J Surg Med. 2019;3(11):793-795.
DOI: 10.28982/josam.637840

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

The effect of electroconvulsive therapy on subclinical inflammation in bipolar disorders

Elektrokonvülsif terapinin bipolar bozukluklarda subklinik inflamasyon üzerine etkisi

Şengül Kocamer Şahin [1], Celal Yaşamalı [1], Muhammet Berkay Özyürek [2], Gülçin Elboğa [1], Abdurrahman Altındağ [1], Enes Elmalı [1], Handan Demirbaş [1]

[1] Department of Psychiatry, Gaziantep University Faculty of Medicine, Gaziantep, Turkey
[2] Department of Psychiatry, Balıkesir University Faculty of Medicine, Balıkesir, Turkey

ORCID ID of the author(s)
ŞKŞ: 0000-0002-5371-3907
CY: 0000-0002-2813-2270
MBÖ: 0000-0002-7016-1411
GE: 0000 0003 3903 1835
AA: 0000-0001-5531-4419
EE: 0000-0002-5425-1150
HD: 0000-0002-0894-5565

Corresponding author / Sorumlu yazar:
Şengül Kocamer Şahin
Address / Adres: Gaziantep Üniversitesi Tıp Fakültesi, Psikiyatri Anabilim Dalı, Gaziantep, Türkiye
e-Mail: snglkcmr@hotmail.com

Ethics Committee Approval: The study was approved by the Gaziantep University Ethics Committee for Clinical Research, 2018/360.
Etik Kurul Onayı: Çalışma Gaziantep Üniversitesi Klinik Araştımalar Etik kurulu tarafından, 2018/360, onaylandı.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Previous presentation: This paper is presented as verbal presentation in 23th Turkey Psychiatry Annual Meeting and Clinical Education Symposium on 10-13 April 2019 Muğla, Turkey.

Published: 11/14/2019
Yayın Tarihi: 14.11.2019

Abstract

Aim: Growing evidence supports the role of inflammation in the etiology of bipolar disorder. Efficacy of electroconvulsive therapy (ECT) in the manic and depressive phases of bipolar disorder is well-known. We aimed to investigate the effect of ECT on the neutrophil/lymphocyte (NLR) and platelet/lymphocyte ratios (PLR), which are newly defined subclinical inflammatory markers in patients with bipolar disorder.

Methods: Patients who received ECT due to the diagnosis of bipolar disorder according to DSM-5 in the last two years and the same number of individuals as the control group were included in this case-control study. NLR and PLR were compared between the patient and control groups, and before and after ECT in the patient group.

Results: A total of 104 individuals were included in the study. Among included patients with bipolar disorder, 39 were in depressive episode and 13 were in manic episode. 52 healthy individuals were identified as control group. Patients' mean age was 36.0 (13.4) years. There were no significant differences between the groups in terms of age, gender, marital status, and smoking. NLR values were significantly higher in the patient group before and after ECT compared to the control group. No difference was found between PLR ratios. There was no significant difference between the NLR, PLR values before and after ECT in the patient group.

Conclusion: This study supports the hypothesis that subclinical inflammation exists in bipolar patients in both manic and depressive phases and it continues after ECT. Large-scale studies are needed to determine the effects of ECT on subclinical inflammation.

Keywords: Neutrophil, Lymphocyte, Monocyte, Electroconvulsive therapy, Bipolar disorder

Öz

Amaç: Biriken kanıtlar, bipolar bozukluğun etiyopatogenezinde enflamasyonun rolünü desteklemektedir. Elektrokonvülsif terapi (EKT) bipolar bozukluğun manik ve depresif dönemlerinde etkindir. Bu çalışmada bipolar bozukluk hastalarında EKT'nin remisyona ulaşan hastalarda yeni bulunan subklinik inflamatuar belirteçler olan nötrofil/lenfosit (N/L), platelet/lenfosit (P/L) oranlarına etkisini araştırmayı amaçladık.

Yöntemler: Bu olgu-kontrol çalışmasına son iki yılda DSM-5'e göre bipolar bozukluk tanısı ile kliniğe yatırılarak EKT uygulanan manik ve depresif dönem hastaları ile aynı sayıda kontrol grubu alındı. Hasta ve kontrol grubu N/L, P/L oranları açısından karşılaştırıldı. Elli iki hasta EKT öncesi ve sonrası N/L, P/L oranları açısından ayrıca karşılaştırıldı.

