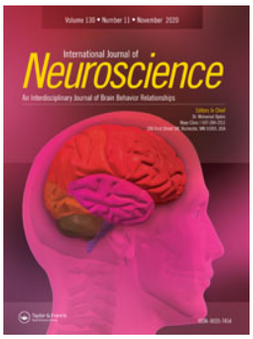

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ORIGINAL ARTICLE

Relationship between generalized epileptic seizure and neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and neutrophil mediated inflammation

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ABSTRACT

Aim: There is a close relationship between systemic inflammation and epileptic seizure. Recently, neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) have been defined as significant inflammation biomarkers. In the present study, it was aimed to determine levels of NLR, PLR, and mean platelet volume (MPV) during generalized tonic clonic epileptic seizures, and to investigate their relationships with epileptic seizures.

Methods: The present study was conducted on 72 patients with epilepsy who applied with primary and secondary generalized tonic clonic epileptic seizures according to classification of the International League Against Epilepsy (ILAE), and 72 healthy individuals as the control group. Neutrophil and lymphocyte counts, NLR, PLR, and MPV values of patients were evaluated both in acute (in the first hour of epileptic seizure) and subacute (in hour 72 of epileptic seizure) phases by biochemical analysis.

Results: Statistically significant differences were determined in laboratory values of white blood cell (WBC) ($p < 0.001$), neutrophil ($p < 0.001$), lymphocyte ($p < 0.001$), NLR ($p < 0.001$), MPV ($p < 0.05$), platelet ($p < 0.001$), C-reactive protein (CRP) ($p < 0.05$) in acute phase; and in lymphocyte ($p < 0.05$), NLR ($p < 0.05$), platelet ($p < 0.001$), and CRP ($p < 0.001$) in subacute phase between patients and healthy controls. Statistically significant differences were determined in laboratory values of WBC ($p < 0.001$), neutrophil ($p < 0.001$), lymphocyte ($p < 0.05$), NLR ($p < 0.001$), CRP ($p < 0.001$), and PLR ($p < 0.05$) in patient group between acute and subacute phases. In patient group, mean lymphocyte count was determined lower in acute phase than subacute phase ($p < 0.05$).

Conclusion: The most striking finding of the present study is determination of 1 unit increase in NLR results in 1.95 folds increase in epileptic seizure risk in binary logistic regression analysis. Additionally, it indicates that epileptic seizure is correlated with NLR, PLR, and neutrophil mediated inflammation. To the best of authors knowledge, this is the first report indicating that there is a relationship between epileptic seizure and PLR, neutrophil mediated inflammation, and that 1 unit increase in NLR increases epileptic seizure risk by 1.95 folds.

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Systemic inflammation; epileptic seizure; neutrophil/lymphocyte ratio; generalized epilepsy; platelet/lymphocyte ratio

Introduction

Epileptic seizures demonstrated to develop due to neuronal damage, and related cognitive disorders [1] are defined as a paroxysmal disorder caused by excessive electrical activity of central nervous system (CNS) neurons [2,3]. It was indicated that there is a significant relationship between epileptic seizure and systemic inflammation [4–6]. It was demonstrated that systemic inflammation may trigger epileptic activity by deteriorating function of blood brain barrier [7]. It was also reported that seizure activity was decreased by 50% in subjects who received anti-inflammatory drugs such as dexamethasone [7,8]. Under the light of these studies, it was decided that systemic inflammation increased epileptic seizures significantly. Although it is known that increase in blood neutrophil count is an important parameter of systemic inflammation [9–11], recently neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) have been defined as new inflammation parameters [12–16]. These new inflammation parameters have been defined to play a role in activities and prognosis of various diseases [12–16]. There are a few studies about relationship between epileptic seizures and NLR. In one of them,

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relationship between NLR and status epilepticus [17] was reported, whereas in the other relationship between febrile seizure [18] and NLR was reported. Nevertheless, there is no study investigating relationship between PLR and epileptic seizure.

