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Evaluation of Hemogram Indices of Children with Epilepsy Receiving Short-Term Levetiracetam Treatment

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Abstract

Objective: The effects of levetiracetam on hemogram parameters are comparable with other antiepileptics. This study aimed to compare the effects of levetiracetam monotherapy for at least 6 months on hemogram indices with valproic acid.

Methods: Cases aged 6-18 years who received levetiracetam (n = 42) or valproic acid (n = 46) monotherapy for at least 6 months were randomly selected. The hemogram data closest to the study cutoff point of those who completed a minimum of 6 months of monotherapy were recorded. White blood cell count, neutrophil count, lymphocyte count, red blood cell distribution width, platelet, mean platelet volume, neutrophil/lymphocyte ratio, red cell distribution width to platelet ratio, mean platelet volume to platelet ratio, platelet to lymphocyte ratio, and lymphopenic case rates were compared between levetiracetam and valproic acid groups.

Results: The number of lymphopenic cases (absolute lymphocyte < 1500/mm^3) was higher in the levetiracetam group (n = 8) compared to the valproic acid group (n = 3) (log-rank analysis, $P = .002$). The lymphocyte count was found to be lower in the levetiracetam group compared to the valproic acid group (mean 2274 ± 964 vs. 2523 ± 653, $P = .153$). The neutrophil/lymphocyte ratio (mean 2.4 ± 2.3 vs. 1.6 ± 1.3, $P = .042$) and platelet to lymphocyte ratio indices (mean 141 ± 63 vs. 105 ± 40, $P = .002$) associated with lymphocyte count were significantly higher in the levetiracetam group.

Conclusion: Levetiracetam has more lymphopenia side effects than valproic acid. Viral, fungal, and opportunistic infections that develop during levetiracetam treatment may be due to lymphopenia. In cases deemed necessary, absolute lymphocyte count, lymphocyte subgroup analysis, and serum immunoglobulin levels should be reviewed.

Keywords: Levetiracetam, leukocytes, lymphocyte, lymphopenia, platelet

INTRODUCTION

Nearly 70%-80% of epileptic seizures can be controlled by antiepileptic drugs (AEDs) used with effective doses and sufficient duration.[1] The remaining 20%-30% of seizures continue to be resistant in spite of effective and tolerable new AEDs developed in recent years.[2] The neurological, psychiatric, and dermatological side effects linked to AEDs are known for a long time. Hematological side effects like thrombocytopenia, pancytopenia, and hypogammaglobulinemia are observed more rarely.[3]

Levetiracetam (LEV) is a new-generation AED that is highly effective for the treatment of partial and generalized epilepsy and that is safe and well tolerable. It is used as both combined and monotherapy for childhood epilepsy. Due to the low side effect profile and favorable pharmacological features, it is currently one of the most commonly chosen AEDs.[4] Behavioral problems such as nervousness and irritability, somnolence, dizziness, and asthenia are among the most frequently reported side effects.[5] More rarely, Stevens–Johnson syndrome, B cell aplasia, and hypogammaglobul inemia were reported.[6]

When we look at the effects of other AEDs on hemogram indices, there are many studies on valproic acid (VPA), phenytoin (PHT), and carbamazepine (CBZ).[7] It has been reported that VPA causes thrombocytopenia and pancytopenia, PHT causes myelosuppression, and CBZ causes agranulocytosis.[8] The thrombocytopenic side effect of LEV is frequently reported in pediatric and adult case reports.[9]

There are limited studies on the effects of LEV on hemogram indices in childhood. There are only 2 prospective studies about hemogram indices after short- and long-term LEV use in children.[10,11] These studies showed a moderate reduction in lymphocyte (L) counts linked to LEV; however, there was no comparison with any other AEDs.

