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The evaluation of neutrophil-lymphocyte ratio in patients with first episode psychosis

İlk atak psikoz hastalarında nötrofil lenfosit oranının değerlendirilmesi

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ABSTRACT

Introduction: There is a growing consensus in the literature that inflammation may play a role in the pathophysiology of schizophrenia. The blood neutrophil-lymphocyte ratio is a simple, inexpensive and reliable marker of inflammation. The aim of this study is to assess the relationship between first episode psychosis (FEP) and neutrophil–lymphocyte ratio (NLR) and to investigate if there is a relation between NLR and severity of disease.

Methods: In this retrospective study we analyzed 58 FEP patients' medical records from January 2011 to June 2014 who had been treated at our hospital. Hematologic parameters, Brief Psychiatric Rating Scale (BPRS) scores and demographic data of the patients were obtained from the medical records of 58 FEP patients. Hematologic parameters and NLR values of 58 patients with FEP compared to values of 37 healthy control group. Correlation between NLR and BPRS scores were calculated.

Results: Mean NLR was significantly higher in patients compared to control group (2.22 ± 1.25 vs. 1.63 ± 0.38, p = 0.041). Neutrophil count was not different between patients and healthy control (4.03 ± 0.70 vs. 4.20 ± 1.48, p = 0.525), but lymphocyte count was significantly lower in patients (2.56 ± 0.55 vs. 2.19 ± 0.77, p = 0.013). In the FEP patients, NLR was not significantly correlate with severity of disease (BPRS score) (n = 58; r = 0.060, p = 0.655).

Conclusion: Our findings suggest that NLR levels are increased in physically healthy antipsychotic- naive first episode psychosis patients compared to physically and mentally healthy individuals.

Keywords*:* Brief psychiatric rating scale, first-episode psychosis, neutrophil-lymphocyte ratio, inflammation

ÖZET

Giriş: İnflamasyonun şizofreni patofizyolojisinde rol oynayabileceği ile ilgili literatürde giderek artan bir fikir birliği vardır. Kan nötrofil lenfosit oranı basit, ucuz ve inflamasyonun güvenilir bir göstergesidir. Bu çalışmanın amacı; ilk atak psikoz ile nötrofil lenfosit oranı arasındaki ilişkiyi incelemek ve eğer bir ilişki varsa bunun hastalık şiddeti ile ilişkisini araştırmaktır.

Yöntem: Bu retrospektif çalışmada Ocak 2011 ile Haziran 2014 tarihleri arasında hastanemizde tedavi edilmiş 58 ilk atak psikoz hastalarının hastane kayıtları analiz edildi. Hastane kayıtlarından hematolojik parametreler, Kısa Psikiyatrik Değerlendirme Ölçeği (KPDÖ) puanları ve demografik veriler elde edildi. İlk atak psikoz tanılı 58 hastanın hematolojik parametreleri ve nötrofil lenfosit oranları 37 kişilik sağlıklı kontrol grubunun değerleri ile karşılaştırıldı. KPDÖ puanları ile nötrofil lenfosit oranları arasındaki korelasyon değerlendirildi.

Bulgular: Ortalama nötrofil lenfosit oranı hastalarda kontrol grubuna göre anlamlı derecede yüksek çıktı (2,22 ± 1,25 vs. 1,63 ± 0,38, p = 0,041). Nötrofil sayısında hastalar ve sağlıklılar arasında fark yoktu (4,03 ± 0,70 vs. 4,20 ± 1,48, p = 0,525), ama lenfosit sayısı hastalarda anlamlı derecede düşüktü (2,56 ± 0,55 vs. 2,19 ± 0,77, p = 0,013). İlk atak psikozlarda nötrofil lenfosit oranı ile hastalık şiddeti (KPDÖ puanı) arasında anlamlı korelasyon yoktu (n = 58; r = 0,060, p = 0,655).