In the present study, it was aimed to determine neutrophil, lymphocyte, and thrombocyte counts as well as NLR, PLR, and mean platelet volume (MPV) levels for the first time during generalized tonic clonic epileptic seizures in patients with epilepsy, and to investigate their relationships with epileptic seizures.

Materials and methods

The retrospective study was conducted in the Neurology Department of Aksaray University Research and Training Hospital. Data of the present study were acquired from the medical records of the patients treated in the neurology clinic between March 2014 and March 2018. The databank of our hospital includes information regarding the epilepsy type, structural or underlying factors, such as infections, and demographic data of the patients. Systemic and neurological examinations are routinely performed on admission in our hospital. Cranial magnetic resonance imaging, complete blood examination, C-reactive protein (CRP) level, liver, and kidney function tests, blood glucose level, electrolyte levels, lipid values, and electroencephalography (EEG) are performed on the first day for all patients with epilepsy admitted to the neurology clinic in our hospital. Moreover, hemogram, biochemistry, and CRP tests are conducted daily for all patients admitted to our hospital. Patients with missing clinical or laboratory data; those with severe tissue damage, endocarditis, myocardial infarcts, poisoning, myocarditis, heart failure, hypoglycemia, hyperglycemia, neurological and systemic malignity, arterial hypertension, systemic and central nervous system vasculitis, acute trauma, and blood disease (such as leukemia affecting neutrophils and lymphocytes); those using medication that affects the neutrophils and lymphocytes; those with ischemic vascular diseases, aneurysm, and arterial dissection; those with hypothyroid, hyperthyroid, liver, and kidney diseases; those with electrolyte disorder (such as hypocalcemia, hyperkalemia, hyponatremia, hypernatremia); and those with systemic and central nervous system infections were excluded from the study. Finally, from the 217 patients identified, 72 patients with generalized tonic–clonic epileptic seizures according to ILAE 2017 classification criteria [19,20] and meeting the participation criteria were included in the study. Patients who had laboratory data during an epileptic seizure (acute) and 72 h after the epileptic seizure (subacute) were included in the study. Furthermore, 72 individuals who were randomly selected from the previous records of healthy individuals admitted for a check-up were included in the study as the control group. Because no subacute period exists for the control group, single laboratory data were included in the study. Biochemical analyses for the patients were performed in the Hematology Laboratory of Aksaray University, Aksaray Research and Training Hospital. Blood examination of the venous blood samples obtained from the patient and control groups were performed using centrifugation followed by the use of an autoanalyzer (Sysmex XN-1000 hematology analyzer, Kobe, Japan) at our hematology center. NLR was calculated by dividing the neutrophil count to the lymphocyte count, whereas PLR was calculated by dividing the platelet count to the lymphocyte count.

Statistical analysis

Analysis was performed by using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) Program. Descriptive statistics were used to describe continuous variables (mean, standard deviation, minimum, median, maximum). Visual and analytic methods (Kolmogorov-Smirnov test) were used to determine whether variables were normally distributed. Comparisons of acute and subacute continuous independent and abnormally distributed variables were performed by using Mann Whitney U test. Comparisons of related variables which were dependent and abnormally distributed were performed by using Wilcoxon test. Binary logistic regression test was performed for evaluation of correlations. Results were presented as odds ratios (ORs) and 95% Confidence Interval (CI). Statistical significance level was determined at $p < 0.05$.

Results

Seventy-two patients present in our database fulfilled inclusion criteria. The mean age of included patients was 47.4 ± 20.5 years, and the mean age of healthy control group was 49.2 ± 15.6 years. Of 72 patients, 35 (48.6%) were males, and 37 (51.4%) were females. Of 72 controls, 36 (50.0%) were males, and 36 (50.0%) were females. Age and gender were similar between the groups. Demographic characteristics of healthy control and patient groups are shown in Table 1.

