RESEARCH ARTICLE

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Serum HMGB1 and Beclin 1 Levels in Patients with a Diagnosis of Schizophrenia

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Objective: It is known that inflammation plays a role in the etiopathogenesis of schizophrenia. In this study, we examined high mobility group box 1 protein (HMGB1) and Beclin 1 levels and their relationship with clinical variables in patients with schizophrenia.

Method: Forty-three patients with schizophrenia and 43 healthy controls were included in this study. The patients were administered sociodemographic data form, the Positive Negative Symptoms Assessment Scale (PANSS) and the Clinical Global Impressions (CGI) scale. After the scales were filled, venous blood samples were taken from both the patient and control groups to measure serum HMGB1 and Beclin 1 levels. Serum samples obtained at the end of centrifugation were measured by Enzyme-Linked ImmunoSorbent Assay (ELISA) method.

Results: The mean serum HMGB1 levels were significantly increased and the mean serum Beclin 1 levels were significantly decreased in the schizophrenia group compared to the control group. In addition, a negative correlation was found between HMGB1 and Beclin 1 levels.

Conclusion: In conclusion, current research shows that HMGB1 is increased and Beclin 1 is decreased in patients with schizophrenia, and these findings may contribute to the role of autophagy in the pathogenesis of schizophrenia.

Keywords: Schizophrenia, High Mobility Group Box 1, Beclin 1, Autophagy

INTRODUCTION

Schizophrenia is a psychiatric disorder characterized by symptoms such as hallucinations, delusions, disorganized speech and behaviors, and withdrawal from society and results in significant disability due to the deterioration of cognitive, emotional, and social functions (APA 2013). The lifetime prevalence of schizophrenia is reported to be 1% (Charlson et al. 2018, McGrath et al. 2008). In recent years, it has been investigated whether neuroinflammatory processes may play a role in the development of psychiatric diseases, and it has also been suggested that these processes contribute to the development of schizophrenia (Arıcıoğlu et al. 2016). It is known that neuroinflammation causes white matter and myelin damage with axonal degeneration in schizophrenia (Najjar and Pearlman 2015). In addition, studies evaluating peripheral blood cytokine levels in patients with schizophrenia have found that some interleukin levels may be associated with clinical symptoms measured using the Positive and Negative Symptom Scale (PANSS) (Dahan et al. 2018). Furthermore, some proteins have been shown to be associated with these inflammatory processes, although this has not yet been fully clarified.

High mobility group box 1 (HMGB1) is a non-histone protein that has the ability to regulate DNA repair, enhance transcription in the nucleus, and regulate cell differentiation, apoptosis, and autophagy in the cytoplasm after cell damage (Livesey et al. 2012, Dumitriu et al. 2005). In addition to acting as a proinflammatory cytokine (Wang et al. 1999), HMGB1 also affects the release of pro-inflammatory cytokines/chemokines, such as tumor necrosis factor, interleukin-1β, and CXCL8 (Bertheloot and Latz 2017). HMGB1 triggers inflammation and disrupts the vascular

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barrier in tissues (Nawaz and Mohammad 2015), and therefore it is a biological marker of neuroinflammation and neurodegeneration that can cause blood-brain barrier dysfunction (Festoff et al. 2016). This protein is considered to be a risk factor for the progression of inflammation in the nervous system in Alzheimer's disease, Parkinson's dementia, and multiple sclerosis (Angelopoulou et al. 2018, Paudel et al. 2020, Andersson et al. 2008). Makris et al. (2021) showed that HMGB1 serum concentrations changed in children with autism spectrum disorder, and HMGB1-mediated inflammatory processes affected certain cognitive features. In another study, the HMGB1 level was found to be high in patients with schizophrenia, and the authors suggested that the neurotoxic effects of this protein could explain neurocognitive disorders and various symptom clusters in schizophrenia (Al-Dujaili et al. 2021).

