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Effects of Valproate and Carbamazepine Monotherapy on Leukocyte Subsets and Neutrophil-Lymphocyte Ratio in Children

Çocuklarda Valproat ve Karbamazepin Monoterapisinin Lökosit Alt Tipleri ve Nötrofil-Lenfosit Oranı Üzerine Etkileri

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ÖZET

Amaç: Epilepsili hastalarda kullanılan nöbet önleyici ilaçların lökopeni ve nötropeni gibi yan etkileri yakından bilinmekle birlikte, lökosit alt tipleri üzerine etkileri iyi bilinmemektedir. Lökosit alt tiplerindeki değişiklikler, vücudun enflamasyon durumunu değerlendirmek için de kullanılmaktadır. Nötrofilin lenfosite oranı (NLR), bu amaçla son yıllarda yaygın kullanılan indekslerdendir. Bu çalışma, iyi bilinen nöbet önleyici ilaçlardan valproat (VPA) ve karbamazepinin (KBZ) monoterapisinin lökosit alt tipleri ve NLR üzerine etkileri ve bu etkinin serum ilaç düzeyleriyle ilişkisini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntemler: İdiopatik epilepsili, KBZ (n=25) veya VPA monoterapisi (n=62) başlanan, tedavi öncesi ve sonrasındaki ilk 1- 6 ay (T1) ve 9-18 ayda (T2) tam kan sayımı incelemesi ve en az bir kez eş zamanlı serum ilaç düzeyi değerlendirilmiş olan hastaların verileri, retrospektif olarak incelendi. Veriler, lökosit, nötrofil, lenfosit ve monosit sayı ve yüzdeleri ve eşzamanlı bakılan serum anti-nöbet ilaç düzeylerini içerdi. Serum ilaç düzeylerinin değişkenlerle ilişkisi, VPA grubunda 130, KBZ grubunda 30 eş zamanlı ölçümle değerlendirildi.

Bulgular: VPA grubunda, tedavi öncesine göre, T1 döneminde, nötrofil sayısı ve NLR'de azalma saptandı (p=0.026, p=0.038). Buna karşın lenfosit ve monosit oranında artış oldu (p=0.015, p<0.001). KBZ grubunda anlamlı değişiklik yoktu. Serum VPA düzeyleri monosit sayısı ile (r=0.2, p=0.022) pozitif korelasyon gösterdi. Serum KBZ düzeyleri nötrofil sayısı (r=-0.574, p=0.001) ve NLR ile (r=-0.413, p=0.023) negatif korelasyon gösterdi.

Sonuç: VPA monoterapisinin NLR oranında anlamlı baskılanmaya neden olması, antienflamatuar etki gösterdiğini desteklemektedir. Serum KBZ düzeylerinin NLR ile negatif korelasyonu, KBZ'nin NLR üzerine dozla ilişkili olarak benzer etkisinin olabileceğini düşündürmüştür. Bu etkilerin dikkate alınması, epilepsili çocuklarda uygun ilaç seçiminde fayda sağlayabilir.

Anahtar Kelimeler: Karbamazepin, nötrofil-lenfosit oranı, lökosit alt grupları, valproat

ABSTRACT

Objective: Although the adverse effects of anti-seizure medications (ASMs), like leukopenia and neutropenia, are widely recognized, little is known about how they affect leukocyte subsets. Changes in leukocyte subsets are also used to assess the inflammation status during diseases. The neutrophil-to-lymphocyte ratio (NLR) is widely used for this purpose. This study aims to evaluate the effects of valproate (VPA) and carbamazepine (CBZ) monotherapy on leukocyte subsets and NLR and to determine the relationship of these effects with serum drug levels.