Statistically significant differences were determined in laboratory values of white blood cell (WBC) ($p < 0.001$), neutrophil ($p < 0.001$), lymphocyte ($p < 0.001$), NLR ($p < 0.001$), MPV ($p < 0.05$), platelet ($p < 0.001$), C-reactive protein (CRP) ($p < 0.05$) in acute phase; and in lymphocyte ($p < 0.05$), NLR ($p < 0.05$), platelet ($p < 0.001$), and CRP ($p < 0.001$) in subacute phase between patients and healthy controls. Statistically significant differences were determined in laboratory values of WBC ($p < 0.001$), neutrophil ($p < 0.001$), lymphocyte ($p < 0.05$), NLR ($p < 0.001$), CRP ($p < 0.001$), and PLR ($p < 0.05$) in patient group between acute and subacute phases. Being more prominent in acute phase, mean lymphocyte counts were determined significantly lower in both acute and subacute phases ($p < 0.05$). Laboratory characteristics of patient and control groups are summarized in Table 2.

As it is summarized in Table 3, there were statistically significant differences in laboratory values of patient group in WBC ($p < 0.001$), neutrophil ($p < 0.001$), lymphocyte ($p < 0.05$), NLR ($p < 0.001$), CRP ($p < 0.001$), and PLR ($p < 0.05$) between acute and subacute phases. The mean lymphocyte count of patient group in acute phase was determined lower than that of in the subacute phase ($p < 0.05$).

During laboratory measurements in acute phase, binary logistic regression analysis indicated that 1 unit increase in WBC resulted in 1.33 folds increase in risk of epileptic seizure, and 1 unit increase in NLR resulted in 1.95 folds increase in risk of epileptic seizure (Table 4).

Table 1. Demographic characteristics of patient and healthy control groups.

		Patient Mean±SD Med. (Min.–Max.)	Control Mean±SD Med. (Min.–Max.)	Total Mean±SD Med. (Min.–Max.)
Age		47.4 ± 20.5 42.5 (17–86)	49.2 ± 15.6 50 (19–87)	48.3 ± 18.2 47.5 (17–87)
		N (%)	N (%)	N (%)
Gender	Male	35 (48.6)	36 (50.0)	71 (49.3)
	Female	37 (51.4)	36 (50.0)	73 (50.7)

Discussion

In recent years, NLR and PLR, which were found to play a key role in the activity and prognosis of various diseases [13–15], have been emphasized and accepted as new inflammatory indicators. Although the WBC,

Table 2. Comparison of laboratory results of patient and healthy control groups.

		Patient Mean±SD Med. (Min.–Max.)	Control Mean±SD Med. (Min.–Max.)	*p*
Acute	WBC (10^9/L)	9.03 ± 3.09 8.45(4.57–20.75)	7.23 ± 2.01 7.25(3.85–12.09)	**<0.001**
	Neutrophils (10^9/L)	6.41 ± 2.98 5.76(2.16–19.25)	4.05 ± 1.51 3.74(1.67–8.42)	**<0.001**
	Lymphocytes (10^9/L)	1.95 ± 0.86 1.92(0.45–4.37)	2.45 ± 0.81 2.4(0.8–5.77)	**<0.001**
	NLR	4.46 ± 4.02 3.2(1.02–21.68)	1.81 ± 0.97 1.61(0.5–6.53)	**<0.001**
	MPV (fL)	10.09 ± 1.29 9.9(7.2–13.9)	10.44 ± 0.71 10.45(8.9–12)	**0.008**
	Platelets (10^9/L)	226.04 ± 90.12 200(110–617)	255.89 ± 62.12 248(133–418)	**<0.001**
	CRP (mg/L)	6.34 ± 7.06 4.26(0.12–38)	3.87 ± 5.19 2.3(0.05–22.4)	**0.005**
	PLR	144.05 ± 97.96 105.47(42.79–540)	114 ± 47.34 106.1(61.4–324)	0.284
Subacute	WBC (10^9/L)	7.57 ± 2.28 7.34(3.66–14.53)	7.23 ± 2.01 7.25(3.85–12.09)	0.516
	Neutrophils (10^9/L)	4.64 ± 1.92 4.46(1.78–10.97)	4.05 ± 1.51 3.74(1.67–8.42)	0.095
	Lymphocytes(10^9/L)	2.2 ± 0.9 2.06(0.84–6.3)	2.45 ± 0.81 2.4(0.8–5.77)	**0.016**
	NLR	2.4 ± 1.34 2.18(0.72–7.97)	1.81 ± 0.97 1.61(0.5–6.53)	**0.003**
	MPV (fL)	10.2 ± 1.33 10.06(7.5–16.3)	10.44 ± 0.71 10.45(8.9–12)	0.067
	Platelets (10^9/L)	220.65 ± 106.77 205.5(32–775)	255.89 ± 62.12 248(133–418)	**<0.001**
	CRP (mg/L)	10.6 ± 11.35 7.12(0–51)	3.87 ± 5.19 2.3(0.05–22.4)	**<0.001**
	PLR	109.27 ± 53.72 101.82(17.11–283.87)	114 ± 47.34 106.1(61.4–324)	0.573