In our clinical practice, we rarely see some effects of LEV on hemogram indices in children. Based on this observation, we aimed to detect abnormal deviations in white blood cell (WBC) count, neutrophil (N) count, L count, red blood cell distribution width (RDW), platelet (PLT) count, mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), RDW/PLT ratio (RPR), MPV/PLT ratio (MPR), and PLT/L ratio (PLR) hemogram indices in children who received LEV monotherapy for at least 6 months. For this purpose, it was aimed to compare the hemogram indices of children who received LEV monotherapy for a minimum of 6 months with those who received VPA monotherapy for the same period.

METHODS

Patient Selection and Exclusion Criteria

Pediatric patients aged 6-18 years who were followed up by the pediatric neurology clinic between January 1, 2018, and December 31, 2020, were included in this study. Digital medical records of those who received LEV or VPA monotherapy for at least 6 months were retrospectively reviewed. Those receiving LEV or VPA dose of 20-30 mg/kg/day dose with height and weight ≥10th and ≤90th percentile were randomly selected. Demographic features like gender and age and diagnoses (generalized or partial epilepsy) were recorded.

It was required that the cases included in the study should be followed up with the diagnosis of epilepsy from our pediatric neurology clinic from January 1, 2018, to December 31, 2020. Patients diagnosed with epilepsy and using LEV or VPA in centers other than our clinic were also included in the study. After controlling the epilepsy diagnosis and drug doses, these patients were included in the study when the requirement to receive monotherapy for at least 6 months was met. Patients using LEV or VPA should have started these treatments at least 6 months before the cutoff date of the study (December 31, 2020). Cases who used LEV or VPA for a minimum of 6 months during the study period and had a hemogram after this 6-month treatment were included in the study. During VPA treatment, blood levels were measured in cases deemed necessary. However, blood level measurement could not be performed during LEV treatment (it is not studied in the laboratory of our institution). The hemogram data at the beginning of the treatment could not be recorded due to the hemogram changes (such as leukocytosis) that may occur in the acute period after the epileptic seizure and the incomplete first hemogram results of the patients whose LEV or VPA treatments were started in other centers. When more than 1 hemogram results of those receiving LEV or VPA monotherapy were detected, the hemogram data nearest to the study cutoff point were recorded (Figure 1). White blood cell count, N count, L count, RDW, PLT, MPV, NLR, RPR, MPR, and PLR indices were recorded. A case-controlled study could not be conducted, and therefore hemogram data of LEV and VPA users were compared.

MAIN POINTS

- The vast majority of epileptic seizures can be controlled with antiepileptic drugs (AEDs) used at effective doses and for sufficient duration.
- Hematological side effects such as pancytopenia, anemia, leukopenia, and thrombocytopenia related to AEDs are rarely seen.
- Levetiracetam (LEV) is a new generation antiepileptic drug that is highly effective, safe and well tolerated in the treatment of childhood epilepsy.
- Although LEV has a low side effect profile, behavioral problems such as irritability, somnolence, dizziness and asthenia are among the most frequently reported side effects.
- Side effects of LEV on hematological series such as leukocytes, erythrocytes, and platelets are still controversial. In selected cases with suspected immunodeficiency, lymphopenic side effects should be kept in mind.

Those with a history of febrile illness or infection in the last 4 weeks were not included in the study. Blood samples were taken from those with no history of febrile illness or infection in the past 4 weeks. Those with poor general health (suspicion of chronic infection and metabolic or rheumatological disease) and poor nutrition (celiac and other malabsorptions, hypothyroidism, and B12 and other vitamin deficiencies) were excluded from the study. In addition, patients with chronic liver, kidney, hematological, or immunological diseases were not included in the study.

Children with spastic tetraparesis, severe hypotonia, or neuropathy who were level III and above according to the gross motor functional classification system were not included in the study.

Those using any medication or antiepileptic other than LEV or VPA were also excluded from the study.

