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Original Article

Investigating neutrophil-to-eosinophil ratio and variations in eosinophil levels in epilepsy patients with generalized tonic-clonic seizures

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Abstract

Aim: Neutrophil-to-eosinophil ratio (NER) shows inflammation, which can play a role in the development of some epilepsies and ictogenesis. The current study aimed to investigate the NER and the variations in neutrophil and eosinophil levels in epilepsy patients with generalized tonic-clonic seizures.

Material and Methods: Epilepsy patients with generalized tonic-clonic seizures were retrospectively evaluated in the present study. Laboratory parameters of the patients in the acute (within 6 hours after the seizure) and subacute (on day 5 after the seizure) phases were compared.

Results: 60 patients (30 males and 30 females) who had generalized tonic-clonic epileptic seizures were included in the study. The median neutrophil count and NER were significantly higher in the acute phase than in the subacute phase ($p<0.001$). The median C-reactive protein and eosinophil values and the mean lymphocyte count were significantly lower in the acute phase than in the subacute phase ($p<0.001$).

Conclusions: NER can be used as a new potential biomarker of systemic inflammation that triggers seizures in generalized tonic-clonic epileptic seizures. Further studies are needed for the role of NER in epilepsy and epileptic seizures.

Keywords: Eosinopenia; epilepsy; generalized tonic-clonic seizure; neutrophil-to-eosinophil ratio; neutrophilia

INTRODUCTION

Epilepsy is a paroxysmal disorder caused by excessive electrical activity of the neurons in the central nervous system (1). Epileptic seizures may lead to neuronal damage (2), poor social and psychological outcomes (3), injuries (4) and even death (5). Such negative outcomes of epilepsy are frequently observed in patients with generalized tonic-clonic epileptic seizures (4). Therefore, it is very important to know the seizure-precipitating factors in patients with epilepsy in order to improve the quality of life of patients, minimize potential negative outcomes and to assist the physician in treatment selection. There are many triggers for epileptic seizures such as fever, emotional stress, quitting the treatment, sleep deprivation and tiredness (6,7). In addition, systemic inflammation and variations in hematological parameters may also play a role in the development of epileptic seizures and ictogenesis. However, the neutrophil-to-eosinophil ratio (NER) and variations in eosinophil count, which indicate systemic inflammation, have never been studied in patients who experience epileptic seizures. Therefore, this retrospective study was conducted to compare the NER and neutrophil and eosinophil levels in the acute and subacute phases of epileptic seizures in epilepsy patients with generalized tonic-clonic seizures.

MATERIAL and METHODS

This retrospective study was conducted with the patients diagnosed with generalized tonic-clonic epilepsy at the Neurology Department of Aksaray University Training and Research Hospital between April 2015 and July 2018. Patients above 18 years of age who received regular drug therapy at the sufficient dose were included. Patients who had missing laboratory or clinical data, those with hypoglycemia, hyperglycemia, seizures other than generalized tonic-clonic seizures, patients who did not receive regular treatment at the sufficient dose and those who had acute stroke, hematologic diseases that affect neutrophils and lymphocytes, liver and kidney diseases, electrolyte disorders and acute trauma were excluded from the study.

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The database of our hospital contains information about the type of epilepsy, underlying factors such as structural causes or infections and patient demographics. As part of routine practice, patients undergo systemic and neurological examination when they present to our hospital. Complete blood count, C-reactive protein (CRP), liver and kidney function tests and an electroencephalography (EEG) are conducted; blood glucose, electrolyte levels and lipid values are measured, in addition to performing cranial magnetic resonance imaging and computed tomography of the brain when necessary, on the first day of admission in all patients admitted to the neurology department of our hospital. This study was conducted using the laboratory data collected within 6 hours (acute phase) after the seizure and on day 5 (subacute phase) after the seizure in patients with epilepsy who presented with generalized tonic-clonic seizures. Analyses of the blood cell counts were performed at our hematology center using an autoanalyzer (Sysmex XN-1000 hematology analyzer, Kobe, Japan). NER was calculated by dividing neutrophil count by eosinophil count. The study was approved by the local authorities and conducted in compliance with the Declaration of Helsinki.

Statistical analysis

The results were presented as median (min- max) for abnormally- distributed data and mean ± standard deviation for normally- distributed data. To investigate the distribution pattern of the data, Kolmogorov- Smirnov normality test was used. To compare the blood parameters in the acute phase and the subacute phase of the seizures, paired samples T test (for normally- distributed data) and Wilcoxon test (for abnormally- distributed data) were used. All statistical analysis was performed using SPSS 23.0 software for Windows (SPSS Inc., Chicago, IL). A P value under 0.05 was considered statistically significant.