Bold values represents level of significance at $p < 0.05$. WBC = white blood cell, NLR = neutrophil/lymphocyte ratio, MPV = mean platelet volume, CRP = c-reactive protein, PLR: platelet/lymphocyte ratio.

Table 3. Comparison of laboratory measurements of patients between acute and subacute phases.

	Acute Mean±SD Med. (Min.–Max.)	Subacute Mean±SD Med. (Min.–Max.)	*p*
WBC (10^9/L)	9.03 ± 3.09 8.45(4.57–20.75)	7.57 ± 2.28 7.34(3.66–14.53)	**<0.001**
Neutrophils (10^9/L)	6.41 ± 2.98 5.76(2.16–19.25)	4.64 ± 1.92 4.46(1.78–10.97)	**<0.001**
Lymphocytes (10^9/L)	1.95 ± 0.86 1.92(0.45–4.37)	2.2 ± 0.9 2.06(0.84–6.3)	**0.005**
NLR	4.46 ± 4.02 3.2(1.02–21.68)	2.4 ± 1.34 2.18(0.72–7.97)	**<0.001**
MPV (fL)	10.09 ± 1.29 9.9(7.2–13.9)	10.2 ± 1.33 10.06(7.5–16.3)	0.062
Platelets (10^9/L)	226.04 ± 90.12 200(110–617)	220.65 ± 106.77 205.5(32–775)	0.328
CRP (mg/L)	6.34 ± 7.06 4.26(0.12–38)	10.6 ± 11.35 7.12(0–51)	**<0.001**
PLR	144.05 ± 97.96 105.47(42.79–540)	109.27 ± 53.72 101.82(17.11–283.87)	**0.001**

Bold values represents level of significance at $p < 0.05$. WBC = white blood cell, NLR = neutrophil/lymphocyte ratio, MPV = mean platelet volume, CRP = C-reactive protein, PLR: platelet/lymphocyte ratio.

Table 4. Binary logistic regression analysis (patients vs. control).

		p	OR	95% CI Lower	95% CI Upper
Acute	WBC	**0.019**	1.333	1.049	1.695
	NLR	**0.001**	1.954	1.335	2.859
	Platelets	**0.010**	0.992	0.987	0.998
	Constant	**0.016**	0.122		
Subacute	NLR	**0.003**	1.731	1.206	2.483
	Platelets	**0.011**	0.994	0.990	0.999
	Constant	0.672	1.308		

Note: Group (Patient vs. Control) variable was assumed as dependent variable in the model. Bold values represents level of significance at $p < 0.05$. OR: odds ratio, CI: confidence interval. WBC = white blood cell, NLR = neutrophil/lymphocyte ratio.

neutrophil, NLR, and PLR values were significantly high, the lymphocyte count was low during the acute phase of the generalized tonic–clonic epileptic seizure—this is the main finding of the present study. Moreover, we detected that each 1-unit increase in NLR increased the epileptic seizure risk by 1.95 fold. To the best of our knowledge, this is the first study that demonstrates the relationship between generalized tonic–clonic epileptic seizure and NLR and PLR.