Blood Sampling, Hemogram Analysis, and Calculations of Indices

Fever was measured with a noncontact temperature-measuring device (Braun BNT400), and blood samples were taken from those with a body temperature below 37.2°C. A fasting blood sample was obtained in the morning, between 9:00 and 10:00 AM, into Ethylene Diamine Tetra Acetic Acid (EDTA)-containing 5 mL sterile tubes at their latest checkup. All hematological parameters were analyzed using the Mindray BC-6200 automated hematology analyzer, according to the manufacturers' instructions. Total WBC count, N count, L count, RDW, PLT count, and MPV were recorded in the whole study population. Neutrophil/lymphocyte ratio was calculated by dividing the absolute N count by the absolute L count. The RDW/PLT ratio (RPR index), MPV/PLT ratio (MPR index), and PLT/L ratio (PLR index) were calculated.

Statistical Analysis

Statistical analysis was performed by using the Statistical Package for Social Sciences Software version 19.0 for Windows (SPSS Inc., Chicago, Ill, USA) program. Categorical data are expressed as numbers and percentages; numerical data are expressed as mean ± SD and median as appropriate. The chi-square test was used for the comparison of categorical data. If the numerical data fit normal distribution, they were evaluated with the independent samples *t*-test. The Mann–Whitney *U*-test was used for the evaluation of numerical data without normal distribution. The RDW/PLT ratio and MPR indices were included in the statistical calculations after logarithmic transformation because they had very small numerical values and did not show normal distribution.

The effects of LEV and VPA use on the number of lymphopenic cases were calculated using log-rank analysis. In addition, the effect of gender on the number of lymphopenic cases was evaluated by log-rank analysis. For log-rank analysis, lymphopenic cases were recorded as "event." $P < .05$ was considered significant in all statistical calculations.

Ethical Approval

The study was planned and conducted according to the ethical standards detailed in the Declaration of Helsinki. Ethical permission was

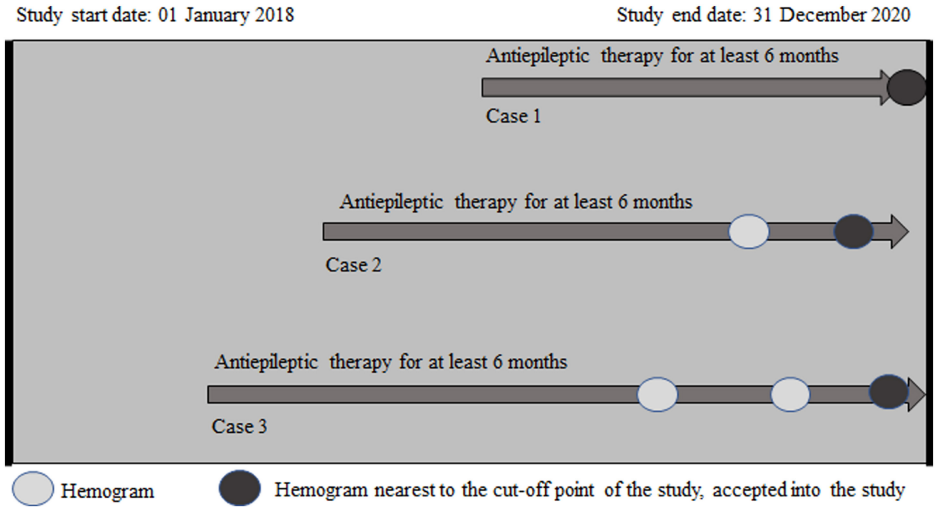

Figure 1. Random selection of cases and hemogram data.

received from the University Clinical Research Ethics committee dated December 19, 2020, with decision number 2011-KAEK-27/2020-E.2000176614.

RESULTS

Demographic Characteristics of Study Population

Digital medical files of a total of 88 cases in this study cohort were retrospectively reviewed. Of these cases, 46 were on VPA and 42 were on LEV monotherapy. The mean age was 11.7 ± 3.2 years in the LEV group and 11.8 ± 3.1 years in the VPA group. (P = .867). The female/male ratio was 1.8 (27/15) in the LEV group and 0.6 (18/28) in the VPA group (P = .018). The diagnosis of generalized epilepsy was 69.3% in the whole population, while that of partial epilepsy was 30.7%. For LEV users, 64.3% were diagnosed with generalized and 35.7% with partial epilepsy. For VPA users, 73.9% were diagnosed with generalized and 26.1% with partial epilepsy (P = .328). Demographic data for LEV and VPA groups are presented in Table 1.