Material and Methods: The data of children with idiopathic epilepsy who began CBZ (n=25) or VPA monotherapy (n=62) and underwent complete blood count examinations before treatment and at 1–6 months (T1) and 9–18 months (T2) after treatment, with at least one concurrent serum ASM level, were collected retrospectively. The data included the number and percentages of leukocytes, neutrophils, lymphocytes, and monocytes, as well as simultaneously measured serum ASM levels. The relationships between serum ASM levels and variables were evaluated with 130 simultaneous measurements in the VPA and 30 in the CBZ groups.

Results: In the VPA group, when compared to baseline, neutrophil count and NLR decreased (p=0.026, p=0.038, respectively), and lymphocyte and monocyte percentages increased (p=0.015, p<0.001, respectively). There were no significant changes in the CBZ group. Serum VPA levels were positively correlated with monocyte counts (r=0.2, p=0.022). Serum CBZ levels were negatively correlated with neutrophil counts (r= -0.574, p=0.001) and NLR (r= -0.413, p=0.023).

Conclusion: VPA monotherapy significantly decreased NLR, supporting its anti-inflammatory effects. The negative correlation of serum CBZ levels with NLR suggested that CBZ may have a dose-related effect on NLR. Consideration of these results may be beneficial in choosing an appropriate ASM for patients with epilepsy.

Keywords: Carbamazepine, leukocyte subsets, neutrophil-lymphocyte ratio, valproate

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INTRODUCTION

Epilepsy is a common disease characterized by spontaneous recurrent seizures, with a prevalence of 0.05-1% in the general pediatric population (1,2). The side effects associated with these drugs should be closely monitored due to the long-term use of anti-seizure medications (ASMs) in these patients. The hematological side effects show a wide spectrum, including leukopenia and neutropenia (3,4). Among the commonly used ASMs, valproate (VPA) and carbamazepine (CBZ) have the potential to cause leukopenia and neutropenia (5). In a study, VPA caused changes in the leukocyte subset distribution without causing neutropenia (6), suggesting that the effects of these drugs on leukocyte subsets may be more extensive than previously recognized. However, these effects are not well known.

In recent years, assessing alterations in leukocyte subsets has gained popularity for evaluating the inflammatory state and determining whether a disease is in its active phase, in addition to being cost-effective. For this purpose, the ratio of the neutrophil count to the lymphocyte count (NLR) is widely used, and its high level is associated with an increase in the inflammatory status (7). Considering the strong evidence that inflammation accompanies both epilepsy and febrile seizures (7,8), understanding the effects of ASMs on leukocyte subsets and NLR could offer valuable insights for choosing appropriate ASM for patients. However, few studies have evaluated ASM-related changes in leukocyte subsets (6,9,10), and the effect on NLR has been evaluated in only one study in adults. This study found no significant differences, although a decrease in NLR levels was observed with VPA (11). In addition, previous studies exhibit certain methodological limitations, such as a small patient sample size (9) and the inclusion of other ASM groups or healthy individuals as control groups (6,11). Epilepsy itself may alter leukocyte subsets and NLR levels, making a healthy control group insufficient for evaluating the effects of ASMs on epileptic patients. Some studies indicate that epileptic patients have higher NLR levels compared to the control group, particularly in the acute and subacute phases following seizures (12). Therefore, this study aimed to determine the temporal effects of VPA and CBZ on leukocyte subsets and NLR in pediatric epilepsy patients and the relationship between these effects and serum ASM levels.

MATERIALS AND METHODS

The records of consecutive epileptic patients who applied to the Pediatric Neurology clinic were retrospectively reviewed after local ethics committee approval (no: 2017/219). The study included children with idiopathic epilepsy who were started on VPA or CBZ as monotherapy between 2013-2018. These children had complete blood count and serum drug levels measured simultaneously during at least one of two periods: 1-6 months after treatment (T1 period) and 9-18 months after treatment (T2 period). Those with additional systemic diseases, chronic drug use, and infection during the examination were excluded from the study.

