

Critical analysis of blood parameters in epilepsy patients

Epilepsy and inflammation

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Abstract

Aim: In this study, it was purposed to assign the neutrophil, lymphocyte, and platelet counts, in concur with neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) levels in patients with epilepsy.

Material and Methods: The retrospective study was carried out at the Neurology Department of Ordu Medicalpark Hospital. Data were obtained from the medical records of the patients in the neurology clinic between January 2018 and April 2019. According to ILAE 2017 epilepsy classification criteria, 113 patients were included in the study. Furthermore, 57 healthy individuals received for a check-up were included in the study as the control group. Venous blood samples obtained from the patient and control groups were performed.

Results: Compared to the control group, WBC, Platelet, neutrophil, and lymphocyte levels were statistically significantly higher in the patient group ($p=0.019$, $p=0.008$, $p=0.012$, $p=0.024$, respectively). Hematocrit levels were statistically significantly lower in the patient group compared to the control group ($p=0.022$). Compared to the control group, NLR and PLR levels were statistically significantly higher in the patient group ($p=0.016$, $p=0.010$, respectively). The risk factors found to be significantly associated with epilepsy in the regression analysis included WBC, lymphocyte, NLR, and PLR.

Discussion: WBC, platelet, neutrophil, lymphocyte NLR, and PLR levels significantly increased in patients with epilepsy. In addition, the risk factors found to be significantly associated with epilepsy in the regression analysis included WBC, lymphocyte, NLR, and PLR. Broader prospective studies are needed to show the mechanisms between epilepsy and these new inflammatory parameters.

Keywords

Epilepsy; Prognostic Factor; Neutrophil-Lymphocyte Ratio; Lymphocyte; Platelet-Lymphocyte Ratio

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Introduction

Epilepsy is one of the most common neurological disorders, affecting up to 1% of the World population. Despite advanced medical and surgical treatments, almost 30% of epileptic patients are still refractory to treatment. The most common focal form is temporal lobe epilepsy; however, focal cortical dysplasia (FCD) and neuro-glial tumors unrecognized on preoperative magnetic resonance imaging (MRI) are increasingly encountered [1]. The main purpose of several experimental and/or clinical studies for many years has been to determine the most important or common causes of epileptogenesis and what can be done to prevent it [2]. It is believed that epilepsy often develops as a result of an initial brain injury, or a precipitating event such as febrile seizure, infection or trauma, inducing inflammatory reactions, and angiogenesis [3]. It is clear that current treatment modalities are mainly symptomatic and/or ineffective in preventing the molecular processes behind epileptogenesis, and finally, chronic epilepsy develops. Understanding the molecular events inducing epileptogenesis or forming complex epileptic networks may lead to treatments to prevent progression of this chronic and devastating neurological condition, often associated with significant morbidity and sometimes mortality and impairing quality of life.

Animal models showed that inflammation may be a contributing factor in the onset and progression of epilepsy, and infiltration of inflammatory cells has been detected in epileptic tissues [4]. However, there is still no consensus as to whether inflammation is a cause or a consequence. Leukocyte or lymphocyte and monocyte infiltration of the hippocampus and temporal cortex was demonstrated in an animal model of epilepsy and in human tissues resected from the temporal lobe [4]. More importantly, increased expression and elevated levels of cytokines and chemokines in both peripheral blood and cerebrospinal fluid of patients with epilepsy suggested that local and systemic inflammatory processes may be involved in epileptogenesis [5, 6]. Recent literature regarding control of seizure in patients with epilepsy suggests that effective anti-inflammatory drugs together associated with traditional anti-epileptic drugs (AED) might be more effective in controlling seizure and preventing disease progression than AEDs alone [7].

Recently, there have been several clinical studies demonstrating that neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can be used as inflammatory markers predicting disease progression [8]. Several studies have shown that higher NLR and PLR correlate positively with disease progression in inflammatory brain disease and indicate poor prognosis or shorter survival in many cancers, including brain glioma and brain metastasis [9-11]. These peripheral inflammatory parameters can be obtained from routine complete blood count (CBC), which is very inexpensive and easily performed.

In the present study, it was purposed to assign the neutrophil, lymphocyte and platelet counts, in concur with neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) levels in patients with epilepsy.

