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Do antiepileptic drugs have any effect on Neutrophil / Lymphocyte and Platelet / Lymphocyte Ratio?

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Abstract

Objective: The aim of this study was to compare the complete blood count values of 40 healthy individuals and 60 patients who are using antiepileptic drugs (AEDs), specifically to evaluate neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR), and basophil-lymphocyte ratio (BLR). This study is important because it is the first study on hematological parameters such as NLR, MLO, PLO and BLO.

Material and Methods: In this study, hemogram and biochemical data of 17 patients who received carbamazepine (CBZ), 21 patients with valproic acid (VPA), 22 patients with levetiracetam (LEV) along with 40 healthy controls were gathered and compared. The differences between the groups were evaluated statistically.

Results: No difference was present between the groups in terms of age or gender ($p > 0.05$). NLR was 2.19±1.42 for patients using CBZ, 1.64±1.34 for VPA users, 2.18±0.73 for LEV users and 2.04±0.85 for control group ($p > 0.05$). NLR, MLR, PLR and BLR were not significantly different from the control group.

Conclusion: To our knowledge, no study has targeted the haematological effects of antiepileptics on NLR, MLR, PLR and BLR. This study was important because it is the first study the effect of various antiepileptics on the hematological parameters such as NLR, MLR, PLR, and BLR. We believe that our study will articulate new studies.

Keywords: Antiepileptic drugs, NLR, PLR

Introduction

The thrombocytopenia effect of valproic acid (VPA) is a well-known and extensively investigated chemical, and it has been demonstrated to have negative effects on coagulation cascade, especially von Willebrand factor such as factor VIII and XIII, and platelet function resulting serious bleeding diathesis (1). Side effects of antiepileptic drugs (AEDs) such as VPA, levetiracetam (LEV), and carbamazepine (CBZ) on blood parameters have been demonstrated (2,3). Although the effects of these AEDs on blood values are well known, their effects on neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR) and platelet-lymphocyte ratio (PLR) are unknown. Earlier studies have elaborated the role of epilepsy in hematopoiesis and its effects on individual blood cell biology and hemorheological characteristics (4-6). Information on the effect of AEDs used in epilepsy on red blood cells is inconsistent. Suwalsky et al. reported a decrease in the number of red blood cells (RBC) in anti-epileptic drug (AED) users compared to control subjects (7), but Beyazıt et al. (8) reported no difference.

Complete blood count (CBC) is simple but contains important follow-up parameters for many diseases (9). In addition, White blood cell (WBC) count and WBC subtypes are commonly used as inflammatory markers. Recently, however, the NLR has emerged as a new marker of systemic inflammation. The NLR is an easily available parameter with CBC and is relatively inexpensive (10). Among the parameters of the haemogram, the erythrocyte distribution width (RDW_CW) is a measure of the distribution of erythrocytes based on the diameter or volume. RDW is a coefficient of variation and is calculated by one standard deviation from the mean erythrocyte volume (MCV) X 100 formula. The association of RDW levels with inflammatory processes has been demonstrated in extensive cohort studies (11). NLR and PLR are cheap and easily computable indices that correlate with the prognosis of systemic inflammatory diseases (12). Platelets are cell fragments involved in the formation of blood clots, which are also related to inflammatory events.

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Mean platelet volume (MPV) and platelet distribution width (PDW) are commonly used to estimate the functional changes and activation of platelets. MPV may increase with acute myocardial infarction, renal artery stenosis, and preeclampsia. Changes in platelet function are expected in neurological disorders such as acute ischemic stroke and intracerebral hemorrhage (13-15). WBC produced in the bone marrow is the disease-fighting agents of the immune system. Neutrophils and lymphocytes are the most important components of the inflammatory response (16). Antiepileptic drug use may affect these immune cells both directly and indirectly and may regulate their function. Neutrophil-lymphocyte ratio and PLR are the parameters available for inflammation markers. The use of high NLR as a prognostic factor in cardiovascular diseases, cancers and autoimmune diseases is investigated (17). PLR was reported to be an independent predictor of overall survival (18).

