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Evaluation of ischemia modified albumin levels in major depression patients

Major depresyon hastalarında iskemi modifiye albumin seviyelerinin değerlendirilmesi

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Abstract

Aim: Depression is an important public health problem, which has been associated with an antioxidant defense system. Ischemia-modified albumin (IMA) is a new biomarker that measures ischemia. The aim of this study was to evaluate IMA levels as a new parameter related to oxidative stress in patients with major depressive disorder (MDD).

Methods: This cross-sectional case-control study included 59 patients aged between 18-65 years who were admitted to our psychiatry outpatient clinic between June 2018 and December 2018, diagnosed with MDD and had not used psychotropic drugs for 3 months. In addition, 59 age and sex matched healthy controls were included in the study. Serum IMA and albumin levels were measured in blood samples taken from each patient and from control groups. Hamilton Depression Rating Scale (HDRS) was applied to the subjects to evaluate the depression level.

Results: Among the MDD group, 27 patients (45.8%) were male and 32 (54.2%) were female. The number of males and females in the control group were 29 (49%) and 30 (51%). Mean ages of the patients in MDD and control groups were 39.40 (12.20) and 38.67 (9.29) years, respectively. No statistically significant difference was found between the groups in terms of age and gender (P=0.942 and P=0.714, respectively). The mean IMA level of MDD and control group patients were 0.84 (0.39) and 0.82 (0.30), respectively; the difference was statistically significant (P<0.001). There was also a statistically significant difference between the albumin levels of the two groups (P=0.01). Correlation analysis showed a positive correlation between serum IMA levels and HDRS scores (r=0.235, P=0.008).

Conclusion: In our study, IMA levels of MDD patients were significantly higher than that of the control group. This result may be an indicator of increased oxidative stress in patients with depression. There is little data in the literature evaluating IMA levels in psychiatric disorders.

Keywords: Ischemia modified albumin, Major depressive disorder, Mood disorders, Oxidative stress, Biomarker

Öz

Amaç: Depresyon, önemli bir halk sağlığı sorunudur. Depresyonun antioksidan savunma sistemi ile ilişkisi olduğu bildirilmiştir. İskemi modifiye albümin (IMA), iskemi varlığını değerlendiren yeni bir biyobelirteçtir. Bu çalışmada Major depresif bozukluğu (MDB) olan hastalarda oksidatif stres ile ilgili yeni bir parametre olan IMA düzeylerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Bu kesitsel vaka-kontrol çalışmasına Haziran 2018 ve Aralık 2018 tarihleri arasında psikiyatri polikliniğimize başvuran 18-65 yaş arasında, MDB tanısı almış, psikotrop ilaç kullanmayan toplam 59 hasta ve 59 sağlıklı kontrol dahil edildi. Hasta ve kontrol grubundan alınan kan örneklerinde serum İMA ve albumin düzeyleri değerlendirildi. Depresyon seviyesini değerlendirmek için deneklere Hamilton Depresyon Derecelendirme Ölçeği (HDRS) uygulandı.

Bulgular: Depresyonlu hastaların 27'si (% 45,8) erkek, 32'si (% 54,2) kadın, kontrol grubunun 29'u (%49) erkek, 30'u (%51) kadındı. MDD grubunun yaş ortalaması 39,40 (12,20) yıl, kontrol grubununki 38,67 (9,29) yıldı. Hasta grubu ile kontrol grubu arasında yaş ve cinsiyet açısından istatistiksel olarak anlamlı fark bulunmadı (sırasıyla P=0,942 ve P=0,714). MDD ve control gruplarının ortalama İMA düzeyleri sırasıyla 0,84 (0,39) ve 0,82 (0,30) olup, aradaki fark istatistiksel olarak anlamlıydı (P<0,001). Ek olarak, iki grubun ortalama albümin seviyeleri arasındaki fark da istatistiksel olarak anlamlı bulundu (P=0,01). Korelasyon analizinde serum IMA düzeyleri ile HDRS skorları arasında pozitif korelasyon tespit edildi (r=0,235, P=0,008).

Sonuç: Çalışmamızda depresyon hastalarının İMA değerlerinin sağlıklı kontrollerden istatistiksel olarak anlamlı biçimde yüksek olduğu tespit edildi. Bu sonuç, depresyonu olan hastalarda artmış oksidatif stresin bir göstergesi olabilir. Literatürde psikiyatrik hastalıklarda İMA düzeylerini değerlendiren nadir veri bulunmaktadır.

Anahtar kelimeler: İskemi modifiye albümin, Major depresif bozukluk, Duygu durum bozuklukları, Oksidatif stres, Biyobelirteç

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Introduction

Major depressive disorder (MDD) is a pervasive and heterogeneous disorder described by anhedonia, depressed mood and altered intellectual capacity. The lifetime prevalence of MDD is 17% of the populace and results in gigantic auxiliary expenses to society [1]. Diagnosis and treatment of MDD depends on generally abstract evaluations of different manifestations speaking to numerous endophenotypes. To date, the natural bases for the heterogeneity of MDD remain ineffectively characterized. Toward this objective, distinguishing proof of natural markers could enhance the determination and arrangement of MDD subtypes in order to stratify patients into additional homogeneous, clinically unmistakable subpopulations. Despite years of research, a non-intrusive, quantitative clinical test to help in the determination and treatment of MDD remains elusive [2].