Bulgular: Çalışmamıza 39 bipolar bozukluk depresif dönem, 13 bipolar bozukluk manik dönem, 52 sağlıklı kontrol olmak üzere toplam 104 olgu alınmıştır. Yaş, cinsiyet, medeni durum, sigara içme açısından sağlıklı kontroller ve hastalar arasında anlamlı fark bulunmamıştır. EKT öncesi hasta grubunda N/L değerleri kontrol grubuna göre anlamlı oranda yüksek bulunmuştur. EKT sonrası N/L değerleri kontrol grubuna göre anlamlı oranda yüksek bulunmuş, P/L oranları arasında fark bulunmamıştır. Hasta grubunda EKT öncesi ve sonrası N/L, P/L değerleri arasında anlamlı fark bulunmamıştır.

Sonuç: Bu çalışma bipolar bozukluk manik/depresif dönem hastalarında subklinik enflamasyonun varlığını ve EKT sonrası bu durumun sürdüğünü desteklemektedir. EKT'nin enflamasyon üzerindeki etkilerini belirlemek için geniş ölçekli çalışmalara gerek vardır.

Anahtar kelimeler: Nötrofil, Lenfosit, Monosit, Elektrokonvülsif terapi, Bipolar bozukluk

How to cite / Atıf için: Şahin ŞK, Yaşamalı C, Özyürek MB, Elboğa G, Altındağ A, Elmalı E, Demirbaş H. The effect of electroconvulsive therapy on subclinical inflammation in bipolar disorders. J Surg Med. 2019;3(11):793-795.

Introduction

The pathophysiology of bipolar disorder is not fully understood. Genetics, circadian rhythms, neurotransmitters, psychosocial factors including childhood traumas, and neuroanatomic changes were blamed in the etiology [1,2]. Accumulative evidence indicates that immune system dysfunction may play a role in the pathophysiology. Elevated levels of proinflammatory cytokines were detected in bipolar disorder [3]. The role of inflammation in mental disorders is not fully established, however, the connection between neurotransmitters and inflammation was shown. Proinflammatory cytokines interact with each other and neurotransmitters in the central nervous system via the cytokine network [4]. The neurotransmitter metabolism changes neuroendocrine function, synaptic plasticity, and related motor activity. These inflammatory cytokines could affect almost all aspects of brain function related to motivational behavior. These effects of the immune system in the brain could cause behavioral consequences and neuropsychiatric disorders [4].

One of the determinants of chronic inflammation is the number of white blood cells and subtypes. The neutrophil/lymphocyte ratio (NLR) is a new parameter indicating systemic inflammatory response [5-7]. Recently, platelet/lymphocyte and lymphocyte/monocyte ratios have been used to determine inflammation [8,9]. It has been reported that NLR and platelet/lymphocyte ratio (PLR), which are subclinical inflammatory markers, are increased in bipolar disorder [10].

Electroconvulsive therapy (ECT) is effective and safe in all manic, depressive, and mixed stages of bipolar disorder [11]. It is a frequently preferred method of treatment for inpatients [12]. Acute immune-inflammatory response increases as an acute stress reaction immediately after ECT sessions. However, after repeated ECT, the inflammatory response decreases at the end of the treatment process [13].

In this study, we report the results of our research on subclinical inflammatory markers, namely, NLR and PLR, and the improvement of symptoms after ECT in patients with bipolar disorder in manic and depressive stages.

Materials and methods

Patients who received ECT due to the diagnosis of bipolar disorder according to DSM-5 in the last two years in the Psychiatry Department of Gaziantep University, Faculty of Medicine and the same number of individuals as the control group were included in this case-control study. Ethics committee approval was obtained from Gaziantep University Clinical Studies Ethics Council (2018/360). 112 patients had undergone ECT for bipolar disorder in the last two years. Patients with severe neurological diseases, diabetes mellitus and other endocrinopathies, liver diseases, malignancies, intellectual disability, alcohol, substance use disorder or addiction history were excluded from the study. Among the remaining 63 bipolar patients in remission in the depression (HAMD<7) and manic (YMRS <12) phases, 11 patients were excluded due to lack of a complete blood count. Among the 52 included, 39 had depressive bipolar and 13 had manic bipolar disorder. Those who had no complaints in the 15 days following ECT (n=52) were identified as the study group. Prior to ECT, all patients had completed evaluations for anesthesia and did not have any active infections. The control group was selected from the last 52 healthy individuals without any disabilities, based on the report issued by the psychiatric outpatient clinic after general screening in the last six months. Sociodemographic variables such as age and gender of the patients were recorded.

