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Neutrophil/Lymphocyte ratio in patients with major depression and the impact of electroconvulsive therapy

ECT and subclinic inflammation in depression

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Abstract
Aim: An accumulation of evidence supports the role of inflammation in the etiology of depression, particularly in severe depression. In this study, we aimed to investigate the effect of electroconvulsive therapy (ECT) treatment on the rates of neutrophil/lymphocytes (N/L), platelets/lymphocyte (P/L) which are subclinical inflammatory markers in patients with moderate/severe depression who went into remission.
Materials and Methods: Patients with major depression who had been admitted to hospital in the preceding 2 years with a diagnosis of major depression according to DSM 5 and who had undergone ECT were included in this study as well as a similar number of patients were included as a control group. The groups were compared with respect to the subclinical inflammatory markers N/L, P/L at baseline and after ECT. Fifty-seven patients were compared with respect to N/L, P/L ratios before and after ECT.
Results: A total of 116 patients were included in the study, of whom 57 had major depression and 59 were in the control group. The N/L values were significantly higher in the pre-ECT patient group compared to the control group. The post-ECT N/L value was significantly higher compared to the control group and no difference was found between the P/L ratios. There was no significant difference between pre and post-ECT N/L, P/L values in the patient group.
Discussion: This study suggests the presence of subclinical inflammation in moderate to severe major depression patients which persists after ECT. Large-scale studies are needed to determine the effects of ECT on inflammation.

Keywords
Neutrophil; Lymphocyte; Platelet; Electroconvulsive therapy; Depression

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Introduction

According to DSM 5, Major Depression is the presence of five of the following criteria: not enjoying life for a period of at least two weeks, depression, fatigue, psychomotor retardation, changes in sleep patterns and appetite, thoughts of self-worthlessness, distraction and suicidal thoughts [1] The severity of depression is one of the most important predictors of treatment and determines its course [2]. The pathophysiology of major depression is still unclear. Psychosocial stress and stress hormones, neurotransmitters, neurotrophic factors, circadian rhythm and the role of inflammation are still being investigated [3]. Accumulated evidence supports the role of inflammation in the etiology of depression like other severe mental disorders [4, 5]. In addition, somatic inflammatory diseases and increased pro-inflammatory markers increase the risk of developing depression [5]. There is evidence that proinflammatory cytokines, CRP, and oxidative parameters increase which supports the role of chronic inflammation in depression [5].

Another determinant of chronic inflammation is the number of white blood cells and its subtypes. The N/L ratio is a new parameter that shows systemic inflammatory responses [6]. Repeated studies have reported an increase in the N/L ratio, a subclinical inflammatory marker in Major Depression [6, 7]. Recently, the P/L ratio has been used to determine inflammation [8]. It has been reported that the P/L ratio increases in psychotic and severe major depression [8].

The number of studies on the anti-inflammatory effects of antidepressants prescribed for major depression has been increasing recently, and it is thought that even anti-inflammatory agents can serve as clinically relevant antidepressants [9, 10]. Electroconvulsive therapy is another important treatment option for major depression. It is effective in the acute treatment of major depression and in therapy-resistant severe depression [11]. Immediately after ECT sessions, acute immune-inflammatory responses increase as an acute stress reaction. However, the inflammatory response decreases at the end of the treatment process after repeated ECTs [11].

In this study, the effect of ECT treatment on the rates of N/L, P/L, which are subclinical inflammatory markers, in patients with major depression who went into remission was investigated.

Material and Methods

Major depression patients who were admitted to the outpatient clinic of the Department of Psychiatry of Gaziantep University School of Medicine and who underwent ECT after being diagnosed with major depression according to DMS 5 were included in this study as well as a similar number of healthy individuals in a control group. Because the study is a retrospective file review, written informed consent was not obtained.

Assessment Tools

Sociodemographic Questionnaire: It prepared by the researcher in accordance with literature. The questions included age, gender, marital status, education level, smoking status and mental illness [12].

Hamilton Depression Rating Scale: The Hamilton depression rating scale is used to measure the severity of depression. The score ranges of the scale (0-7) represent no depression; (8–16) mild depression; (17-23) moderate depression; (≥24) and severe depression[13]. A 50% decrease in the HamD scale equates to response to [14] treatment. In the Remission HamD scale, a score of 7 and below is considered a decrease [15]. HAMD is regularly used in clinical assessments.