Considering late investigations of MDD, expectation toward enlightening diagnosis and treatment was increased. While no certain single biomarker was found, there is mounting proof of different dysregulated contributing elements, such as growth factors and additionally proinflammatory cytokines. In mood disorders, there is well studied evidence for altered endocrine factors (e.g., hypothalamic–pituitary–adrenal (HPA), thyroid, sex steroids) and metabolic dysregulation (e.g., insulin resistance). As an alternative to the single biomarker approach, developing biomarker panels to include various biological abnormalities, defining profile of different kind of serum growth factors, cytokines, hormones and metabolic markers may contribute to the heterogeneity of MDD, as well as treatment response. To define subgroups, severity and response, more patient samples are needed. Moreover, analytical devices for evaluating biomarkers are now available [3,4].

Systemic markers of oxidative stress include ischemia-modified albumin (IMA) and prolidase. Albumin is a protein of 585 amino acids. Bonding heavy transition metals (nickel, cobalt), the final amino acid terminal in the structure of albumin has the capacity to cause free radical damage and deterioration of the cell membrane integrity. It reduces the binding of metals to the N-terminal of albumin and this damaged new formed albumin is called IMA [5,6]. IMA has recently been proposed as a marker for oxidative stress. In addition, recent studies have emphasized that it increases the inflammation process [7-9]. On the other hand, it is also argued that oxidative damage caused by iron increases ischemia-modified albumin and in this context ischemia-modified albumin may appear as a new marker in determining oxidative damage caused by iron [10].

As far as we know, a study evaluating IMA levels in drug-free depression patients has not been found in the literature. The aim of this study was to evaluate IMA levels as a new parameter related to oxidative stress in patients with major depressive disorder.

Materials and methods

This case-control study included 59 patients aged between 18-65 years who were admitted to our psychiatry outpatient clinic between June 2018-December 2018, diagnosed with MDD and had not been using psychotropic drugs for 3 months. In addition, 59 age and sex matched healthy controls were included in the study. All participants were evaluated by 2 psychiatrists to confirm the appropriate diagnosis using the DSM-V (Diagnostic and Statistical Manual of Mental Disorders). Subjects with comorbid psychiatric or systemic disease, history of chronic drug use due to any disease, acute infection, iron deficiency anemia, bone marrow disease, smoking, morbid obesity, alcohol and substance use, pregnancy or breastfeeding were not included in the study. Serum IMA and albumin levels were measured in blood samples taken from the MDD and control groups. Biochemical tubes without preservatives were filled with 9 ml of blood and centrifuged at 2500 g for 10 minutes in half an hour. Serum IMA was measured spectrophotometrically in accordance with the method described by Bar-Or et al [11]. Yozgat Bozok University Clinic Research Ethics Committee approved the study (2017-KAEK - 189_2017.12.21_11) and it was performed under the ethical principles of the Declaration of Helsinki for medical research involving human subjects.

Assessment Tools

1. Data Collection Form

It is a form prepared by the researchers that includes the participants' age, gender, educational background, disease and remission period, medications, smoking, height and weight.

2. Hamilton Depression Rating Scale (HDRS)

The original version of the scale was conceived by Hamilton in 1960. Later, Williams advanced a recent version of the HDRS to improve the inter-rater reliability (Structured Interview for Hamilton Depression Rating Scale-21) [12]. It measures the level of depression and severity change in the patient. The scale is scored between 0-4 with 17 items and the highest score is 53. Depression severity is graded according to HDRS levels: low to 8-13, moderate to 14-18, severe to 19 and above. The validity and reliability study of the scale was conducted in our country [13].

Statistical analysis

Statistical analysis was performed using SPSS 22.0 (Statistical Package for Social Sciences, IBM Inc., Chicago, IL, USA) software. The descriptive statistics of the data were calculated, and Kolmogorov Smirnov tests were applied for testing the normality distribution. Mann-Whitney U test was used for data comparison not showing a normal distribution. The Pearson's correlation test was used for the normally distributed data and the Spearman's correlation test was used for data not showing a normal distribution. A *P*-value of less than 0.05 was considered statistically significant.

Results

Among the MDD group, 27 patients (45.8%) were male and 32 (54.2%) were female. The number of males and females in the control group were 29 (49%) and 30 (51%). Mean ages of the patients in MDD and control groups were 39.40 (12.20) and 38.67 (9.29) years, respectively. No statistically significant difference was found between the groups in terms of age and gender (P=0.942 and P=0.714, respectively) (Table 1). The mean IMA level of MDD and control group patients were 0.84 (0.39) and 0.82 (0.30), respectively; the difference was statistically significant (P<0.001). Mean albumin levels in MDD

and control groups were 4.16 (0.36) and 4.03 (0.32), which was statistically significantly different (P=0.01) (Table 2). There was no statistically significant difference between male and female genders in terms of serum IMA levels in both patient and control groups (P=0.294 and P=0.117, respectively).