Collected data included the patients' sex, age, starting time of treatment, counts, and percentages of the leukocytes, neutrophils, lymphocytes, and monocytes measured at pre-treatment, T1 and T2 periods, and simultaneous serum ASM levels. The ratio of neutrophils to lymphocytes (NLR) was calculated for each patient. Complete blood count was evaluated using cell counter, and serum ASM levels were evaluated using spectrophotometric method. Therapeutic ranges for VPA and CBZ were established as 50–100 µg/mL and 4–12 µg/mL, respectively. Leukopenia was defined as a leukocyte count of less than 4000/mL, neutropenia as a neutrophil count of less than 1500/mL, and lymphopenia as a lymphocyte count of less than 1500/mL.

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD). The groups' distribution was assessed for normality using the Kolmogorov-Smirnov test. Friedman two-way analysis of variance and post-hoc Wilcoxon test were used to compare the data in the ASM groups at baseline, T1, and T2 periods. Student T or Mann Whitney U tests were used to compare ASM groups based on the normality of variable distribution; a Pearson's chi-square test was used to compare sex distribution across the ASM groups. The association between serum ASM levels and other variables was evaluated using Spearman or Pearson's correlation analysis, depending on the normality of the data. The statistical significance level was accepted as $p<0.05$.

RESULTS

General findings:

The study included 62 patients in the VPA group and 25 in the CBZ group. There were 33 males and 29 females in the VPA group, mean age was 8.1±3.5 years. There were 11 males and 14 females in the CBZ group, with a mean age of 8.5±2.5 years. The distribution of age and sex did not differ between ASM groups (p=0.312, p=0.436, respectively, Table 1).

Thirty measurements of serum ASM levels were taken simultaneously in the CBZ group and 130 in the VPA group. No leukopenia, neutropenia, or lymphopenia was observed in any patient after treatment with either drug.

Comparison of the values in the pre-treatment, T1, and T2 periods:

Compared to pre-treatment values, VPA treatment reduced neutrophil counts and NLR (p=0.026, p=0.038, respectively), while increasing the percentages of lymphocytes and monocytes (p=0.015, p<0.001). The lymphocyte count was the only value higher in the T2 period when comparing the T1 and T2 periods (p=0.042, Wilcoxon test). Although serum VPA levels were lower in the T2 period compared to the T1 period (p=0.028, Wilcoxon test), other findings were similar (Table 2, Figure 1).

Comparison of pre-treatment values with values in the T1 and T2 periods did not show a significant difference in the CBZ group (Table 1).

Comparison of drug groups:

Pre-treatment values did not show significant differences between the two ASM groups. In the T1 period, the VPA

Table 1. Comparison of ASM Groups (VPA and CBZ)

Variables (mean±SD)	VPA group	CBZ group	p-value
Age at the treatment starting (years)	8.1±3.5	8.5±2.5	0.312
Sex (M/F)	33/29	11/14	0.436*
Pre-treatment			
Leukocyte count (x10³/µL)	8.9±2.97	8.1±2.2	0.262
Neutrophil count (x10³/µL)	4.97±2.62	4.67±2.31	0.840
Neutrophil (%)	52.2±15	56.1±13.2	0.153
Lymphocyte count (x10³/µL)	3±1.15	2.6±0.9	0.088**
Lymphocyte (%)	36.4±12.9	33.5±11.4	0.216
NLR	2.14±2.29	2.3±2.1	0.234
Monocyte count (x10³/µL)	0.7±0.3	0.6±0.2	0.476
Monocyte (%)	7.9±3	7.6±2.5	0.485
T1 period			
Leukocyte count (x10³/µL)	8.3±3.2	7.7±1.8	0.991
Neutrophil count (x10³/µL)	3.9±2.3	3.9±1.6	0.196
Neutrophil (%)	44.4±12.5	50.5±11.1	0.049**
Lymphocyte count (x10³/µL)	3.3±1.3	2.8±0.8	0.024
Lymphocyte (%)	42.1±10.9	37.2±10	0.069**
NLR	1.24±0.73	1.55±0.94	0.087
Monocyte count (x10³/µL)	0.7±0.2	0.6±0.2	0.008
Monocyte (%)	9.6±2.6	8±2.3	0.017**
T2 period			
Leukocyte count (x10³/µL)	8.4±5.5	7.1±1.9	0.156
Neutrophil count (x10³/µL)	3.4±1.2	3.7±1.7	0.421**
Neutrophil (%)	42±9.7	49.8±11.2	0.007
Lymphocyte count (x10³/µL)	3.4±1.1	2.6±0.5	0.001
Lymphocyte (%)	44.5±8.7	38.3±9.6	0.015**
NLR	1.04±0.43	1.45±0.66	0.01
Monocyte count (x10³/µL)	0.7±0.2	0.7±0.4	0.035
Monocyte (%)	9.5±2.7	8.1±1.5	0.025**