Comparison of Hemogram Indices in Levetiracetam and Valproic Acid Users

The mean ± SD and median (maximum–minimum) values for WBC, N, L, RDW, PLT, MPV, NLR, RPR, MPR, and PLR indices in the study groups are presented in Table 2. According to the table, there were no significant differences identified between those using LEV and VPA for a minimum of 6 months' duration in terms of WBC, N, L, RDW, PLT, MPV, $\log_{10}$ RPR, and $\log_{10}$ MPR hemogram indices. The L counts in

Table 1. Demographic Characteristics of Those Receiving LEV and VPA Monotherapy

	LEV (n = 42)	VPA (n = 46)	*P*-Value
Age (years)	Mean 11.7 ± 3.2 Median 11.0 (7-17)	Mean 11.8 ± 3.1 Median 12.0 (7-17)	.867[μ]
Female/male ratio	1.8 (27/15)	0.6 (18/28)	**.018**[χ]
Seizure type			
Generalized (n)	27	34	.328
Partial (n)	15	12	

LEV, levetiracetam; VPA, valproic acid.
[μ]Mann–Whitney *U*-test; [χ]Pearson chi-square test.
P < .05 was considered significant in all statistical calculations and values in bold are significant.

Table 2. Comparison of Hemogram Parameters of Those Receiving LEV and VPA Monotherapy

	LEV (n = 42)	VPA (n = 46)	*P*
WBC (×10³/mm³)	Mean 7.3 ± 2.4 Median 7.0 (3.6-12.3)	Mean 7.1 ± 1.7 Median 6.9 (4.1-11.9)	.610[†]
N count (/mm³)	Mean 4278 ± 2170 Median 3800 (1320-10 400)	Mean 3781 ± 1748 Median 3250 (1600-9700)	.289[μ]
L count (/mm³)	Mean 2274 ± 964 Median 2250 (600-4190)	Mean 2523 ± 653 Median 2500 (1100-4000)	.153[†]
RDW (%)	Mean 13.8 ± 1.5 Median 13.4 (11.1-19.6)	Mean 13.6 ± 0.9 Median 13.5 (11.9-17.8)	.831[μ]
PLT (×10⁶/mL)	Mean 274 ± 68 Median 259 (165-434)	Mean 251 ± 78 Median 240 (136-461)	.150[†]
MPV (fL)	Mean 8.5 ± 1.2 Median 8.4 (6.4-10.8)	Mean 8.8 ± 1.5 Median 8.5 (6.5-16.1)	.425[μ]
NLR (N/L)	Mean 2.4 ± 2.3 Median 1.7 (0.3-10.4)	Mean 1.6 ± 1.3 Median 1.3 (0.5-8.1)	**.042**[μ]
$\log_{10}$ RPR (RDW/PLT)	Mean –4.2 ± 0.1 Median –4.3 [(–4.4) – (–3.9)]	Mean –4.2 ± 0.1 Median –4.2 [(–4.5) – (–3.9)]	.139[†]
$\log_{10}$ MPR (MPV/PLT)	Mean –4.4 ± 0.1 Median –4.5 [(–4.7) – (–4.2)]	Mean –4.4 ± 0.1 Median –4.4 [(–4.7) – (–4.1)]	.075[†]
PLR (PLT/L)	Mean 141 ± 63 Median 132 (60-365)	Mean 105 ± 40 Median 100 (54-224)	**.002**[μ]
Lymphopenia (absolute lymphocyte count <1500/mm³), n (%)	8 (19)	3 (6.5)	.076[χ]
Treatment time (month)	Mean 6.7 ± 1.0 Median 6.0 (6.0-10.0)	Mean 7.8 ± 1.6 Median 8.0 (6.0-12.0)	**.001**[μ]