ECT was administered bilaterally under general anesthesia after administration of 1 mg/kg propofol seven times a week, on Monday, Wednesday, and Friday at 800 mA with MECTA 5000Q ECT, allowing the patients to have seizures for a period of 30-60 seconds. Patients continued to use additional medication at the beginning of the study. Among 39 patients with bipolar depressive episode, 10 were using lamotrigine, 16 were using valproate, and 6 were using lithium. Five patients were using antidepressants in addition to mood stabilizers. Seven patients who did not use mood stabilizers had quetiapine in their combination. All of 13 the bipolar manic patients were on antipsychotics. 4 of them were using lithium and 4 of them were using valproate in combination with antipsychotics. Four patients with bipolar manic episode had discontinued their medication, and emergency hospitalization had been planned due to manic episode. Haloperidol, biperiden, chlorpromazine injections and additional antipsychotics were used for the treatment of these patients for 3 days and ECT was administered due to exacerbation. They continued to take antipsychotics orally during ECT. There were no patients who did not receive any medication.

52 patients and 52 healthy control individuals were compared in terms of NLR and PLR before and after ECT.

Statistical analysis

Descriptive statistics for demographic characteristics were used to evaluate the data of the patient group. $\chi 2$ test was used to compare categorical variables. T-test was used to compare normally distributed variables, and paired t-test was used for the pre-ECT and post-ECT comparisons of NLR and PLR. Data were analyzed with SPSS v24.0 (IBM Corporation York, United States) for Windows.

Results

The mean age of the patients was 36.05 (13.4) years. The average duration of education was 6.40 (3.5) years. The bipolar patient group consisted of 25 men and 27 women. No significant difference was found between healthy controls and patients in terms of age, sex, marital status, or smoking (Table 1).

Table 1: Sociodemographic data

		ECT	Control	*P*-value
Gender	Male n(%)	25(48.1)	24(46)	0.48
	Female n(%)	27(51.9)	36(54)	
Age mean (SD)		36.05 (13.4)	40.09 (14.8)	0.51
Education (years) mean (SD)		6.40 (3.5)	6.33 (3.99	0.92
Smoking	Yes	31	23	0.11
	No	21	29	

ECT: Electroconvulsive therapy, SD: Standard deviation

NLR values were significantly higher in patients with bipolar disorder than the control group before ECT (P<0.001). PLR did not differ between healthy and control groups (Table 2). After ECT, NLR remained significantly higher in the patient group than in the controls (P=0.003). There was no difference in PLR values (Table 2). No significant difference was found

between NLR and PLR in the pre-ECT and post-ECT evaluation (Table 3), and depressive and manic episodes.

Table 2: Comparisons of NLR and PLR between the patient and control groups before and after ECT

			NLR and PLR comparison before ECT		NLR and PLR comparison after ECT	
		n	Mean (SD)	*P*-value	Mean (SD)	*P*-value
NLR	patient	52	2.74 (1.24)	<0.001	3.22 (3.179	0.003
	control	52	1.91 (0.65)		1.91 (0.659	
PLR	patient	52	135.19 (49.68)	0.739	131.21 (59.77)	0.503
	control	52	138.43 (49.23)		138.43 (49.23)	

ECT: Electroconvulsive therapy, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, SD: Standard deviation

Table 3: Comparisons of NLR and PLR before and after ECT

		n	Mean (SD)	*P*-value
NLR	Before ECT	52	2,74 (1.24)	0.273
	After ECT	52	3.22 (3.17)	
PLR	Before PLR	52	135.19 (49.68)	0.611
	After PLR	52	131.21 (59.77)	

ECT: Electroconvulsive therapy, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, SD: Standard deviation

Discussion

The first finding of our study was that NLR was higher in patients with bipolar disorder who were on medication than healthy controls. Studies support the role of inflammation in bipolar disorder [3]. The prevalence of bipolar disorder has been shown to increase in patients with autoimmune disorders, cardiovascular diseases, and metabolic dysfunction [14]. Interleukin IL-4, IL-6, IL-10, soluble IL-2 receptor concentrations, tumor necrosis factor (TNF) -alpha, and soluble TNF receptor-1 were significantly higher in patients in the manic and euthymic periods compared to healthy controls [15]. TNF-alpha and IL-6 were found to increase in bipolar depressive period [16,17]. In another study, inflammation was reported as an important predictor of relapse in the course of bipolar disorder, especially during the depressive period [18]. Neutrophil-lymphocyte and platelet-lymphocyte ratios were significantly higher in bipolar disorder in both manic and euthymic patients than in the control group [10]. Our study, in which we found that the NLR values of patients using drugs due to bipolar disorder were higher, also supports these findings.