Autophagy, the cleaning system for cellular waste, is particularly important in neurons since it balances the production and destruction of cellular components. Blocking autophagy in neurons results in the accumulation of misfolded protein aggregates and damaged organelles, leading to apoptosis and consequently neurodegeneration (Mortensen et al. 2010, Hara et al. 2006). To date, more than 30 mammalian autophagy genes have been identified to play an important role in the occurrence and regulation of the autophagy process. In addition, many other proteins, including HMGB1, have been investigated in terms of their role in the autophagy process. HMGB1 is involved in the regulation of autophagy in the cell cytoplasm together with Beclin-1. HMGB1 induces autophagy by binding to Beclin-1, which plays a role in the regulation of autophagosome formation and maturation in autophagy (Kang and Tang 2016). Beclin-1 is a protein in the regulation of autophagy and plays a role in the formation of autophagosomes (Qu et al. 2003); therefore, a decrease in the level of Beclin-1 can trigger apoptotic processes (Wang 2008).

In the central nervous system, basal autophagy can degrade misfolded and damaged protein aggregates that cause neurodegenerative diseases, reduce protein toxicity, and oxidative stress, and prolong neural cell lifespan. In addition, disruptions in autophagy pathways, dysfunctional autophagosome accumulation, and overstimulation of autophagy can also lead to cell death (Puyal et al. 2012). Beclin-1 is a protein-structured molecule synthesized from neurons and glia (Liang et al. 1998), known to play a role in the pathogenesis of certain heart diseases and Parkinson's and Alzheimer's diseases (Esteyes et al. 2019, Zhu and He 2015, Spencer et al. 2009). It has been suggested that this protein may also have a role in autism due to the defect in the autophagy system (Dana et al. 2020). In schizophrenia, disruptions during autophagy in neurons can lead to cellular dysfunction and global changes in different brain regions, thereby contributing to the development of disease symptoms (Schneider et al. 2016). A decrease in Beclin-1 levels was detected in the hippocampus of these patients, and this protein was shown to play a very important role in the initiation of the autophagy process associated with the initiation of apoptosis (Wagner et al. 2015). HMGB1 is a new Beclin-1-binding protein that is important in maintaining autophagy (Kang et al. 2010). It has been shown that HMGB1 causes autophagy dysfunction by affecting Beclin-1 levels and results in neurotoxicity (Huang et al. 2017). However, to our knowledge, it has not yet been clarified whether this relationship is related to the development of any disease.

It has been reported that the cytoplasmic HMGB1-Beclin-1 complex is increased in resistant oral squamous cell cancer (Min et al. 2019). Similarly, Beclin-1 inhibition has been found to have decreased in epithelial ovarian tumors, and that HMGB1 has been shown to play a role in the pathogenesis of this disease (Ju et al. 2016). Therefore, in the current study, our hypothesis is that the serum levels of HMGB1 and Beclin-1 proteins, which play a role in inflammation, are affected in patients with schizophrenia and can be considered among factors involved in disease etiopathogenesis. In our review of the literature, we did not find any study examining the relationship between schizophrenia, a disease associated with inflammatory responses, and HMGB1 and Beclin-1, proteins that play a role in inflammation. Therefore, this study aimed to compare the serum concentrations of HMGB1 and Beclin-1 between patients with schizophrenia and healthy controls and to examine the possible relationship between HMGB1 and Beclin-1 and schizophrenia symptoms.

METHOD

Approval for this study was obtained from the Non-Invasive Ethics Committee of the Faculty of Medicine of Fırat University (Elazığ, Turkey) (approval number: E-97132852-050.01.04-87772). All stages of the study were carried out in accordance with the ethical standards of the Declaration of Helsinki as revised in 1983. Patients that were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) at the High-Security Forensic Psychiatry Ward of Elazığ Fethi Sekin Hospital were included in the study. Since the women's section of this ward was not active, all the patients and controls were men. The healthy control group consisted of individuals educated in our hospital and agreed to participate in the study. All the participants were provided detailed information concerning the study, and written consent was obtained from their legal guardians, if any. After obtaining the psychiatric history of the patients with schizophrenia, those that were diagnosed with malignancy or active infection and those that used corticosteroids or any other drug that

could affect the immune system within the last six months were excluded from the study. The control group consisted of volunteer hospital workers who did not have a history of mental disorder, history of alcohol and substance use disorder, diagnosis of malignancy or active infection, and had not used corticosteroids or any other drug that could affect the immune system within the past six months.