T1 period: 1-6 months after treatment initiation, T2 period: 9-18 months after treatment initiation. Statistical tests: * Pearson's chi-square test, ** Student-T test, others used Mann-Whitney U test. ASM, anti-seizure medication; CBZ, carbamazepine; F, female; M, male; SD, standard deviation; VPA, valproate.

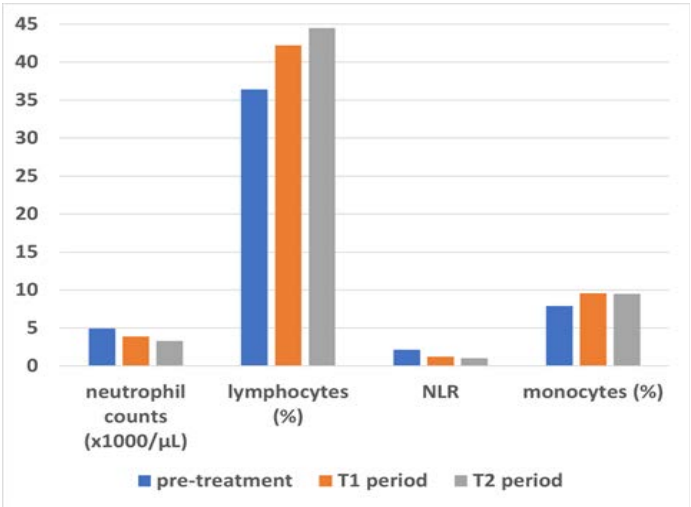

Figure 1. Variables Showing Significant Differences Over Time in the VPA Group

Following treatment, the percentages of lymphocytes and monocytes increased, while the neutrophil count and NLRs decreased. NLR, neutrophil to lymphocyte ratio; VPA, valproate

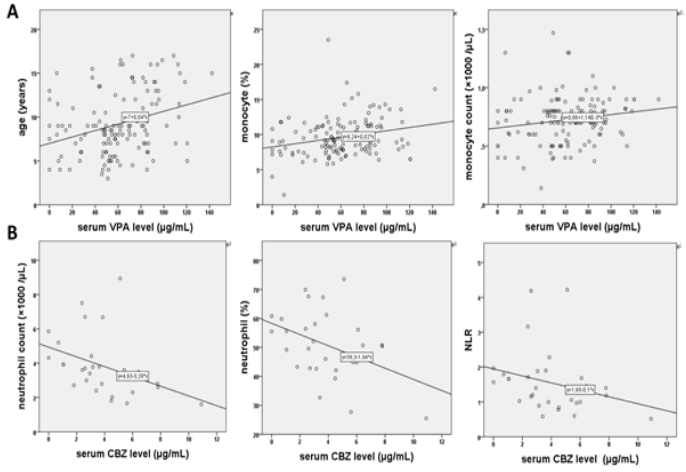

Figure 2. Variables Showing Significant Correlations with Serum ASM Levels

(A) Serum VPA levels were positively correlated with age (r=0.296, p=0.001) and counts and percentages of monocytes (r=0.2, p=0.022 and r=0.238, p=0.006, respectively). (B) Serum CBZ levels were negatively correlated with NLR (r= -0.413, p=0.023) and counts and percentages of neutrophils (r= -0.574, p=0.001 and r= -0.414, p=0.023, respectively). ASM, anti-seizure medication; CBZ, carbamazepine; NLR, neutrophil to lymphocyte ratio; VPA, valproate