Patient recruitment process: The approval of the ethics committee was obtained prior to the study. The impact size (d=0.35) was chosen for the study to be conducted to investigate the change in pre-and post ECT N/L values in depression patients to be statistically significant and the minimum number of participants was determined to be 52 (α=0.05, 1-β=0.80). The analysis was performed using G power 3.1 version.

After determining the required number of patients, 127 patients who had undergone ECT treatment for major depression in the preceding 2 years were screened. Patients with severe neurological disease, malignant diseases, mental retardation, alcohol, substance disorder or a history of addiction were excluded from the study. Patients with diabetes mellitus and other endocrinopathies due to chronic inflammation as well as patients with liver disease were also excluded from the study.

The Hamilton depression rating scale was above 19 for the remaining 78 patients after the exclusion process. The results of the HAMD scale indicated that all patients participating in the study had moderate to severe depression. A 50% decrease in the HamD scale was observed in all patients, and was interpreted as equating to a response to treatment. Of the 66 patients (85.07%) who went into remission, 9 patients could not be included in the study because they did not have full blood counts. Fifty-seven of these patients were identified as members of the study group, showing up for a check-up within the first 15 days after ECT, who had no complaints.

For Pre-ECT anesthesia, a pre-evaluation was undertaken for all patients, their data were fully evaluated and they had no active infections. The control group was selected from 59 healthy individuals who came to the psychiatry outpatient clinic for general screening after applying to the Health Commission to get a clean bill of health for a job application in the preceding 6 months and who were found to have no disabilities. The sociodemographic data for all patients such as age and gender were recorded.

Propofol 1 mg/kg, ECT was administered bilaterally under general anesthesia 7 times a week on Mondays, Wednesdays, and Fridays using the MECTA 5000Q ECT device at a dosage of 800 mA. Patients were given seizures lasting 30 to 60 seconds as part of the treatment. Three patients had a total of 9 ECT treatments and the others had a total of 7 ECT treatments. Patients continued to use additional medication at the doses prescribed at the commencement of the study. The patients were taking antidepressants.

Fifty-seven patients and the control group of 59 patients were compared with respect to the subclinical inflammatory markers neutrophils/lymphocytes, platelets/lymphocytes at baseline and after ECT. Fifty-seven patients were separately compared in terms of neutrophil/lymphocyte, platelet/lymphocyte ratios before and after ECT.

Statistical analysis

Descriptive statistics were used to evaluate the patient

and control group data and to explain the demographic characteristics. The Shapiro-Wilk and the Kolmogorov-Smirnov tests were used to evaluate the normal distribution of variables. It was found that age, education length, N/L and P/L ratio variables used in the analyzes were not normally distributed for each group (p<0.05). Accordingly, the Mann-Whitney U test was used for comparisons between patient and control groups, and the Wilcoxon test was used to compare values before and after ECT. In addition, the Chi-square test was used to compare the patient and control groups according to gender and smoking habits. The analyses were conducted using SPSS 22.0 software.

Results

One hundred sixteen patients were included in the study, of whom 57 had major depression and 59 were from the control group. There was no statistically significant difference between the patient and control groups in terms of age and duration of education (p>0.05). Similarly, the patient and control groups did not have statistically significant differences in terms of gender and smoking habits (p>0.05) (Table 1).

Table 1. Comparison of sociodemographic characteristics of the patient and control groups

Variables		CASE CONTROL		p
		ECT	CONTROL	
Gender	Male	27 (47.4%)	22 (37.3%)	p=0.272
	Female	30 (52.6%)	37 (62.7%)	
Age		39.79+13.26	41.54+15.48	p=0.538
Smoking	Yes	30 (52.6%)	31 (52.5%)	p=0.992
	No	27 (47.4%)	28 (47.5%)	
Education (years)		6.40+3.32	6.33+3.81	p=0.682

The N/L ratio of patient and control groups before ECT showed statistically significant differences (p<0.05). The pre-ECT N/L ratio was found to be higher in patients with major depression compared to the control group. The P/L ratio of the patient and control groups before ECT did not show statistically significant differences (p>0.05). The N/L ratio of the patient and control groups after ECT showed statistically significant differences (p<0.05). The post-ECT N/L ratio was found to be higher in patients with major depression compared to the control group. The P/L ratio of the patient and control groups after ECT did not show statistically significant differences (p>0.05) (Table 2).