Using hematological parameters is an easy and inexpensive method when obtaining accurate information from patients is not possible (19). NLR and PLR are the values obtained by the combined calculation of two of the CBC parameters and recently investigated on various other conditions. The ratios are important because they are derived from two different blood parameters (12). These are limited data on the haematological effects of antiepileptics related to NLR, PLR, neutrophil (NEU), lymphocyte (LYM), monocyte (MONO), basophil (BASO), and eosinophil (EOS) percentages. To our knowledge, the MLR and basophil-lymphocyte ratio (BLR) have not been investigated in depth. Studies involving the association of MLR with various cancers are present and were reported to be an independent prognostic factor (12,13,19). Although we are aware of the association of MLR with various diseases, we did not find any study in the literature reporting the role of MLR in AED users. In this study, we aimed to investigate the CBC values along with NEC, PLR, BLR, and MLR together with their diagnostic values.

Material and Methods

In this study, CBC, especially WBC, RBC, HGB, HTC, mean corpuscular volume (MCV), RDW_CW, platelet count (PLT), MPV, NEU, LYM, MONO, EOS and BASO values were evaluated. Seventeen individuals (7 females, 10 males, mean age: 32.24±11.38 years) receiving CBZ monotherapy, 21 individuals (5 females, 16 males, mean age: 31.19±11.73 years) with VPA monotherapy, and 22 individuals (14 females, 8 males, mean age: 32.46±18.61) with LEV monotherapy were selected as cases. All of the patients were admitted to and being followed-up at Adiyaman University Education and Research Hospital, Epilepsy Polyclinic.

A total of 40 healthy individuals (19 females, 21 males, mean age: 30.48±10.55) without any history of disease or drug use were included in the study as the control group. NLR, PLR, BLR and MLR ratios were compared between the patient groups and control group. The mean duration of drug use of CBZ, VPA, and LEV group was three months. Patients with CBZ, VPA and LEV and were included in the study did not received any other AEDs.

Inclusion criteria were as follows: (a) selected individuals were between 15-45 years old and were able to do daily activities. (b) They were on a normal diet. (c) They had been using CBZ, VPA or LEV for at least 6 months. (d) They did not use any other other medication that would affect neutrophils, lymphocytes, and platelet metabolism. (e) They did not have a thyroid dysfunction. (f) They did not have a liver or kidney disease. (g) They did not use multiple AEDs. (h) All the females were at the premenopausal period with the regular menstrual cycles and no history of oral contraceptive drug use.

Exclusion criteria of the study were presence of systemic inflammatory diseases, hematological diseases, cancer, severe liver, heart or kidney failure or a history of surgery/major trauma in the past one month, leukocytosis (WBC> 12000) with a fever of 37.5 or above, infection in the last two weeks, and use of antibiotics, antiaggregants, anticoagulants or immune suppressants.

The control group consisted of 40 volunteers with similar age and gender to the experimental group and visited to our outpatient clinic between January 2018 and December 2018 for reasons other than cerebrovascular disease and epilepsy and without any systemic disease. Ethics committee approval (2018/5-27) for the study was obtained from Adiyaman University Ethics Committee. In this study, the missing data about the patients were gathered by contacting the patients or their relatives from the telephone numbers registered in the system. Patients who could not be contacted for the missing data were excluded from the study.

Hematological analysis

Venous blood samples were obtained from the antecubital veins of both the patient and the control group between 08:00 and 10:00 after fasting for at least 8 hours. Samples were centrifuged in 30 minutes and on the same day centrifuged on the CELL-DYN 3700 SL analyzer (Abbott Diagnostics, Chicago, USA) in the biochemistry laboratory of Adiyaman University Education and Research Hospital. The reference intervals were determined as PLT: 142-424 (103/uL), MPV: 6.8-10.8 (fL), MCV: 80-97 (fL), RDW_CW: 11.6 -15.8 (%).

Statistical analyses

The data obtained from the study were uploaded to SPSS program (Ver: 22.0). Mean, standard deviation, median, lowest and highest frequency values and ratios were estimated as descriptive statistics of the data. The distribution of variables was measured by Kolmogorov Simirnov test. Mann-Whitney U test was used for the analysis of quantitative data. Chi-square test was used for the analysis of qualitative data and Fisher exact test was used when the chi-square test criteria was not met. The effect of NLR and PLR as a prognostic marker in epileptic patients was investigated by univariate and multivariate logistic regression analyzes. In addition, the rates associated with lymphocytes were compared between two groups. A value less than 0.05 was considered statistically significant.