There were a few studies investigating the effect of ECT on the inflammatory system. More studies are focused on the alteration of inflammatory markers in the treatment of major depression in ECT [19,20]. In our literature review, we could not find a study directly investigating the effect of ECT on NLR and PLR in bipolar disorder. In a study which examined oxidant levels, total antioxidant levels increased with ECT in depressive bipolar patients, and total oxidant levels decreased in manic patients [21]. As an anti-inflammatory agent, celecoxib did not significantly affect BDNF level or treatment response after ECT in bipolar manic patients [22]. In our study, there was no significant alteration in NLR or PLR after ECT.

The retrospective design of the study, the scarce number of patients and the lack of the evaluation of body mass index were the limitations of our study. However, studies investigating the body mass index in relation to inflammation found a very low correlation [23]. Another limitation of the study was that patients were taking various medications. However, the inclusion of antidepressants in complex therapy is thought to alleviate chronic inflammation [24]. Studies reporting that mood regulators decrease inflammatory markers are dominant in the literature [25,26]. There was no significant relationship between antipsychotic use and inflammatory markers [27].

This study demonstrates the presence of subclinical inflammation in bipolar disorder, which continues after ECT. To determine the effects of ECT on inflammation, further studies are needed in large-scale patient groups who do not use drugs.

References

1. Freund N, Juckel G. Bipolar Disorder: Its Etiology and How to Model in Rodents. Psychiatric Disorders. Humana, New York, NY 2019;61-77.
2. Adigüzel V, Özdemir N, Şahin ŞK. Childhood traumas in euthymic patients with bipolar disorder in Eastern Turkey and its relations with suicide risk and aggression. Nordic Journal of Psychiatry. 2019;73(8):490-6.
3. Rosenblat JD, McIntyre RS. Bipolar Disorder and Inflammation. Psychiatr Clin North Am. 2016;39:125-37. doi: 10.1016/j.psc.2015.09.006.
4. Wang TY, Lee SY, Hu MC, Chen SL, Chang YH, Chu CH, et al. More inflammation but less brain-derived neurotrophic factor in antisocial personality disorder. Psychoneuroendocrinology. 2017;85:42-8.
5. Sunbul M, Gerin F, Durmus E, Kivrak T, Sari I, Tigen K, et al. Neutrophil to lymphocyte and platelet to lymphocyte ratio in patients with dipper versus non-dipper hypertension. Clin Exp Hypertens. 2014;36:217-21.
6. Yıldırım ÖT, Akşit E, Aydın F, Aydın AH, Dağtekin E. Can neutrophil to lymphocyte ratio and platelet to lymphocyte ratio be used as biomarkers for non-dipper blood pressure? J Surg Med. 2018;3(1):4-7.
7. Çelen S, Günseren KÖ, Özlülerden Y, Mete A, Tuncay ÖL, Yavaşcaoğlu İ. Does neutrophil-lymphocyte ratio show recurrence in patients who underwent curative resection for non-muscle-invasive bladder cancer? J Surg Med. 2019;3(4):324-7.
8. Krenn-Pilko S, Langsenlehner U, Thurner EM, Stojakovic T, Pichler M, Gerger A, et al. The elevated preoperative platelet-to-lymphocyte ratio predicts poor prognosis in breast cancer patients. Br J Cancer. 2014;13;110:2524-30.
9. Cummings M, Merone L, Keeble C, Burland L, Grzelinski M, Sutton K, et al. Preoperative neutrophil:lymphocyte and platelet:lymphocyte ratios predict endometrial cancer survival. Br J Cancer. 2015;14(113):311-20.
10. Kalelioglu T, Akkus M, Karamustafalioglu N, Genc A, Genc ES, Cansiz A, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratios as inflammation markers for bipolar disorder. Psychiatry Res. 2015;30(228):925-7. doi: 10.1016/j.psychres.2015.05.110.