LEV, levetiracetam; VPA, valproic acid; WBC, white blood cell; N, neutrophil; L, lymphocyte; RDW, red blood cell distribution width; PLT, platelet count; MPV, mean platelet volume; NLR, neutrophil/lymphocyte ratio; RDW, red cell distribution width; RPR, RDW/PLT ratio; MPV, mean platelet volume; MPR, MPV/PLT ratio; PLR, PLT/L ratio.
[†]Independent samples *t*-test; [μ]Mann–Whitney *U* test; [χ]Pearson chi-square test.
P < .05 was considered significant in all statistical calculations and values in bold are significant.

those receiving LEV monotherapy [mean 2274 ± 964 and median 2250 (600-4190)] were identified to be relatively lower compared to those using VPA [mean 2523 ± 653 and median 2500 (1100-4000)], but this difference was not statistically significant (P = .153, Table 2).

According to Table 2, there were significant variations in the NLR and PLR indices related to L count after a minimum of 6 months' use of LEV. The mean and median values of the NLR index were 2.4 ± 2.3 and 1.7 (0.3-10.4), respectively, in the LEV group and 1.6 ± 1.3 and 1.3 (0.5-8.1), respectively, in the VPA group (P = .042). Similarly, the mean and median values of the PLR index were 141 ± 63 and 132 (60-365), respectively, in the LEV group and 105 ± 40 and 100 (54-224), respectively, in the VPA group (P = .002).

The L count was <1500 mm^3 for 19% (8/42) in the LEV group and 6.5% (3/46) in the VPA group. However, this difference was not statistically significant according to the Mann–Whitney U-test (P = .076, Table 2).

The mean and median follow-up times of the cases treated with LEV and VPA were very close to each other. However, this difference was found to be significant in the Mann–Whitney U-test (P = .001, Table 2).

The Effect of Antiepileptics (Levetiracetam and Valproic Acid) and Gender on the Number of Lymphopenic Cases by Survival Analysis

There were 8 lymphopenic (absolute L < 1500/mm^3) cases in the LEV group and 3 in the VPA group. This numerical case difference between the groups was found to be statistically significant in the log-rank analysis (P = .002, Figure 2).

Regardless of the antiepileptics (LEV and VPA), it was observed that the gender factor had no effect on the number of lymphopenic cases by log-rank analysis (P = .494, Figure 3).

DISCUSSION

According to the results of our study, the L counts of those using LEV were numerically lower compared to those using VPA. Although it could not be demonstrated by the Mann–Whitney U-test, it is noteworthy that there is a decreasing trend in L numbers with short-term LEV monotherapy (P = .153, Table 2). The number of lymphopenic cases was 8 after at least 6 months of LEV monotherapy and 3 after VPA monotherapy. The difference in the number of lymphopenic cases between the 2 groups was found to be significant in the log-rank test (P = .002, Figure 2). There was a significant difference in hemogram indices like NLR and PLR related to the L count (P = .042 and P = .002, respectively; Table 2).

Clinically low lymphocyte count alone may not cause a significant symptom or sign.[12] It is mostly detected incidentally during complete blood count in patients receiving LEV therapy. Recurrent or unresolved infections and fever are the most common findings in severe lymphopenia. However, findings suggestive of respiratory viral infection such as cough, runny nose, and fever may also be seen. In lymphopenia developed under LEV treatment, the differential diagnosis of chronic infections such as human immunodeficiency virus and tuberculosis, acute infections such as influenza and hepatitis, rheumatological diseases,