Previous studies have shown that systemic inflammation plays a significant role in the physiopathology of epileptic seizures [2,6–8]. Neutrophils are the most common leucocytes in humans, and they play a fundamental role in natural immunity [10]. As detected in our study, the neutrophil count significantly increased during systemic inflammation. It is considered that in patients going through an epileptic seizure, the interleukin-1 beta (IL-1β) increases in serum owing to systemic inflammation and causes the disruption of blood–brain barrier [7,21]; this disruption further contributes to the neuronal hyperexcitability and epileptic seizure onset [4,5,21]. The significantly higher neutrophil count and NLR values observed during the acute phase than in the subacute phase in our study suggests that the epileptic seizure is associated with the neutrophil-mediated systemic inflammation. Similarly, Özdemir *et al.* (2017) have observed that status epilepticus was associated with the neutrophil-mediated inflammation [17].

Although several recent studies have detected that NLR is effective in the activity and prognosis of diseases, such as ischemic stroke [15,22], spontaneous intracerebral hemorrhage [14,23,24], myasthenia gravis [12], Guillain–Barre syndrome [13,25], diabetic polyneuropathy [26], traumatic brain injury [27], and various systemic malignancies [28–30], its relationship with generalized tonic–clonic seizure remains unknown. In the present study, we detected a strong association between NLR and epileptic seizures. Our NLR results were consistent with those of other studies on status epilepticus and complex febrile seizures. For instance, in their study on patients with status epilepticus, Özdemir *et al.* (2017) have observed that average NLR values were significantly higher in the acute phase of these patients. Similarly, Yiğit *et al.* (2017), in their study examining the relationship between febrile seizures and NLR, have detected a significant increase in the NLR levels in complex febrile seizures compared with that in simple febrile seizures. NLR has been considered a cheap and effective biomarker for acute epileptic seizures that can be easily calculated by dividing the peripheral blood neutrophil count to the lymphocyte count.

The present study found that WBC, neutrophil, NLR, and PLR levels were higher, and CRP and lymphocyte levels were lower during the acute phase of the epileptic seizure than those during the subacute phase. Similar results, excluding PLR and CRP, were detected on comparing the acute phase of patients with epileptic seizure and the control group. No significant difference was observed on comparing the PLR level in the acute phase of the epileptic seizure to that in the control group. It is attributed to the platelet levels of the patients with epileptic seizure being lower than that the control group and to the unchanged platelet levels of the patients in the acute and subacute phases of epileptic seizure. On comparing the CRP levels of the patients with epileptic seizure with those of the control group, it was found that patients with epileptic seizure had higher levels both in the acute and subacute phases, and it was evidently higher during the subacute phase. This could be attributed to the

delayed increase of the acute phase protein CRP [6] in the blood.

Although MPV is related to the activity of certain diseases, such as Behçet's disease [31] and ankylosing spondylarthrosis [32], no relationship was detected between MPV and epileptic seizures in our study. Therefore, it was inferred that MPV was not considerably associated with generalized tonic–clonic epileptic seizures, unlike its association with other diseases.

In conclusion, the present study detected that epileptic seizures were related to NLR, PLR, and neutrophil-mediated inflammation and that 1-unit increase in NLR increased the risk of epileptic seizure by 1.95 fold. However, further prospective studies with a larger scope to demonstrate the mechanisms between epileptic seizures and these new inflammatory parameters are warranted.

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