

	Ceruloplasmin ($\mu\text{g/dl}$)*	Statistical Analysis
Patients (n=60)	592.65 ± 149.76	$t=18.84, df=98, p<0.001$
Controls (n=40)	222.35 ± 56.17	
Male patients (n=24)	440.05 ± 109.44	$t=3.52, df=58, p<0.001$
Female patients (n=36)	583.39 ± 148.34	
Male controls (n=17)	224.76 ± 54.39	$t=0.171, df=38, p=0.819$
Female controls (n=23)	220.57 ± 58.60	

*Mean \pm Standart Deviation

containing oxidative enzymes. Also, they suggested that increase in ceruloplasmin levels may result in increased levels of copper, which ultimately proves deleterious effect in schizophrenia. Wolf et al. reported that elevation in ceruloplasmin levels have also been observed both in treated and untreated subjects (13). Comparatively, our findings suggest that there was no association between the ceruloplasmin levels and the PANNS total, positive, negative or general psychopathology subscale scores. Additionally, there was no association between the ceruloplasmin levels and BPRS or CGI-severity scores in our study. Although, some of our patients were in the first year of their illness, none of them was in a state of acute exacerbation, and all of them were under regular antipsychotic treatment. Moreover, we found no association between ceruloplasmin levels and the length of the disease state.

Elevations in ceruloplasmin levels have also been reported in conditions besides in schizophrenia, such as pregnancy, infections, and other disease-states (24,25). None of our patients had a similar physical disease or conditions.

The role of ceruloplasmin in the pathophysiology of schizophrenia is unclear. The previous studies mostly focused on association of ceruloplasmin level and copper content in schizophrenia as discussed earlier. On the other hand, although it has been referred rarely in the literature, the ceruloplasmin level and serotonin (26), and copper content and serotonin (5-hydroxytryptamine, 5-HT) relationship should also be considered in schizophrenia (27). Since ceruloplasmin has a role in oxidation of serotonin and copper induces oxidation of serotonin, the products of 5-HT oxidation have the potential to be neurotoxic especially on the serotonergic receptors. Copper structurally alters serotonin and converts into non-functional 5-HT dimeric species (27). It has been suggested that this process may play a role in copper related neurodegenerative diseases (3,27). Pathophysiology of schizophrenia might also be associated with brain serotonergic system. This hypothesis is based on that atypical antipsychotics, which have proposed similar influence on positive symptoms and better effect on

negative and cognitive symptoms compared to the typical antipsychotics, atypical antipsychotics lead to an interaction between dopamine and serotonin systems, and they also have a higher rate of 5HT_{2A/D2} receptor antagonism (28-30).

The second significant finding of the present study is that female patients with schizophrenia have a higher level of ceruloplasmin than male patients, while there were no gender differences in healthy controls. To our knowledge, no previous study has reported similar results before. It is possible that gender hormones might have influenced the serum ceruloplasmin levels and such an attribute to estrogens/progesterone level has been reported previously (31). Conspicuous increase in plasma ceruloplasmin level in female patients might reflect the possibility that the course of schizophrenia is different in women from men (32).

It should be noted the sample size is relatively small to generalize these findings and the subtypes are limited for comparing the subgroups. Also, all patients were under antipsychotic treatment and were in remission at the time of the study. Therefore, we could not compare our results with the results of some previous reports in which the patients were drug-free or on treatment or in acute or in chronic phase of schizophrenia (5-7). The copper content has not been studied per se, however, the influence of copper content was implied by the level of ceruloplasmin. It is because, the role of ceruloplasmin in the pathophysiology of schizophrenia has been discussed in relation to copper content. However, for the first time even indirectly, we emphasized that the role of ceruloplasmin in schizophrenia through the copper and serotonin relationship to be taken into consideration.

In conclusion, the present study suggests that ceruloplasmin may have a role in pathophysiology of schizophrenia, but further studies are needed to better understand the relationship between the ceruloplasmin level and schizophrenia. The gender differences in plasma ceruloplasmin levels needs to be taken into consideration during the evaluation of the patients.

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