Table 2. Statistical Comparison of the Leukocyte Count, Leukocyte Subset Counts and Percentages, Serum ASM Concentrations, and NLRs at the Pre-treatment, T1, and T2 Periods

Variables (mean±SD)	Pre-treatment	T1 period	T2 period	p-value
VPA group				
Serum VPA level (µg/mL)	-	65±4.4	50±4.7	0.028
Leukocyte count (x10^3/µL)	8.87±2.98	8.28±3.2	8.36±5.48	0.135
Neutrophil count (x10^3/µL)	4.97±2.8	3.9±2.3	3.3±1.2	0.026
Neutrophil (%)	52.2±15	44.4±12.45	42±9.7	0.059
Lymphocyte count (x10^3/µL)	3±1.15	3.3±1.25	3.4±1.07	0.062
Lymphocyte (%)	36.4±12.9	42.2±10.9	44.5±8.7	0.015
NLR	2.14±2.29	1.24±0.7	1.04±0.43	0.038
Monocyte count (x10^3/µL)	0.69±0.3	0.75±0.2	0.72±0.2	0.07
Monocyte (%)	7.9±3	9.6±2.6	9.5±2.7	<0.001
CBZ group				
Serum CBZ level (µg/mL)	-	3.6±2.4	4.2±3	0.249
Leukocyte count (x10^3/µL)	8.06±2.17	7.7±1.8	7.07±1.9	0.526
Neutrophil count (x10^3/µL)	4.7±2.3	3.9±1.6	3.7±1.7	0.807
Neutrophil (%)	56.1±13.2	50.5±11.1	49.8±11.2	0.931
Lymphocyte count (x10^3/µL)	2.6±0.9	2.8±0.8	2.6±0.47	0.807
Lymphocyte (%)	33.5±11.4	37.2±10	38.3±9.6	0.931
NLR	2.3±2.1	1.55±0.94	1.45±0.66	0.931
Monocyte count (x10^3/µL)	0.59±0.18	0.62±0.19	0.65±0.35	1.00
Monocyte (%)	7.6±2.5	8±2.3	8±1.5	0.492

T1 period: 1-6 months after treatment initiation, T2 period, 9-18 months after treatment initiation. Statistical tests: Friedman's two-way analysis of variance was used. ASM, anti-seizure medication; CBZ, carbamazepine; NLR, neutrophil to lymphocyte ratio; SD, standard deviation; VPA, valproate.

group had higher monocyte counts and percentages as well as lymphocyte counts (p=0.008, p=0.017, and p=0.024, respectively), and lower neutrophil percentages (p=0.049) than the CBZ group. Alongside these changes, there were also lower NLRs and higher lymphocyte percentages (p=0.01 and p=0.015, respectively) in the T2 period (Table 1).

Correlation analysis results:

Serum VPA levels showed statistically significant positive correlations with age (r=0.296, p=0.001), monocyte counts (r=0.2, p=0.022), and monocyte percentages (r=0.238, p=0.006) (Figure 2).

There was a strong negative correlation between serum CBZ levels and neutrophil counts (r=-0.574, p=0.001). Serum CBZ levels also showed statistically significant negative correlations with neutrophil percentages and NLRs (r=-0.414 and r=-0.413, respectively, p=0.023, for both) (Figure 2).