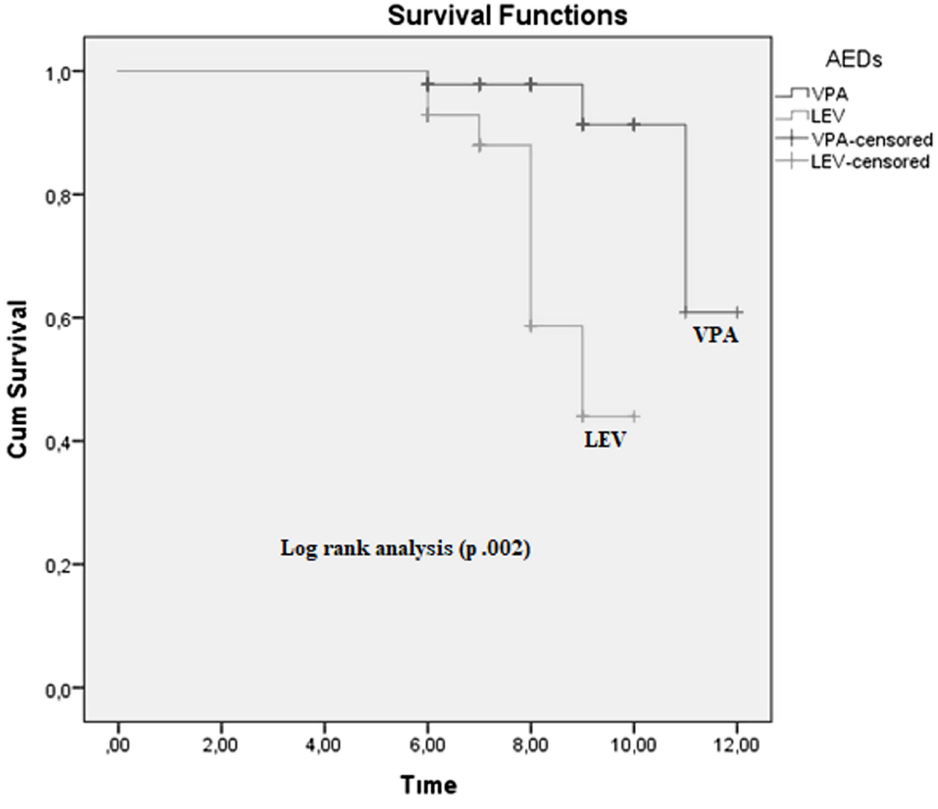

Figure 2. The effect of antiepileptics (LEV and VPA) on the number of lymphopenic cases by survival analysis. LEV, levetiracetam; VPA, valproic acid.