Results

The daily drug dose was between 400-1200 mg/day in the CBZ group. The daily drug dose of patients using VLP ranged between 500-1500 mg/day. The daily dose of medication was between 500 and 1500 mg/day for the cases using LEV. Patients who received CBZ, VPA or LEV monotherapy were compared with the control group.

There was no statistically significant difference in age or gender between the patients and controls (p>0.05) (Table 1). The mean age was 32.24±11.38 in CBZ group, 32.16±11.73 in VPA group, 32.46±18.61 in the LEV group, and 30.48±10.55 in the control group (Table 2). No significant difference was found in age of CBZ and VPA patients in in comparison to the control group, but significant difference was found in patients with LEV (Table 2). The hematological parameters of the patient and control groups are demonstrated in Table 2.

The NLR values were 2.19±1.42 in the CBZ group, 1.64±1.34 in the VPA group, 2.18±0.73 in the LEV group and 2.04±0.85 in the control group. The MLR values were 0.24±0.10 in the CBZ group, 0.27±0.31 in the VPA group, 0.26±0.09 in the LEV group, and 0.24±0.16 in the control group. The BLR values were 0.03±0.01 in the group using CBZ, 0.03±0.02 in the VPA group, 0.04±0.04 in the LEV group, and 0.04±0.06 in the control group. There was no significant difference between the monotherapy drug users and control group for NLR, MLR and PLR (p>0.05).

PLR values were 100.03±40.85 in the CBZ group, 79.78±30.30 in the VPA group, 112.70±35.61 in the LEV group, and 97.86±29.70 in the control group. Although PLR values were higher in CBZ and LEV group compared to the control group, the difference was not statistically significant (p>0.05).

There was a statistically significant difference in PLT level between the experimental cases and control groups (p<0.05). Furthermore, RDW_CW values were significantly lower in cases with VPA and LEV (p<0.05), but was not same in patients using CBZ. There were no significant differences in Hgb, WBC, HTC, NLR, PLR, MLR and MPV values in patient and control groups (p>0.05) (Table 2). Neutrophil, lymphocyte and platelet levels were not significantly different in the patients who received medication compared to the control group and three-month post-medication (p>0.05). In patients using CBZ, HTC and MPV levels were found to be significantly higher after three-month treatment in comparison to those obtained from pretreatment (p<0.05). PLR values were significantly lower in patients with three-month VPA treatment compare to the pretreatment (p<0.05) (Table 3). In the group using VPA, the MPV and HTC levels were significantly lower in the three-month CBZ group than pretreatment (Table 3).

Table 1. Demographic characteristics of the patients (n: 100)

Parameter		Patients group (n: 60) (%)	Control group (n: 40) (%)	P value
Gender	Male	26 (43.3)	19 (47.5)	0.682
	Female	34 (56.6)	21 (52.5	
Age* (year)		31.95±14.33	30.48±1055	0.578

*Data presented as mean ± Standard deviation

Table 2. Comparison of socio-demographic variables and complete blood count values of antiepileptic drugs user and control groups. (*p < 0.05)

	CBZ	P value	VPA	P value	LEV	Control	P value
Age (years)	32.24±11.38	0.76	31.19±11.73	0.27	32.46±18.61	30.48±10.55	**0.03***
WBC (10^3/uL)	8.45±2.99	0.46	8.01±2.74	0.11	8.53±2.44	7.98±2.14	0.93
HGB (g/dL).	15.17±1.80	0.94	15.51±1.33	0.07	13.52±1.83	14.47±1.81	0.96
HTC (%)	44.40±4.56	0.52	45.81±3.30	0.05	42.27±5.33	43.54±4.61	0.33
NEU (10^6/uL)	5.00±2.23	0.66	4.17±1.91	0.24	5.18±1.92	4.76±1.83	0.40
LYM (10^3/uL)	2.58±1.19	0.61	2.94±1.14	**0.04***	2.47±0.68	2.46±0.67	**0.04***
PLT (10^3/uL)	227.22±60.48	**0.03***	213.77±63.61	**0.02***	260.87±51.59	223.91±37.23	**0.04***
MONO (10^3/uL)	0.56±0.16	0.49	0.65±0.38	0.11	0.62±0.14	0.53±0.18	**0.04***
EOS (10^3/uL)	0.21±0.17	0.13	0.17±0.03	0.47	0.15±0.09	0.15±0.09	0.84
BASO (10^3/uL)	0.09±0.05	0.73	0.09±0.04	0.84	0.09±0.07	0.08±0.06	0.56
NLR	2.19±1.42	0.52	1.64±1.34	0.97	2.18±0.73	2.04±0.85	0.28
PLR	100.03±40.85	0.30	79.78±30.30	0.65	112.70±35.61	97.86±29.70	0.28
MLR	0.24±0.10	0.98	0.27±0.31	0.28	0.26±0.09	0.24±0.16	0.56
BLR	0.03±0.01	0.70	0.03±0.02	0.52	0.04±0.04	0.04±0.06	0.93
MPV (fL)	7.31±1.14	0.06	7.94±1.60	0.25	7.22±1.37	8.90±2.11	0.08
RDW_CW (%)	11.84±0.86	0.06	11.81±0.84	**0.02***	12.02±0.10	12.46±1.48	**0.04***