RESULTS

Sixty patients (30 males and 30 females) with generalized tonic-clonic epileptic seizure were included in this study. The mean age of the study group was 47.9 ± 20.9 (range: 17-86) years. The median values of white blood cell (WBC), CRP, neutrophil, eosinophil, NER, mean platelet volume (MPV), platelet and calcium; and the mean values of lymphocyte in the acute phase and subacute phase of the seizures were shown in Table 1. The median platelet and calcium values were not significantly different between the acute and subacute phases of the seizures ($p = 0.827$ and $p = 0.333$, respectively). However, the median WBC, neutrophil and NER values in the acute phase of the seizures were significantly higher compared to those in the subacute phase of the seizures ($p = 0.001$, $p < 0.001$ and $p < 0.001$, respectively). Additionally, the median CRP, eosinophil, MPV and mean lymphocyte values were significantly lower in the acute phase of the seizures compared to those in the subacute phase of the seizures ($p < 0.001$, $p < 0.001$, $p = 0.027$ and $p < 0.001$, respectively).

Table 1. The acute phase and subacute phase blood parameters of the patients with generalized tonic- clonic epileptic seizures

	Acute	Subacute	P value
White blood cell (10^9/L)	8.28 (4.77-20.75)	7.28 (3.66-14.53)	0.001
C-reactive protein (mg/dL)	4.97 (0.12-38.00)	7.4 (0-51)	<0.001
Neutrophil (10^9/L)	5.58 (2.62-19.25)	4.42 (1.81-10.97)	<0.001
Eosinophil (10^9/L)	0.07 (0.00-0.51)	0.13 (0.01-0.68)	<0.001
Neutrophil / eosinophil ratio	82.93 (9.94-6840)	33.8 (6.38-512)	<0.001
Lymphocyte (10^9/L)	1.84±0.76	2.13±0.77	<0.001
Mean platelet volume (fL)	9.9 (7.2-13.9)	10.1 (7.5-16.3)	0.027
Platelet (10^9/L)	205.5 (110-617)	206.5 (32-775)	0.827
Calcium (mg/dL)	9.06 (7.52-10.27)	8.98 (7.98-9.67)	0.333

DISCUSSION

This study showed that the WBC and neutrophil counts and NER values were higher, whereas eosinophil and lymphocyte levels were lower in the acute phase than in the subacute phase of generalized tonic-clonic epileptic seizures. These results suggest that NER can be used as a marker of inflammation in the acute phase of epileptic seizures in patients with generalized tonic-clonic epileptic seizures. Neutrophil-to-lymphocyte ratio has been studied in febrile seizures (8) and convulsive status epilepticus (9). However, to the best of our knowledge, the current study is the first one to investigate NER in epileptic seizures.

The large amount of evidence that has accumulated in the recent years strongly supports the role of systemic inflammation in epileptic seizures and in the pathophysiology of epilepsy (10-13). The key role of systemic inflammation in epileptic seizures stems from its effects on the blood-brain barrier (BBB). It was reported that systemic inflammation caused upregulation of proinflammatory cytokines such as interleukin (IL)-1 beta,

which disrupted the homeostasis in the BBB (14). Such disruptions in the BBB cause neuronal hyperexcitability in an epileptic brain, leading to epileptic seizures (14). It was shown that the anti-inflammatory molecule IL-1 receptor antagonist reduced seizures in epilepsy models (15) and stopped the seizures in a patient with epilepsy (16), and these confirm the role of systemic inflammation in epileptic seizures. In the present study, it was found that NER was high in the acute phase of epileptic seizure. Systemic inflammation causes increased neutrophil count (17) and decreased eosinophil count (18). Therefore, it was contemplated that NER, which can be easily calculated by dividing neutrophil count by eosinophil count in peripheral blood, can be used as a new biomarker of systemic inflammation.

It is known that eosinopenia is observed in acute inflammation (19,20). Previous studies have shown that eosinopenia is associated with the prognosis of diseases such as ischemic stroke (21,22) and hemorrhagic stroke (23). Eosinopenia was also observed in the present study in the acute phase of generalized tonic-clonic epileptic seizures. Eosinopenia can be associated with the prognosis of epilepsy. While it is known that eosinopenia develops secondary to systemic inflammation, whether or not eosinopenia is associated with ictogenesis or epileptogenesis remains to be revealed. Further studies are necessary to understand this.

CRP is an acute phase reactant that indicates systemic inflammation (24). It has been reported that patients with any type of epilepsy had elevated CRP levels and increased body temperature during seizures (25). However, it was underlined that the patients with epilepsy who have persistent high body temperature or a CRP value higher than 6 mg/dL 8 hours after the seizure should be under close follow-up for systemic infections (25). In this study, CRP level in the acute phase was lower than that in the subacute phase of epileptic seizure. This was thought to stem from the late elevation of the serum CRP level.

This study is the first one investigating NER, but it has some limitations: the study was retrospective and did not include a control group that consisted of healthy subjects.

CONCLUSION

In the present study, it was concluded that NER can be used as a new potential biomarker of systemic inflammation that triggers seizures in generalized tonic-clonic epilepsy. In the future, with good investigation of the mechanisms of inflammation associated with epileptogenesis and ictogenesis, new treatment strategies for epileptic seizures can be developed and potential treatment options can be increased.

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