Correlation analysis showed a positive correlation between serum IMA levels and HDRS scores (r=0.235, P=0.008).

Table 1: Sociodemographic characteristics in patient and control groups

	Patient n=59	Control n=59	*P*-value Z value
Age Mean (SD)	39.40 (12.20) (min=18,max=65, median=45)	38.67 (9.29) (min=23,max=60, median=35)	0.942 -0.073
Gender n (%)	27 (45%) male 32 (55%) female	29 (49%) male 30 (51%) female	0.714 -0.367
BMI Mean (SD)	23.1 (1.84)	22.92 (1.57)	0.949 -0.064

BMI: Body Mass Index, Z: Mann-Whitney U test, SD: Standard deviation

Table 2: Distribution of HDRS, serum IMA and albumin levels in patient and control groups

	Patient n=59	Control n=59	*P*-value Z value
HDRS Mean (SD)	28.76 (8.29) (min=14, max=46, median=30)	2.58 (1.55) (min=0, max=6, median=2)	<0.001 -9.392
IMA Mean (SD)	0.84 (0.39) (min=0.66, max=0.92, median=0.84)	0.82 (0.30) (min=0.73, max=0.90, median=0.82)	<0.001 -3.33
Albumin Mean (SD)	4.16 (0.36) (Min=2.28, max=4.82, median=4.19)	4.03 (0.32) (Min=2.99, max=4.85, median=4.06)	0.01 -2.570

IMA: Ischemia Modified Albumin, HDRS: Hamilton Depression Rating Scale, Z:Mann- Whitney U test, SD: Standard deviation

Discussion

In our study, IMA levels of MDD patients were significantly higher than that of the control group. There was also a positive correlation between the severity of depression and IMA levels. Recent studies have shown that depression is associated with oxidative stress [14]. Although the mechanisms by which oxidative stress may be associated with depressive symptoms have not yet been fully elucidated, it has been noted that the brain is vulnerable to oxidative damage due to its relatively weak antioxidant defenses against the development of oxidative cellular injury and necrosis caused by free radicals resulting from the use of high oxygen [15]. Studies have shown that proinflammatory cytokine levels in the blood of depressed individuals are also increased [16]. In meta-analyzes, inflammation related markers such as Interleukin-6, tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) were reported to increase in depression patients [17,18].

For typical psychiatric diagnoses such as severe depression or schizophrenia, the probability of any biomarker achieving a sufficiently high degree of sensitivity and specificity is relatively low [2]. Utilization of different biomarkers may resolve this problem. Albeit singular biomarkers may give some more noteworthy dimension of genuine versus false positive and negatives, the prescient capacities may enhance when a few diverse biomarkers are collected into a gathering, or biopanel, of indicator attributes. Furthermore, the evaluation of a panel of markers could potentially contribute to the subdivision of a heterogeneous disease in a clinical interview with a similar phenotype. To define MDD phenotype, biomarkers can be gathered in subgroups which may be closely related to specific etiological pathways. This kind of grouping is going to show more certainly defined etiological reason of MDD subgroup. This could prompt progressively compelling, etiologically based treatments for subgroups of patients [19-21].

IMA has recently been proposed as a marker for oxidative stress and has been reported to increase the inflammation process. On the other hand, it is argued that oxidative damage caused by iron increase enhances IMA. In this context, IMA may be a new marker in determining iron induced oxidative injury. In our study, higher IMA levels were determined in depression patients than in healthy controls. There was also a positive correlation between the severity of depression and IMA levels. This result may be an indicator of increased oxidative stress in patients with depression.

In a study, no significant difference was found in serum IMA levels in bipolar disorder patients during the remission period when compared with the control group [22]. However, another study showed increased IMA levels in bipolar disorder patients during the remission period as compared to the control group, but no significant difference was found in unipolar depression patients [23]. Data from a limited number of studies evaluating IMA levels in psychiatric disorders differ. In our study, patients with moderate depression during the drug-free period were included in the study and patients who had conditions affecting oxidative parameters such as smoking and alcohol use, chronic disease and obesity were not included.

Limitations

Limitations of our study include being cross-sectional study and evaluation of a single oxidative parameter. Although attempts to reduce the factors that affect the oxidative system were made, some factors such as diet, exercise and sleep could not be standardized.

Conclusion

IMA levels, an important indicator of oxidative stress, were increased in patients with depression. This increase is correlated with the severity of depression. However more consistent data are needed to understand the role of IMA levels and oxidative stress in psychiatric disorders for evaluation as a biomarker. Therefore, a larger sample, treatment and follow-up studies in different patient groups will contribute to the literature.

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