Sonuç: Çalışmamızda; fiziksel olarak sağlıklı, daha önce hiç antipsikotik kullanmamış ilk atak psikoz hastalarında nötrofil lenfosit oranı fiziksel ve ruhsal olarak sağlıklı katılımcılara göre yüksek çıkmıştır.

Anahtar kelimeler: Kısa psikiyatrik değerlendirme ölçeği, ilk atak psikoz, nötrofil lenfosit oranı, inflamasyon

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INTRODUCTION

Schizophrenia (SCZ) is a multi-factorial mental disorder affecting approximately 1% of the world population and is characterized by the presence of psychotic symptoms and cognitive, affective and psychosocial impairment. The exact underlying mechanism in the development of SCZ remains obscure (1). Numerous theories have been proposed regarding the cause of schizophrenia. Recent studies on pathophysiology of schizophrenia revealed impact of immunological and inflammatory mechanisms on disease predisposition, onset and progression (2). The neuropathological studies found associations between schizophrenia and both abnormal levels of inflammatory cytokines, and increased frequency of activated lymphocytes (3). In light of these considerations, treatment strategies based on immune mechanisms have been investigated in patients with schizophrenia in recent studies (1).

The neutrophil–lymphocyte ratio (NLR) is a simple, inexpensive and reliable method to evaluate the extent of stress and systemic inflammation (4). Elevated levels of NLR were associated with increased risk of death and the risk of recurrence in patients who undergo surgery for colorectal liver metastases (5) and increased NLR is also found to be related with poor survival in gastric cancer (6). Although NLR has been extensively studied in other clinical fields including; oncology, cardiovascular surgery and cardiology, there has been only a few studies published examining the relationship between NLR and neuropsychiatric diseases. Two previous studies have been investigated the relationship between NLR and cognitive functioning in carotid endarterectomy patients and Alzheimer's disease (7, 8). Furthermore the other two studies about psychiatric disorders and NLR compared schizophrenic patients and major depressive disorder patients with healthy control group. They have found significantly higher NLR compared with healthy control group; but no correlation between NLR and severity of disease (9, 10).

The aim of this study is to assess the relationship between first episode psychosis (FEP) and NLR and to investigate if there is a relation between NLR and severity of disease.

METHODS

The patients who were admitted to psychiatry inpatient clinic of our hospital between January 2011 and June 2014 with the diagnosis of psychotic disorder were enrolled into this study.

In this retrospective study we analyzed the medical records of 3258 patients with psychotic disorder. 277 of these patients were found to be antipsychotic-naive first episode psychosis according to medical report examinations. We considered as “antipsychotic-naive” those patients who had not taken antipsychotic medication before administration to hospital. Patients were excluded if they met the following criteria: alcohol or substance abuse, hypertension, diabetes mellitus, heart disease, hepatic or renal failure, clinical evidence of active infection, active or chronic inflammatory or autoimmune diseases and treatment with anti-inflammatory or immunosuppressive medication.

After the exclusion criteria applied to those, 219 FEP were excluded and 58 first episode psychosis patients were included. Parameters including neutrophil count, lymphocyte count, hemoglobin, hematocrit, white blood cell count, Brief Psychiatric Rating Scale (BPRS) scores and demographic data of the patients were obtained from the medical records of 58 FEP patients. NLR was found by dividing absolute neutrophil count to absolute lymphocyte count. NLR values of 58 patients with FEP calculated and compared to NLR of 37 healthy control group in similar age and gender distribution with the study group who had applied to family medicine for routine examination before marriage and had examined by a family doctor. In this study similar exclusion criteria were used for healthy control group. In addition, they had a mental health screening through a psychiatric interview for exclusion of any history of Axis-I diagnoses.

The study complied with the Declaration of Helsinki, and was approved by institutional ethics committee of Selçuk University.