Procedure

After obtaining written consent from all the participants, a sociodemographic data form, PNSS, and the Clinical Global Impression (CGI) scale were administered to both the patients and control groups by a mental health specialist in the patient interview room over 45-minute interview periods. The height and weight measurements of both groups were made using the Seca machine, and body mass index (BMI) was calculated. Venous blood samples were taken from both groups immediately after the measurements were finished.

Data Collection Tools

PANSS

PANSS is a semi-structured 30-item scale that measures psychopathology based on positive, negative, and general schizophrenia symptoms. As a result of measurements, four scores are obtained: positive, negative and general psychopathology scores and the total PANSS score (Kay et al. 1987). The validity and reliability analyses of the Turkish version of PANSS were undertaken by Kostakoğlu et al. (1999).

CGI scale

This scale was developed to make a general assessment of the severity of depression and the patient's response to treatment during clinical studies and is divided into two main categories as the severity of the disease and general improvement achieved with drug therapy (Guy 1976).

Determination of serum HMGB1 and Beclin-1 Levels

Venous blood samples taken from the left forearm were placed into heparinized tubes between 08.00-09.00 o'clock after overnight fasting. To remove the plasma, the blood samples were centrifuged at 3,000 rpm for 10 minutes at 4 °C. The serum samples were stored at -80 °C until analysis. Commercial enzyme-linked immunosorbent assay kits [Human HMGB-1 (High Mobility Group Protein B1); Catalog No: E-EL-H1554; Elabscience Biotechnology Inc., Human BECN1 (Beclin-1); Catalog No: E-EL-H0564; Elabscience Biotechnology Inc.] were used to measure the serum concentrations of HMGB1 and Beclin-1 according to the manufacturer's instructions. The serum HMGB1 levels were recorded as pg/mL, and Beclin-1 levels as ng/mL.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) v. 20 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. The Kolmogorov-Smirnov test was conducted to determine the normality of the distribution of variables. Data were presented as mean and standard deviation and evaluated using descriptive analyses. Relationships between categorical data were evaluated with the chi-square test. The psychiatric outcomes and biochemical parameters of the patient and control groups were compared using Student's t-test or the Mann-Whitney U test. The Spearman rank correlation coefficient was used to analyze correlations between clinical features and serum HMGB1 and Beclin-1 levels. P values of <0.05 were considered significant.

RESULTS

Sociodemographic Characteristics

The study included 43 male patients with schizophrenia and 43 healthy controls with similar sociodemographic characteristics. Descriptive statistics regarding the sociodemographic data of the patients are given in Table 1. There was no significant difference between the two groups in terms of age and BMI ($p>0.05$). Of the patients with schizophrenia, 26 (56%) were married, and 17(%) were single or widowed, and in the healthy control group, 11(36%) were married, and 32(64%) were single or widowed ($t=12.592$, $p=0.002$).

Thirty-eight of the patients were still using medication. While 26(60.5%) of these patients were using a single antipsychotic, 12(27.9%) were using multiple antipsychotics. The number of patients that did not use medication was 5(11.6%).

Thirty (65%) individuals diagnosed with schizophrenia and 19(41%) of the healthy control group were smokers ($x^2=5.740$, $p=0.017$). In addition, a history of alcohol use was present in six (13%) patients in the schizophrenia group but none of the controls had such a history ($x^2=6.450$, $p=0.011$).

Group Comparisons

The patients' mean PANSS positive score was 18±4.7, the mean PANSS negative score was 16.2±5.1, the mean PANSS general psychopathology score was 33.7±5.9, and the mean PANSS total score was 67.7±10.2. Lastly, the mean CGI score of the patients was 7.9±1.8 (Table 1).

Serum HMGB1 and Beclin-1 Levels

As a result of the analyses, the mean serum HMGB1 level was measured as 2115.80±444.48 pg/ml in the patients with schizophrenia and 1632.58±396.21 pg/ml in the control group. The serum HMGB1 level was found to be significantly

Table 1. Demographic and Clinical Characteristics of the Patients with Schizophrenia and Controls