Material and Methods

The study protocol was reviewed and approved by the Ethics Committee of Ordu University with the approval number 2019/74. According to ILAE 2017 epilepsy classification criteria, 113 patients were included in the study. Furthermore, 57 healthy individuals received for a check-up were included in the study as the control group. Venous blood samples obtained from the patient and control groups were performed. Informed consent was not taken from patients since this study was a retrospective chart analysis.

The retrospective study was carried out at the department of neurology in Ordu Medikalpark Hospital. Data were obtained from the medical records of the patients in the neurology clinic between January 2018 and April 2019. Patients with missing clinical or laboratory data, those with endocarditis, severe tissue damage, poisoning, heart failure, hyperglycemia, arterial hypertension, systemic and neurological malignancy, acute trauma, vascular diseases, thyroid diseases, systemic and central nervous system arterial diseases, liver and kidney diseases, and blood disease (that is affecting neutrophils and lymphocytes) were excluded from the study. Finally, according to ILAE epilepsy classification criteria, 113 patients were included in the study [12]. Furthermore, 57 healthy individuals received for a check-up were included in the study as the control group. Venous blood samples taken from the patient and control groups were performed. Biochemical analyses were done in the laboratory of Ordu Medikalpark hospital. Tests of venous blood samples obtained from the control and patient groups were done using centrifugation followed by the use of an auto analyzer. NLR was measured by dividing the neutrophil count to the lymphocyte count and PLR was measured by dividing the thrombocyte count to the lymphocyte count.

Statistical analysis

The normality control of the data was done with the Shapiro-Wilk test. The Student's t-test was used for comparing the means of normally distributed parameters, and the Mann-Whitney U test was used for the comparison of parameters that did not conform to normal distribution. In multiple comparisons, the Kruskal-Wallis variance analysis was used. Descriptive statistics were expressed with Odds ratio and 95% confidence intervals. Multivariate analyses used the Cox proportional hazards model, with factors before treatment including WBC, lymphocyte, NLR, and PLR. $P < 0.05$ was considered statistically significant.

Results

A comparison of laboratory and socio-demographic findings between the groups of the patients and controls is shown in Table 1. The average age of the patients was $51,61 \pm 21,3$ years. In the control group, the mean age was $52,86 \pm 21,10$ years. There was no statistically significant difference between the groups in terms of age and gender ($p > 0.05$). Compared to the control group, WBC, Platelet, neutrophil, and lymphocyte levels were statistically significantly higher in the patient group ($p = 0.019$, $p = 0.008$, $p = 0.012$, $p = 0.024$, respectively). Hematocrit levels were statistically significantly lower in the patient group compared to the control group ($p = 0.022$). Compared

Table 1. Comparison of laboratory and socio-demographic findings

	Patient (n=113)	Control (n=57)	P- value
Age (years)	51,61±21,3	52,86±21,10	0,745*
Gender (n, %)			
male	55 (48.7%)	32 (56.1%)	
female	58 (51.3%)	25 (43.9%)	0,359*
WBC (/mm ³)	8,03 (4,3-20,3)	6,85 (4,5-18,7)	0,019*
RBC (μL)	4,52±0,7	4,67±0,5	0,142**
Hemoglobin (g/dl)	13,03±2,1	13,60±1,7	0,063**
Hematocrit (%)	39,20 (20,6-47,9)	41,10 (31,8-52,2)	0,022*
MCV (fL)	87,30 (51,9-114,4)	87,58 (79,7-98,6)	0,273*
MCH (pg)	28,9±3,1	29,12±1,6	0,604**
MCHC (g/dl)	33,60 (30,7-36,7)	33,24 (30,7-36,2)	0,080*
RDW (%)	14,26±2,0	13,82±1,2	0,090**
Platelet (/mm ³)	223,62±69,9	258,32±66,9	0,008**
MPV (fL)	9,70 (8,4-11,8)	9,60 (8,7-12,1)	0,987*
Neutrophil (/mm ³)	4,60 (1,7-18,5)	3,86 (1,5-16,7)	0,012*
Lymphocyte (/mm ³)	3,10 (0,8-7,2)	2,05 (0,7-6,1)	0,024*
NLR	3,26 (0,1-14,5)	1,77 (0,5-23,0)	0,016*
PLR	150,10 (41,7-474,7)	114,45 (46,9-554,7)	0,010*

*: Mann-Whitney U test; **: Student t-test; WBC: White blood cell; RBC: Red blood cell; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; RDW: Red cell distribution width; MPV: Mean platelet volume; NLR: neutrophil-lymphocyte ratio; PLR: Platelet- lymphocyte ratio.