Statistical analysis

The statistical analyses were performed using software (SPSS 21 SPSS Inc., Chicago, IL). In this study, two group comparisons for categorical variables were assessed using Pearson's chi-square test. Normally distributed variables were compared using the Independent T-Test, abnormally distributed variables were compared using Mann-Whitney U test. The correlation coefficients and their significance were calculated using the Pearson test. $P<0.05$ was considered as statistically significant.

RESULTS

There were no differences between first episode psychosis patients and healthy controls in age and gender.

Mean NLR was significantly higher in patients compared to control group (2.22 ± 1.25 vs. 1.63 ± 0.38, $p=0.041$). Neutrophil count was not different between patients and healthy control (4.03 ± 0.70 vs. 4.20 ± 1.48, $p=0.525$), but lymphocyte count was significantly lower in patients (2.56 ± 0.55 vs. 2.19 ± 0.77, $p=0.013$) (Table 1).

The NLR was significantly higher in female patients than female healthy controls (1.61 ± 0.36 vs 2.16 ± 0.90 $p=0.033$). However, there was no significant difference between male patients and male controls (1.65 ± 0.41 vs 2.28 ± 1.54 $p=0.437$) (Table 2).

Red blood cell count, percentage of hematocrit and hemoglobin were significantly higher in male patients than female patients. Platelet count was significantly higher in female patients than male patients, NLR and white blood cell count was similar between male and female patients (Table 3).

In the first episode psychosis patients, NLR was not significantly correlate with severity (BPRS score) ($n=58$; $r=0.060$, $p=0.655$).

Table 1. Demographic properties and laboratory parameters of the study population[¥], *%(n)*

	Patient (n=58)	Control (n=37)	
Age (years)	29.08 ± 9.24 (17-59)	28.40 ± 6.82 (19-49)	0.924
Gender			
Male	50.0 (29)	37.8 (14)	0.293
Female	50.0 (29)	62.2 (23)	
Hemoglobin (g/dl)	14.50 (9.50-17.30)	14.00 (11.60-17.80)	0.967
Hematocrit%	43.15 ± 4.45 (30.0-50.91)	43.17 ± 4.85 (36.50-53.40)	0.981
Red Blood Cell Count 10^6 /mL	4.93 ± 0.43 (3.84-5.70)	5.8 ± 0.49 (4.07-6.01)	0.128
White Blood Cell Count 10^3 /mL	7.02 (3.75-29.0)	7.24 (5.34-9.71)	0.421
Platelet Count 10^3 /mL	255.53 ± 65.06 (141-414)	254.72 ± 49.35 (170-375)	0.949
Neutrophil Count 10^3 /mL	4.20 ± 1.48 (1.63-8.02)	4.03 ± 0.70(2.91-5.49)	0.525
Lymphocyte Count 10^3 /mL	2.19 ± 0.77 (0.75-3.95)	2.56 ± 0.55 (1.56-4.10)	0.013*
NLR	2.02 (0.52-6.80)	1.55 (0.82-2.44)	0.041*

[¥] Data reported as mean ± SD (range, minimum to maximum), % (number of subjects) * Significant $p < 0.05$

Table 2. Comparison of NLR between patient and control group[¥], *%(n)*

	Patient (n=58)	Control (n=37)	
NLR median (range)			
Male	1.76 (0.52-6.80)	1.61 (0.98-2.44)	0.437
Female	2.04 (0.82-4.20)	1.52 (0.82-2.21)	0.033*

[¥] Data reported as median (range, minimum to maximum) * Significant $p < 0.05$

Table 3. Comparison of Male and Female with FEP[¥], *%(n)*

	Male (n=29)	Female (n=29)	
NLR	1.76(0.52-6.80)	2.04 (0.82-4.20)	0.635
BPRS score	37.2 ± 8.4	36.1 ± 8.0	0.612
Hemoglobin (g/dl)	15.70 (13.60-17.30)	13.40 (9.50-14.80)	0.0001*
Hematocrit %	46.07 ± 2.65 (40.10-50.91)	40.23 ± 3.94 (30.0-45.80)	0.0001*
Red Blood Cell Count 106 /mL	5.21 ± 0.28 (4.60-5.70)	4.65 ± 0.38 (3.84-5.29)	0.0001*
White Blood Cell Count 103 /mL	7.30 (3.75-11.27)	6.89 (3.85-29.0)	0.461
Platelet Count 103 /mL	223.55 ± 49.62 (141-359)	287.51 ± 63.53 (143-414)	0.0001*