	Schizophrenia Group (n = 43)	Control Group (n= 43)	t/x^2	p
Age (years)	39.3 ± 13.4	39.9 ± 14.7	-0.176	0.861
Marital status Single/married/widowed	26/12/5	11/28/4	12.592	0.002
Education level Primary school/high school/university	23/11/9	29/10/4	2.663	0.264
Employment status Employed/unemployed	18/25	24/19	1.675	0.196
Smoking status Smoker/non-smoker	30/13	19/24	5.740	0.017
Alcohol use Present/absent	6/37	0/43	6.450	0.011
Body mass index	27.2 ± 4.4	27.6 ± 4.0	-0.418	0.677
History of suicide attempt Present/absent	5/38	0/43	5.309	0.021
Disease duration (years)	9.97 ± 8.01			
PANSS positive score	18 ± 4.7			
PANSS negative score	16.2 ± 5.1			
PANSS general psychopathology score	33.7 ± 5.9			
PANSS total score	67.7 ± 10.2			
CGI scale score	7.9 ± 1.8			

PANSS: Positive and Negative Syndrome Scale
CGI: Clinical Global Impression
Student t-test; Chi-square test

Table 2. HMGB1 and Beclin-1 Levels of the Patients with Schizophrenia and Controls

	Schizophrenia Group (n = 43)	Control Group (n = 43)	t	p
HMGB1 (pg/ml)	2.115.80 ± 444.48	1.632.58 ± 396.21	0.167[a]	<0.001*
Beclin-1 (ng/ml)	1.02 ± 0.40	1.34 ± 0.35	-3.852[a]	<0.001*

*p<0.001; [a]Student t-test

Table 3. Correlation Between the Biochemical and Clinical Parameters in the Patients with Schizophrenia

	BMI	PANSS positive	PANSS negative	PANSS general	PANSS total	CGI	HMGB1	Beclin-1
Age	-0.056	0.176	0.310*	0.328*	0.427*	0.237	0.272	-0.143
BMI	-	0.176	-0.066	0.096	0.105	0.065	0.075	0.1490
PANSS positive		-	-0.356*	0.101	0.327*	0.449**	-0.120	-0.041
PANSS negative			-	0.446**	0.620**	0.258	-0.159	0.173
PANSS general				-	0.865**	0.374*	-0.090	0.051
PANSS total					-	0.542**	-0.152	0.089
CGI						-	-0.212	0.128
HMGB1							-	-0.386*

Pearson correlation test; *p<0.05 **p<0.01
BMI: body mass index
PANSS: Positive and Negative Syndrome Scale
CGI: Clinical Global Impression

higher in the schizophrenia group compared to the control group (t=0.167, p<0.001) (Table 2).

The mean serum Beclin-1 level was found to be 1.02±0.40 ng/ml in the schizophrenia group and 1.34±0.35 ng/ml in the control group, indicating a significantly lower value in the patient group (t=0-3.852, p<0.001) (Table 2).

Correlation Analyses

No correlation was found between the HMGB1 and Beclin-1 levels and clinical parameters (p>0.05) (Table 3).

DISCUSSION

In this study, the serum HMGB1 and Beclin-1 levels of the patients with schizophrenia and healthy controls were examined. The main finding of our study is that the serum HMGB1 levels were significantly higher, and the serum Beclin-1 levels were significantly lower in the schizophrenia group compared to the healthy control group. To our knowledge, there is no other study comparing the serum HMGB1 and Beclin-1 levels of patients with schizophrenia and healthy controls. Therefore, this is the first study to describe this relationship.

Consistent with the literature, in our study, we determined the HMGB1 level to be higher in patients with schizophrenia than in the healthy control group. In a study conducted with 68 patients with chronic schizophrenia, it was shown that the HMGB1 levels were significantly higher in the patient group than in healthy controls, and this was attributed to the association of this disease with neuroinflammation (Kozlowska et al. 2021). Although that study was also conducted with schizophrenic patients, the authors did not exclude those using antipsychotics, which are known to affect serum cytokine levels (Tourjman et al. 2013). In a 2021 study, the serum HMGB1 levels were found to be significantly higher in 30 patients with schizophrenia in the exacerbation period of the disease and in 29 patients with schizophrenia in the remission period of the disease compared to the healthy control group. A positive correlation was observed between the HMGB1 levels and symptom severity scores in patients in remission, and it was suggested that HMGB1 could be a biomarker in the remission period of schizophrenia (Yılmaz et al. 2021). Similarly, Zhu et al. (2015) reported that the serum HMGB1 levels were higher in schizophrenic patients compared to controls. The authors suggested that HMGB1 could play a proinflammatory role in schizophrenia, and a decrease in the HMGB1 level after risperidone treatment might be an indicator of remission of mental symptoms. Although some studies state that antipsychotic use and disease duration do not affect the serum levels of HMGB1 (Lee et al. 2017, Xiu et al. 2015), it has also been reported that antipsychotic drugs can reduce serum cytokine levels (Borovcanin et al. 2013). It is known that HMGB1 increases by secretion, especially in microglia cells in the hippocampal region, especially immediately after exposure to stress. Therefore, the known effects of HMGB1 on stress-induced neuroinflammatory response (Yao et al. 2019, Weber et al. 2015) may explain the high serum HMGB1 levels in patients with schizophrenia, as also observed in our study.