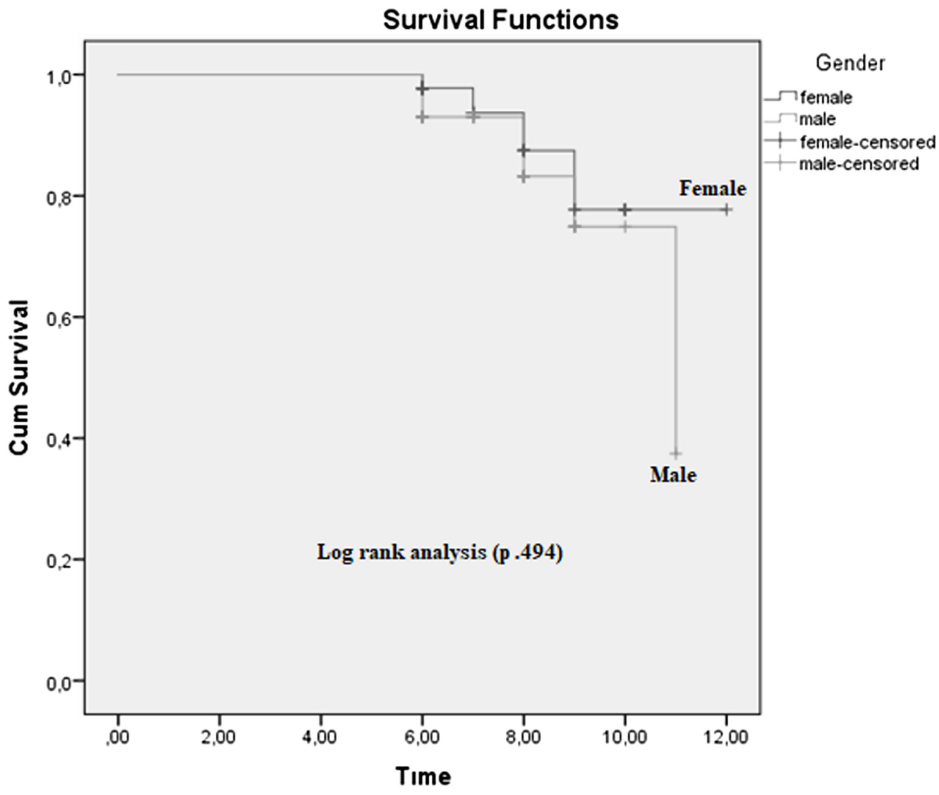

Figure 3. The effect of gender on the number of lymphopenic cases by survival analysis.

malignancies such as leukemia and lymphoma, and conditions such as undernutrition should be made carefully.[13] Measurement of plasma immunoglobulins in lymphopenic cases may give clues about the number and functions of the B lymphocyte subtype. In cases with persistent lymphopenia, T, B, and NK cells can be evaluated separately by performing lymphocyte subgroup analysis.[14]

In a previous study, Attilakos et al[11] showed an increase in N counts, with significant reductions in L and PLT counts after 12 months of LEV use. However, this study did not compare with a different antiepileptic, and only 15% of patients were reported to have low absolute L count according to age. In our study, lymphopenia (absolute L count < 1500/mm^3) was identified in 19% (8/42) of the LEV group, and this difference was shown to be significant in the log-rank test (Figure 2). A more noteworthy situation in the study by Attilakos et al (2018) is that the age interval of the patients (1-15 years) was very heterogeneous. Though the absolute L count was reported to fall below the 10th percentile in only 15% of cases, the variations in L counts according to age make interpretation difficult. This is because the L counts in children fall very rapidly to 40%-35% levels after 5-6 years of age.[15] The dose interval for LEV reported in the same study was also very broad (10-35 mg/kg/day).[11] For this reason, it is also difficult to determine the correlation between the broad LEV treatment dose and low L counts. The effective LEV treatment dose reported in the literature is 20-40 mg/kg/day.[16,17] The narrower therapeutic LEV dose (20-30 mg/kg/day) used in our study is more compatible with the literature in this sense. The heterogeneity of the age range in our study was reduced, and a narrower range (6-18 years) was preferred compared to Attilakos et al (2018). Additionally, in our study, there was no change shown in N and PLT counts compared to Attilakos et al (2018) (Table 2). However, a study published in 2014 by the same researchers reported there was no variation in hemogram parameters, apart from significant L reduction, after 6 months of LEV use.[10] This result partly overlaps with the results of our study.

Levetiracetam is new-generation AED and its chemical structure is (S)-α-ethyl 2-oxo-1-pyrrolidine acetamide. Levetiracetam is rapidly absorbed after oral administration and has linear pharmacokinetics. It has little or no interaction with other drugs and antiepileptics. It has a favorable antiepileptic profile due to its low side effect profile.[18] It may cause many psychiatric and behavioral problems (such as aggressive behavior, agitation, anger, and anxiety) and central nervous system depression (such as somnolence, asthenia, fatigue, and dizziness) in the childhood period.[19] Hypersensitivity reactions such as maculopapular rash and Stevens–Johnson syndromes were reported less frequently.[20] Side effects on hematologic parameters like WBC, N, L and PLT are still controversial, and most data accumulating about this topic are based on case reports rather than large cross-sectional and prospective studies. For example, Taberner Bonastre et al[21] reported leukopenia and neutropenia after LEV use in an adult oncology case. Some adult case reports found hematological side effects like pancytopenia and thrombocytopenia.[22-24] A review researching the safety profile of LEV reported a significant fall in WBC and N counts in the first months of treatment; however, this situation was not clinically significant.[25] In our study, the LEV group had significant elevations in indices like NLR and PLR related to low L count compared with those using VPA (Table 2). An adult study by Bachmann et al[26] reported significant WBC increase compared to the control group in women using LEV. The same study showed increased WBC among women using VPA, lamotrigine, and CBZ. Interestingly in this study, there was a significant reduction in PLT counts among those using LEV. This result being found against VPA is very notable because there is a lot of data about

thrombocytopenia as a side effect of VPA (compared to LEV).[27,28] In our study, the PLT count was lower in the VPA group; however, the difference was not significant (P = .150, Table 2). Dinopoulos et al[10] identified a reduction in only L counts after 6 months of LEV use, similar to our findings. The same study reported that PLT counts increased.