DISCUSSION

This study demonstrated that VPA significantly reduced the neutrophil count and NLR while increasing the percentage of lymphocytes and monocytes, even in the first six months of the treatment. CBZ did not affect leukocyte subsets and NLR compared to the pre-treatment period. However, correlation analysis results suggested that as serum CBZ levels increased, the counts and percentages of neutrophils and NLR levels decreased.

To our knowledge, this is the first study to assess the temporal effects of VPA and CBZ on NLR, particularly in pediatric patients. In the only study we could find evaluating the effects of ASMs on NLR, adult patients receiving VPA, CBZ, and levetiracetam were compared to healthy controls, and changes in NLR levels were found statistically insignificant (11). The results of that study may differ from the current study due to the following factors: comparison with healthy controls, evaluation of the adult age group, failure to consider temporal NLR changes, and the smaller number of patients in the VPA and CBZ groups (21 and 17, respectively).

The results of this study indicate that VPA may improve the anti-inflammatory response even in the first six months following treatment initiation because VPA suppresses neutrophil count and NLR. Even though serum VPA levels were significantly lower in the T2 period than in the T1 period, those effects of VPA persisted, demonstrating that they are not affected by dosing or drug levels. However, the strong positive correlation between serum VPA levels and monocyte count and percentage suggests that VPA has a dose-dependent effect on monocyte activation. In the study by Bartels et al., serum VPA levels did not correlate with monocyte activation but showed a negative correlation with neutrophil percentage (6). That study did not account for treatment duration, which could be why the current study results differed from theirs. However, the effects of VPA on monocytes are supported by evidence. Some studies suggest that VPA induces the differentiation of myeloid hematopoietic progenitor cells into monocytic lineages. This effect is attributed to the increased acetylation of histones H3 and H4 and the increased expression of p21, which is crucial for monocyte development (13,14).

Similar to this study, several studies have addressed the suppressive effect of VPA on neutrophil counts. In a study involving pediatric and adult patients, VPA significantly

decreased the neutrophil counts and increased the lymphocyte counts compared to patients using phenytoin and CBZ (6). In 15 adult patients evaluated before and three months after VPA treatment, decreases were observed in leukocytes, neutrophil counts, and neutrophil percentage after treatment (9). Those studies showed no significant difference in monocyte percentages, possibly due to adult patient evaluation, comparison with other ASMs, and small patient groups. In a study including a larger number of patients hospitalized due to COVID-19, a comparison of 165 adult patients with epilepsy using VPA and 330 control patients without epilepsy showed higher lymphocyte and monocyte counts, fewer lung infiltrates, and fewer intensive care unit admissions in the VPA group (15). In another study, 50 epileptic children who were started on VPA were followed up for nine weeks after treatment; no significant change was found in leukocyte counts, but leukocyte subsets were not evaluated (16).

Valproate is a histone deacetylase (HDAC) inhibitor, which may have a role in its effects on leukocyte subsets. In human hematopoietic stem cells, lymphoid and more limitedly myeloid-related genes are associated with acetylated histones H3 and H4 (17). Histones, crucial in nucleosome formation, have been recognized as essential components of epigenetic regulation in recent years. Histone modifications influence gene expression patterns by either facilitating or hindering access to transcription factors or regulatory proteins, leading to the genetic activation or silencing of genes (14,18). VPA inhibits HDACs classified as class Ia, Ib, and IIa, leading to increased acetylation of histones H2, H3, and H4. This modification alters gene expression associated with apoptosis, the cell cycle, differentiation, and the protection against tumor cells (14). Reports have indicated that HDAC inhibitors influence the regulation of normal hematopoiesis, with VPA showing effectiveness in cell fate determination, particularly in myeloid development. VPA inhibits the differentiation of myeloid cells towards the granulocyte/macrophage series and blocks neutrophil differentiation at increasing doses (19). In bone marrow mesenchymal stromal cells, VPA increases the secretion of several trophic factors, the ability to prevent oxidative damage, and migration capacity (20). The effects of VPA treatment on lymphocyte development are poorly understood; however in vitro and in vivo studies have shown that VPA and other HDAC inhibitors increase the number and function of regulatory T cells (6,21).