Notes: CBZ: Carbamazepin; VPA: Valproate; LEV: Levetiracetam; WBC: White Blood Cell; HGB: Hemoglobin; HTC: Hematocrit; RDW_CW: Red Blood Cell Distribution Width Coefficent of Variation; PLT: Platelet; MPV: Mean Platelet Volume; NEU: Neutrophil; LYM: Lymphocyte; MONO: Monocyte; EOS: Eosinophil; BASO: Basophil; NLR: Neutrophil to Lymphocyte Ratio; PLR: Platelet to Lymphocyte Ratio; MLR: Monocyte to Lymphocyte Ratio; BLR: Basophil to Lymphocyte Ratio

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Table 3. Demographic data and hematological parameters of patients receiving monotherapy AED. In the group using VPA, the MPV and HTC levels were significantly lower in the three-month CBZ group (II) than pretreatment (I). (*p < 0.05)

	CBZ			VPA			LEV		
	I	II	P value	I	II	P value	I	II	P value
WBC (10^3/uL)	8.32±2.53	8.45±2.98	0.86	8.38±3.50	8.01±2.75	0.47	8.09±2.22	8.53±2.44	0.43
HGB (g/dL)	14.92±1.74	1.16±1.80	0.26	15.38±1.24	15.50±1.33	0.62	13.95±1.82	13.52±1.83	0.06
HTC (%)	44.40±4.56	45.90±5.29	**0.03***	45.81±3.30	46.99±4.41	0.15	42.27±5.33	41.21±5.27	0.17
NEU(10^6/uL)	4.76±1.62	5.00±2.22	0.70	5.25±3.63	4.17±1.91	0.11	4.78±2.10	5.18±1.92	0.47
LYM (10^3/uL)	2.57±1.20	2.58±1.19	0.96	2.38±0.71	2.94±1.14	0.07	2.50±0.78	2.47±0.68	0.81
PLT (10^3/uL)	233.77±53.61	227.22±60.48	0.26	229.42±73.07	213.77±63.61	0.11	271.25±67.91	260.87±51.59	0.26
MONO(10^3/uL)	0.66±0.28	0.56±0.16	0.23	0.52±0.16	0.65±0.37	0.16	0.57±0.15	0.62±0.14	0.19
EOS (10^3/uL)	0.21±0.19	0.20±0.16	0.82	0.16±0.12	0.17±0.13	0.56	0.17±0.12	0.15±0.09	0.13
BASO (10^3/uL)	0.11±0.08	0.08±0.04	0.09	0.07±0.03	0.08±0.04	0.11	0.07±0.02	0.09±0.06	0.19
NLR	2.13±0.98	2.19±1.42	0.89	2.58±3.01	1.63±1.34	0.21	2.07±1.07	2.17±0.73	0.67
PLR	102.17±34.15	100.03±40.84	0.85	104.84±44.08	79.78±30.30	**0.02***	112.46±25.44	112.70±35.61	0.97
MLR	0.27±0.08	0.24±0.09	0.30	0.22±0.06	0.27±0.31	0.46	0.25±0.13	0.25±0.09	0.88
BLR	0.40±0.15	0.35±0.11	0.22	0.28±0.11	0.31±0.18	0.68	0.29±0.11	0.39±0.38	0.25
MPV (fL)	7.99±1.63	7.31±1.14	**0.03***	8.26±1.62	7.94±1.60	0.38	7.89±1.49	7.71±1.37	0.56
RDW_CW(%)	12.10±1.07	11.84±0.86	0.24	12.18±1.36	11.81±0.84	0.19	12.86±2.87	12.02±0.98	0.17