A case report by Ozdemir et al (2018)[6] reported B cell aplasia and hypog ammaglobulinemia after LEV use for the first time in the literature. The detection of low IgG and IgA especially and no detection of B cells in peripheral blood flow cytometry are notable. Similarly, a hypogammag lobulinemia case related to LEV was reported by Azar and Ballas.[23] Of course, it is not logical to reach definite evidence about LEV based on these incidental case reports. However, Piña-Garza et al[29] reported that 81% of cases with 48-week adjunctive LEV treatment had infection-related adverse events (upper respiratory tract infections 27%, nasopharyngitis 17%, diarrhea 16%, ear infection 11%, and otitis media 10%), which naturally involves questions related to possible effects of LEV on the humoral immune systems. However, as the L count and gamma globulin levels were not mentioned in this study, it is not possible to make clear inferences.

Limitations

The small sample size is insufficient to show the power of our study. However, it is not easy to design a large prospective study group in a certain age group and with similar gender ratios who receive monotherapy and do not have additional comorbidities. In addition, LEV is used in combination therapy rather than monotherapy in childhood epilepsy. Also, this situation affects the number of study populations of LEV monotherapy in children. Similar to our study, partial standardization of small-group studies can increase the power and effectiveness of future meta-analyses.

In our study, data related to erythrocyte series like hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin concentration were not recorded for patients. Though we wanted to obtain this data, the retrospective design of the study and anonymous data made it impossible to retrospectively obtain data related to erythrocytic series. Our lack of experience with gross variations (like anemia or polycythemia) related to HB and HCT in our patients using LEV for years in our pediatric neurology clinic and the lack of reporting of these side effects related to LEV in the literature affected the design of our study from the start. Another situation is the predominance of the male gender in the VPA group. As is known, VPA is an antiepileptic with endocrinological side effects in female children of pubertal age. When we noted the age interval and averages of patients included in our study, it reflects that we chose VPA less often in clinical applications for this age group. After excluding recurrent infections, oral candidiasis, or rheumatological problems in children with lymphopenia identified (absolute L count < 1500/mm^3), they were included in clinical follow-up. None of these patients had any changes to LEV or VPA treatment, and the information related to these patients is not presented in detail. Additionally, comparisons related to VPA, chosen most commonly and with side effects known best, were not given in detail to prevent lengthening of the "Discussion" section.

CONCLUSION

Levetiracetam is currently one of the most commonly chosen AEDs for both partial and generalized epilepsy. Levetiracetam caused lymphopenia in a numerically more number of cases than VPA. In addition, significant changes in favor of LEV were detected in hemogram indices related to L counts such as NLR and PLR. Therefore, in selected cases with recurrent infection history, oral candidiasis, or lymphopenic immune failure suspicion, assessment of absolute L count, L subgroup analysis, and serum gamma globulins should be taken into consideration in the agenda.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article. Raw data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Çanakkale Onsekiz Mart University (Date: December 19, 2020, Decision No: 2011- KAEK- 27/20 20-E. 20001 76614).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – T.C.; Design – T.C.; Supervision – T.C., T.K.; Resources – T.C., T.K.; Materials – T.C., T.K.; Data Collection and/or Processing – T.K.; Analysis and/or Interpretation – T.C.; Literature Search – T.C., T.K.; Writing Manuscript – T.C.; Critical Review – T.C., T.K.; Other – T.C., T.K.

Declaration of Interests: The authors have no conflicts of interest to declare.

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