[¥] Data reported as mean ± SD (range, minimum to maximum) and median) * Significant $p < 0.05$

DISCUSSION

A growing body of evidence indicates relations between inflammation and immune function and risk of schizophrenia. Over 40 cytokine alterations studies examining the changes in the IL-6 levels, soluble IL-2 receptor and TNF-alpha levels in schizophrenia suggests that an increase in first-episode psychosis patients and relapsed patients than healthy controls (11). Recent meta-analysis of the literature shows that increased blood levels of IL1β, IL6 and TNFα are consistently reported in patients at the onset of this disorder (12). Recent studies postulated that an imbalance between T-helper type 1 (Th1) and type 2 (Th2) cytokines has been implicated in schizophrenia. Chiang et al. have observed a clear Th2 shift in schizophrenia, but not in schizophrenia-related disorders in their study. They indicated that the Th2 shift in schizophrenia appeared to be an aberrant developmental phenomenon (13). It is necessary to clarify the role of immune alterations and inflammatory mechanisms observed in schizophrenia that could eventually allow researchers to engage the new treatment strategies in field.

NLR is a simple, noninvasive marker of systemic inflammation. It has been studied in various diseases including malignancies (14-16), coroner hearth diseases (17, 18) and

inflammatory diseases (19) and reported that elevated NLR is an independent useful prognostic parameter. Papa et al. mentioned that high NLR was associated with cardiac mortality. The study held by Chen et al. demonstrated that elevated NLR significantly increases the risk of tumor recurrence and death and indicated that NLR is a novel independent predictor for prognosis after hepatic resection in patients with ICC. In the present study we found that NLR was higher in physically healthy FEP patients compared to healthy controls. However, there was no relationship between NLR and disease severity.

Semiz et al. have evaluated NLR in 156 schizophrenic patients, and have found that NLR was higher in patients compared to healthy controls. They have also observed insignificant correlation between elevated NLR levels and psychopathology severity, these results are in line with our findings (9). Halazun et al. have found that higher NLR is associated with a threefold increased risk of cognitive dysfunction 1 day after carotid endarterectomy; they have mentioned that systemic inflammation increases atherosclerosis and neuronal injury (8). In line with this result; Kuyumcu et al. (2012) have evaluated NLR in 241 patients with Alzheimer's disease and found that NLR was significantly higher than normal cognitive function group (7). As the previous studies suggest, neurodegeneration may play a role in the pathophysiology of schizophrenia (20-22), elevated NLR levels may indicate a neurodegenerative process.

The study has several limitations. This was a single-center study with retrospectively collected data. As a result, we could not reach all of the data from the records of patients like BMI that may affect blood cell levels, and we could not compare NLR levels after antipsychotic treatment. Also we excluded some comorbid conditions that may increase NLR levels; there may be some other confounders that we could not measure. Lastly, we could not evaluate the data of other inflammatory and immune markers (i.e., C- reactive protein, sedimentation, and cytokines) to verify if NLR is an independent marker in the pathogenesis of schizophrenia.

CONCLUSION

To the best of our knowledge it is the first study investigating NLR levels in FEP. Our findings suggest that NLR levels are increased in drug naive first episode psychosis patients compared to physically and mentally healthy individuals and inflammation may plays a role in the pathogenesis of schizophrenia. Further larger prospective trials are necessary to determine relationship between NLR and schizophrenia and the effect of drugs on NLR.

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