Table 2. Comparison of N/L and P/L values before and after ECT of the patient and control groups

Variables			N/L vs. P/L before ECT		N/L vs. P/L after ECT	
	Case-control	N	Average± Standard Deviation	P	Average± Standard Deviation	P
N/L	Patient	57	2.60± 1.10	p=0.001	3.23± 2.53	p=0.001
	Control	59	1.90±0.62		1.90± 0.62	
P/L	Patient	57	122.67± 43.92	p=0.052	135.49± 71.94	p=0.181
	Control	59	141.11±48.32		141.11± 48.32	

When the N/L and P/L values of the patient group were compared before and after ECT, no statistically significant differences were found (p>0.05) (Table 3).

Table 3. Comparison of N/L and P/L values before and after ECT in the patient group

Variables		N	Mean	Standard deviation	p
N/L	N/L before	57	2.60	1.10	p=0.292
	N/L after	57	3.23	2.53	
P/L	P/L before	57	122.67	43.93	p=0.254
	P/L after	57	135.49	71.95	

Discussion

The first finding of the study is that N/L ratios are higher in patients with severe depression who are on medication compared to those in the control group. Studies demonstrate the role of inflammation in major depression [5, 16]. Inflammatory markers were found to be high in severe and treatment-resistant depression, and this increase is associated with a poor response to treatment [17]. CRP, an inflammatory marker, was high in women due to the severity of depression [18]. The N/L ratio was found to be higher in patients with major depression not receiving treatment compared to the control group [7]. The current study supports these findings and shows that the N/L ratio is high in patients with moderate-severe depression who use antidepressants. Furthermore, it is assumed that the inclusion of antidepressants in the complex therapy of depression may alleviate chronic inflammation [19].

In a study conducted with post-stroke patients, it was reported that elevated P/L ratios may be predictive as an independent marker for the development of depression [20]. In this current study, the P/L ratio was found to be higher in patients with major depression compared to the control group. This significant difference disappeared after ECT. However, it has been established that ECT has no significant effect on P/L values before and after ECT. These results support the presence of a subclinical inflammation dependent on the severity of major depression.

Studies examining inflammation in the pathophysiology of major depression suggest that antidepressants tend to reduce inflammation [9, 10]. What role does ECT play in inflammation, used in particular in the treatment of resistant and severe depression? Unfortunately, studies investigating the effect of ECT on the inflammatory system are limited in scope. A study on cytokines found a decrease in IL-6 and an increase in TNF-alpha after treatment, and [21] another study found a decrease in the IL-level [22]. Immediately after an ECT session, an acute immune-inflammatory response occurs by way of an acute stress response. However, it has been reported that ECT leads to a long-term decrease in cortisol plasma levels and a decrease in TNF-alpha and interleukin-6 levels at the end of treatment [11]. In this study, it was not possible to evaluate acute stress response due to a lack of complete blood count values immediately after ECT. However, the lack of any difference between the N/L and P/L ratios may suggest that

it has no effect on inflammation. However, the results may seem meaningless due to the sensitivity and specificity of the parameters.

There is a relationship between inflammation and oxidative balance. Oxidative stress is seen as an imbalance between the production of reactive oxygen species (ROS] and the elimination of protective mechanisms that can lead to chronic inflammation [23]. The total antioxidant content was lower with respect to spoilt oxidant equilibrium in major depression. [24]. Oxidative stress parameters were measured before and after ECT, and total antioxidant levels were found to increase after ECT. However, no changes in the total oxidant level were found [24]. In the current study, there was no significant change in N/L, P/L ratios after ECT. Although there was an increase in the N/L ratio, it was not statistically significant. Large-scale studies are needed to determine the effects of ECT on inflammation.

The retrospective nature of the study and the limited number of patients constituted the main limitations of the study. Although it is known that patients receive pharmacotherapy, not knowing whether they use monotherapy or combined medications and which ones display psychotic tendencies, is also a limitation. The fact that the body mass index of the patients was not available was another limitation of the study. However, studies incorporating the body mass index into their analyses have found that it has a very low impact in the equation [25].

To conclude, this study shows the presence of subclinical inflammation in moderate to severe major depression patients which persists after ECT. Prospective studies are needed to determine the effects of ECT on inflammation in patients separated according to large-scale drug groups.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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