This study showed that CBZ did not significantly affect leukocyte counts or subset distribution. However, the strong inverse relationship between serum CBZ levels and neutrophil count, percentage, and NLR implies that CBZ may suppress neutrophil activation and NLR in a dose-dependent manner. In another study comparing patients taking CBZ and those taking folic acid in addition to CBZ, the results showed that, one year later, the leukocyte and neutrophil counts of the CBZ-only group were significantly lower (22). In a study involving ten epileptic patients, a decrease in leukocyte count was observed at one month following CBZ treatment, but T and B lymphocyte percentages remained unaffected (10). In a pediatric study, CBZ monotherapy reduced the number of lymphocytes, compared to the control group (23). The inconsistent results in these studies are likely due to variations in control groups, age group inclusion, and the number of patients included. The mechanism of action of CBZ on neutrophils is not clear; however, an invitro study showed that CBZ inhibited neutrophil chemotaxis via peripheral benzodiazepine receptors (pBZrs) in a dose-dependent manner and increased pBZrs expression in neutrophils, which could potentially affect neutrophil count (24). CBZ-associated neutropenia may be caused by its dose-dependent inhibition of granulopoiesis (25). Another proposed mechanism for the hematological effects of CBZ is that it is metabolized by the myeloperoxidase enzyme contained by neutrophil precursors in the bone marrow. This leads to the formation of intermediate metabolites that cause covalent binding to neutrophils and may also lead to bone marrow-related side effects (26).

In this study, VPA and CBZ did not cause pathological alterations in the quantity of leukocytes and their subsets. According to some studies, children using VPA may have leukopenia as high as with a rate of 12.5% (27). Mild and transient neutropenia with VPA occurs only in isolated pediatric cases, usually during the first few weeks of treatment, and regresses within a few days when the drug is discontinued (5). VPA-related hematological changes may occur immediately after starting the drug therapy or after prolonged use but are most frequently seen when the serum drug level exceeds 100 µg/mL (6,28). Transient leukopenia occurs in children receiving CBZ, but significant leukopenia and neutropenia are rare, reversible, and asymptomatic. Benign leukopenia is seen in 10–12% of adults and children using CBZ and is not thought to be related to aplastic anemia (29). Leukopenia was the most common abnormality in a study involving 200 children with epilepsy receiving CBZ. However, it resolved without discontinuing CBZ treatment, and only four patients experienced persistent or recurrent leukopenia (30). Although there have been reports of CBZ-related lymphopenia (31,32), agranulocytosis is uncommon (4).

One limitation of the study is its retrospective design. However, evaluating the temporal effects of VPA and CBZ is a strengthening factor. Another limitation is that, although examinations during the infection period were excluded, the retrospective review may not have completely excluded them. Therefore, additional comparisons of drug groups aimed to eliminate this problem and supported the effects of VPA. The study's limitations include a lack of control for confounding variables like seizure types and recurrences. A recent seizure before the blood test may impact NLR levels. A study found that NLR levels in the first 24 hours after a seizure in epilepsy patients were higher than those measured 5-14 days later, and these levels were associated with seizure severity and recurrence (33). Therefore, lower NLR levels may also result from the seizure control that ASMs provide. This issue is partially resolved by the study's comparison of the VPA and CBZ groups. Another limitation of the study is its single-center design, limiting the generalizability of study results. However,

a multicenter study may also have disadvantages, such as the inability to standardize laboratory data in a retrospective study.

CONCLUSION

In conclusion, this study found that VPA caused changes in leukocyte subsets and decreased NLR, suggesting an anti-inflammatory effect regardless of serum VPA levels. The study's findings provide evidence that, depending on serum drug levels, CBZ may affect NLR similarly. In epilepsy cases accompanied by inflammation, it may be beneficial to consider these features in ASM selection.

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