Table 2. Binary logistic regression analysis of factors used for differentiating epilepsy from control

	OR (95% CI)	P- value
WBC (/mm ³)	1.050 (0.776-1.422)	0.021
Lymphocyte (/mm ³)	0.568 (0.369-0.873)	0.010
NLR	1.239 (1.007-1.525)	0.043
PLR	1.007 (1.001-1.013)	0.028

WBC: White blood cell; NLR: neutrophil-lymphocyte ratio; PLR: Platelet- lymphocyte ratio

to the control group, NLR, and PLR levels were statistically significantly higher in the patient group ($p=0.016$, $p=0.010$, respectively). There wasn't any statistical significance between the groups in terms of other parameters (Table 1).

Binary logistic regression analysis of factors used for epilepsy was shown in Table 2. The risk factors found to be significantly associated with epilepsy in the regression analysis included WBC, lymphocyte, NLR and PLR. Binary logistic regression analysis showed that 1 unit rise in WBC resulted in 1.05 folds rise in the risk of epileptic seizure, 1 unit rise in lymphocyte resulted in 0.56 folds rise in risk of epileptic seizure, 1 unit rise in NLR resulted in 1.23 folds rise in the risk of epileptic seizure and 1 unit rise in PLR resulted in 1.00 folds increase in the rise of epileptic seizure (Table 2).

Discussion

In our study, there was a statistically significant relationship between patient with epilepsy and WBC, hematocrit, platelet, neutrophil, and lymphocyte levels. However, compared to the healthy control group, NLR, and PLR levels significantly increased in patients with epilepsy. In addition, the risk factors found to be significantly associated with epilepsy in the regression analysis included WBC, lymphocyte, NLR, and PLR. In the literature, PLR and NLR have been highlighted and accepted as new inflammatory indicators which were found to play an important role in the prognosis of various activities [13, 14]. Although the WBC, neutrophil, lymphocyte, PLR, and NLR values were significantly high, the hematocrit count was low in the epileptic seizure patients in our study. Furthermore, we showed that each 1-unit rise in NLR raised the epileptic seizure risk by 1.23.

Previous researches have reported that systemic inflammation plays an important role in the pathophysiology of epileptic seizures [15-17]. Neutrophils are the most common leukocytes in the body and play a significant role in natural immunity [18]. As showed in our study, the neutrophil count significantly raised during systemic inflammation in epilepsy. In patients with epileptic seizures, it is believed that interleukin-1 beta (IL-1 β) raises in serum due to systemic inflammation and causes impaired blood-brain barrier; this disruption also contributes to the onset of neuronal hyperexcitability and epileptic seizures [19, 20]. During the epileptic seizure, the higher neutrophil count and NLR values significantly observed in our study showed that the epileptic seizure is associated with the neutrophil-mediated systemic inflammation. However, Özdemir et al. (2017) showed that status epilepticus was related to the neutrophil-mediated inflammation [21].

It has been well established that epilepsy is closely correlated with chronic inflammation, and the recent literature shows that PLR may be used as inflammation indices in several inflammatory disorders, including brain glioma [9, 22]. Retrospective studies reported that PLR elevation can be used for detecting, staging and monitoring solid cancers, such as colorectal or lung tumors [23, 24]. A few retrospective studies showed that high PLR predicts glioma recurrence and that levels correlate with glioma staging [9, 22]. High PLR can also be used as an index for differentiating between glioblastoma and brain metastasis [9]. In our study, compared with the healthy control group, PLR levels significantly increased in patients with epilepsy. Furthermore, we showed that each 1-unit raise in PLR raised the epileptic seizure risk by 1.00.

The most important limitation in this prospective study was the small number of patients with epilepsy. However, given that the current literature does have limited prospective studies evaluating preoperative systemic inflammatory markers in patients with epilepsy, this limitation simply means that our study should be considered preliminary. We suggest that larger epilepsy cohorts with long-term follow-up should be studied, to provide more comprehensive results and more information about inflammation in epilepsy.

In conclusion, we showed that WBC, platelet, neutrophil, lymphocyte, NLR, and PLR levels significantly increased in patients with epilepsy. In addition, the risk factors found to be significantly associated with epilepsy in the regression analysis included WBC, lymphocyte, NLR, and PLR. However, broader prospective studies are needed to show the pathophysiologic mechanisms between epileptic seizures and these new inflammatory parameters.

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

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