In the literature, we did not find any study investigating serum Beclin-1 levels in individuals diagnosed with schizophrenia; therefore, our study is the first one in this regard. It is known that autophagy plays a role in the pathogenesis of psychiatric diseases, such as major depressive disorder, schizophrenia, and bipolar disorder, and Beclin-1 plays a regulatory role in autophagy (Kang et al. 2011, Bar-Yosef et al. 2019). It has been shown that serum Beclin-1 levels in patients with a diagnosis of major depressive disorder who do not respond to antidepressant treatment are significantly higher compared to those that respond to antidepressant treatment, suggesting that the serum Beclin-1 level may be a predictive biomarker of response to antidepressant treatment (He et al. 2019). In a study conducted in rats, Zheng et al. (2017) determined that the prefrontal cortex was sensitive to stress, and increased exposure to stress resulted in changes in Beclin-1 levels due to autophagy. In human and mouse models of schizophrenia, low Beclin-1 mRNA and protein levels were found in the postmortem hippocampus, and antipsychotic treatment was shown to increase the Beclin-1 level (Merelender et al. 2014). In addition, it has been stated that adequate Beclin-1 expression and apoptosis are needed to effectively treat schizophrenia (Merelender et al. 2014). Furthermore, it has been determined that a protein regulated by Beclin-1 may lead to the development of schizophrenia and autism by leading to autophagosome formation (La Barbera et al. 2019). We also found that the serum Beclin-1 levels of the patients with a diagnosis of schizophrenia were lower than those of the healthy controls. This suggests that this decrease may be related to the disruptions in autophagosome formation in the pathogenesis of the disease.

HMGB1 competes with Bcl2 to interact with Beclin-1 and directs the latter toward autophagosomes (Kang et al. 2010). Preventing HMGB1 from binding to Beclin-1 in mice inhibits autophagy, thus leading to improvement in neurological functions (Pan et al. 2020). A study conducted in vitro showed that while the HMGB1 level increased in lung injury, Beclin-1 decreased (Le et al. 2020). In our literature review, we did not find any study examining the relationship between serum HMGB1 and Beclin-1 at the disease level. According to our results, there was no correlation between these two proteins measured by kits and other clinical parameters, but we found a negative correlation between HMGB1 and Beclin-1 (r=-0.417 p<0.001). We can state that our study is the first one in this respect.

Limitations

The strength of our study is that the participants were only male schizophrenic patients. However, the cross-sectional design and the lack of evidence showing that the measured parameters reflected the concentrations of serum levels in the brain are among our limitations. In addition, the patient group diagnosed with schizophrenia included people that used antipsychotic drugs, which are known to affect inflammatory markers (Momtazmanesh et al. 2019). Furthermore, the sample included individuals admitted to the forensic psychiatry ward after committing crimes, and the results may have been different due to the more impulsive behaviors of this patient population. There is a need for longitudinal studies to evaluate unmedicated or more homogeneous antipsychotic treatment groups.

CONCLUSION

Our results showed that the HMGB1 levels were higher, and the Beclin-1 levels were lower in the patients with schizophrenia compared to the healthy controls. We consider that these two parameters may play a role in the pathogenesis of schizophrenia. To our knowledge, serum HMGB1 and Beclin-1 levels have not been previously investigated in patients with a diagnosis of schizophrenia; therefore, this is the first study on this subject. The clarification of the role of HMGB1 and Beclin-1 in the etiopathogenesis of schizophrenia can contribute to the development of new treatment methods.

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