Notes: CBZ: Carbamazepin; VPA: Valproate; LEV: Levetiracetam; WBC: White Blood Cell; HGB: Hemoglobin; HTC: Hematocrit; RDW_CW: Red Blood Cell Distribution Width Coefficent of Variation; PLT: Platelet; MPV: Mean Platelet Volume; NEU: Neutrophil; LYM: Lymphocyte; MONO: Monocyte; EOS: Eosinophil; BASO: Basophil; NLR: Neutrophil to Lymphocyte Ratio; PLR: Platelet to Lymphocyte Ratio; MLR: Monocyte to Lymphocyte Ratio; BLR: Basophil to Lymphocyte Ratio

Discussion

Platelet-lymphocyte ratio was found to be low in patients with epilepsy using AEDs (especially in VPA users) three months after drug use and this decrease supports the idea that AEDs such as VPA may cause hematological side effects. To the best of our knowledge, our study was the first to show the relationship between PLR and epilepsy patients receiving AED.

Many AEDs are associated with hematological disorders ranging from mild thrombocytopenia or neutropenia to anemia, from red cell aplasia to bone marrow failure. Fortunately, potentially lethal hematological disorders such as aplastic anemia are very rare (17,20). The pathogenetic mechanisms associated with antiepileptics are still unknown. They appear to be associated with an immunological mechanism, but pharmacokinetics and pharmacodynamic interactions of drugs may also play an important role (21). In addition to the known side effects, the negative effects of AEDs, especially VPA, on the mechanism of haemostasis were documented in some studies (22-24). Nevertheless, the mechanism of these adverse effects is not to be clearly elucidated yet. VPA's hematological side effects include dose-related thrombocytopenia, platelet dysfunction, and leukopenia (19,22,23). Valproate is one of the most commonly used drugs to induce thrombocytopenia (25).

In our study, statistically significant increase in neutropenia and thrombocytopenia were found in patients who used VPA compared to the control group and results support abovementioned studies.

Although the pharmacology and side effects of CBZ have been reviewed, a mechanism causing agranulocytosis has not been described (26). Carbamazepine was also reported to cause leukopenia, thrombocytopenia, agranulocytosis and aplastic anemia (20,27,28). In addition, CBZ has been shown to perform aplastic anemia, agranulocytosis, pancytopenia, mild anemia thrombocytopenia, leukopenia, and neutropenia (29). There were several cases that report rare side effects, such as blood dyscrasias. According to FDA Safety Information, reported hematological abnormalities include reduced erythrocytes, white cells and neutrophil counts, increased eosinophil counts, and agranulocytosis cases (30). CBZ-induced thrombocytopenia usually occurs two to four weeks after the start of treatment followed by a rapid improvement after prolonged application (31). Similar to the previous studies, thrombocytopenia was detected in patients receiving CBZ in our study.

Levetiracetam was reported to have hematological side effects such as neutropenia (6,32). Levetiracetam was demonstrated to induce anemia, leukopenia, neutropenia, and pancytopenia in various studies.

Jayendra R. Gohil and Tushar S. Agarwal reported a series of cases of pancytopenia with a large reduction in both neutrophil and platelet/ erythrocyte series associated with LEV usage (33). Although secondary pancytopenia is rare in LEV usage, it is still possible. A comprehensive literature review yielded a limited number of pancytopenia cases with the use of LEV (34). The specific mechanisms of action of LEV are not known, nevertheless, it is reasonable to assume that pancytopenia is associated with aplastic pancytopenia or bone marrow aplasia rather than microangiopathic hemolytic anemia or thrombotic thrombocytopenic purpura. These specific mechanisms of action were not found in case reports. Similar to case reports, lymphopenia, thrombocytopenia and monocyte deficiency were detected in patients receiving LEV in our study.

Conclusion

Easily obtained from whole blood count without any additional costs, NLR, MLR, PLR, and BLR values were not significantly different in epileptic patients on medical treatment in comparison to the control group in the present study.

Thus, although hematologic changes are rarely seen as a result of AED use, new findings are not different from the previous ones. However, hematological monitoring is suggested especially in the use of CBZ, VPA, and LEV. Further research is needed to evaluate the true pathogenetic mechanism based on hematological complications caused by antiepileptic drugs.

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Ethical issues: All Authors declare, Originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the Authors responsibilities.

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