11. Perugi G, Medda P, Toni C, Mariani MG, Socci C, Mauri M. The Role of Electroconvulsive Therapy (ECT) in Bipolar Disorder: Effectiveness in 522 Patients with Bipolar Depression, Mixed-state, Mania and Catatonic Features. Curr Neuropharmacol. 2017;15:359-371. doi: 10.2174/1570159X14666161017233642.
12. Eroğlu MZ, İçbay E, Tamam L. Bir üniversite hastanesi psikiyatri kliniğinde elektrokonvülzif tedavi uygulanan hastaların demografik ve klinik özellikleri. Dicle Tıp Dergisi. 2012;39(3):371-6.
13. Yrondi A, Sporer M, Péran P, Schmitt L, Arbus C, Sauvaget A. Electroconvulsive therapy, depression, the immune system and inflammation: A systematic review. Brain Stimul. 2018;11:29-51. doi: 10.1016/j.brs.2017.10.013. Epub 2017 Oct 19.
14. Rosenblat JD, McIntyre RS. Are medical comorbid conditions of bipolar disorder due to immune dysfunction? Acta Psychiatr Scand. 2015;132:180-91. doi: 10.1111/acps.12414.
15. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biol Psychiatry. 2013;1;74:15-25. doi: 10.1016/j.biopsych.2013.01.007.
16. Ortiz-Domínguez A, Hernández ME, Berlanga C, Gutiérrez-Mora D, Moreno J, Heinze G, et al. Immune variations in bipolar disorder: phasic differences. Bipolar Disord. 2007;9:596-602.
17. Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'anna M, Mascarenhas M, Escosteguy Vargas A, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J Affect Disord. 2009;116:214-7.
18. Bond DJ, Andreazza AC, Hughes J, Dhanoa T, Torres IJ, Kozicky JM, et al. Association of peripheral inflammation with body mass index and depressive relapse in bipolar disorder. Psychoneuroendocrinology. 2016;65:76-83. doi: 10.1016/j.psyneuen.2015.12.012.
19. Freire TFV, Rocha NSD, Fleck MPA. The association of electroconvulsive therapy to pharmacological treatment and its influence on cytokines. J Psychiatr Res. 2017 Sep;92:205-11. doi:10.1016/j.jpsychires.2017.05.004.
20. Yrondi A, Sporer M, Péran P, Schmitt L, Arbus C, Sauvaget A. Electroconvulsive therapy, depression, the immune system and inflammation: A systematic review. Brain Stimul. 2018;11:29-51. doi: 10.1016/j.brs.2017.10.013.
21. Bulut M, Altındağ A, Deveci Z, Kaya MC, Bülbül F, Taşkın A, et al. Oxidative parameters in bipolar patients treated with electroconvulsive therapy and pharmacotherapy. Journal of Mood Disorders. 2013;3:93-9.
22. Kargar M, Yoosefi A, Akhondzadeh S, Artonian V, Ashouri A, Ghaeli P. Effect of Adjunctive Celecoxib on BDNF in Manic Patients Undergoing Electroconvulsive Therapy: a Randomized Double Blind Controlled Trial. Pharmacopsychiatry. 2015;48:268-73. doi: 10.1055/s-0035-1559667.
23. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009;71(2):171-86. doi: 10.1097/PSY.0b013e3181907c1b.
24. Huang G, Chen H, Wang Q, Hong X, Hu P, Xiao M, et al. High platelet-to-lymphocyte ratio is associated with post-stroke depression. J Affect Disord. 2018;246:105-11. doi: 10.1016/j.jad.2018.12.012.
25. Himmerich H, Bartsch S, Hamer H, Mergl R, Schönherr J, Petersein C, et al. Modulation of cytokine production by drugs with antiepileptic or mood stabilizer properties in anti-CD3-and anti-Cd40-stimulated blood in vitro. Oxid Med Cell Longev. 2014;2014:806162
26. Boufidou F, Nikolaou C, Alevizos B, Liappas IA, Christodoulou GN. Cytokine production in bipolar affective disorder patients under lithium treatment. Journal of Affective Disorders. 2004;82(2):309-13.
27. Mørch RH, Dieset I, Færden A, Hope S, Aas M, Nerhus M, Aukrust P. Inflammatory evidence for the psychosis continuum model. Psychoneuroendocrinology. 2016;67:189-97.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine