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ORIGINAL ARTICLE

Levetiracetam Effect on Hematological Indices in Children with Idiopathic Epilepsy

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ABSTRACT:

Background: Levetiracetam is a well-known broad-spectrum antiepileptic drug, approved by FDA, for proper and effective control of both focal and generalized epilepsy. It exerts its effect by binding to synaptic vesicle glycoprotein 2A (SV2A) protein which mediates calcium dependent vesicular neurotransmitter release. Due to the need for long-term use, several studies have discussed levetiracetam effect on hematological parameters. They have noted some case reports of pancytopenia, thrombocytopenia and lymphopenia. **Methods**: This prospective cohort study involved fifty-eight participants divided in two groups; the first one (the case group) included children who were diagnosed idiopathic epilepsy on levetiracetam as monotherapy with six months follow up while the other group (the control group) had healthy children of the same age range. Hematological indices (complete blood count (CBC) and coagulation profile (prothrombin time, partial thromboplastin time and international randomized ratio (pT, pTT, INR)) were compared among cases before and six months after levetiracetam. **Results**: Of 29 cases, 10 were female and 19 were male with ranging age between 1 to 14 years. Our study showed that absolute neutrophilic count (ANC) has significantly declined after six months of levetiracetam monotherapy, while other parameters (Hb: Hemoglobin, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, lymphocytes, platelets pT, pTT, INR) remained statistically unchanged. **Conclusion**: In children with idiopathic epilepsy, levetiracetam monotherapy may induce significant change in hematological indices mainly on ANC especially on long term.

Keywords: Children, hematological indices, levetiracetam, monotherapy, idiopathic epilepsy.

INTRODUCTION

Epilepsy is considered one of the most common neurological disorders, especially in children, with some cognitive, psychological and neurobiological burden **[1].** In 2017, The International League Against Epilepsy (ILAE) made an operational classification for epilepsy, with specific focus on the group of idiopathic generalized epilepsies (IGE). This distinct group has a favorable prognosis for seizure control with clinical and genetic overlap among its types. Also, all four types of IGE share similar generalized spike waves on Electroencephalography (EEG) with normal brain imaging **[2].**

Patients often present by one or a combination of the following generalized seizures: absence, myoclonic, tonic and tonic-clonic. Generalized tonic-clonic seizures may have early focal or asymmetric features. Most of IGE syndromes respond well to antiseizure medications (ASMs) but may need long term treatment **[3].**

Levetiracetam has been introduced as an antiepileptic with a distinctive mechanism of action since 1999. It modulates synaptic transmitter release through binding to synaptic vesicle glycoprotein 2A (SV2A) protein in the brain. This has been proved to be effective against focal and generalized

epilepsies, as both add-on therapy and monotherapy **[4].**

Moreover, levetiracetam has been regarded as an alternative for valproate especially in treating IGE seizures. This can be attributed to its characteristic mechanism, excellent pharmacokinetic features, available different administrative preparations and minimal adverse effects particularly in children **[5].**

Few studies have reported some hematological adverse effects in patients on levetiracetam especially after long term therapy with some incidents of recurrent infections like pharyngitis. Also, some cases of leucopenia, eosinophilia and pancytopenia have been noted. Thus, we dedicate this study to monitor the possible adverse effects of levetiracetam, as monotherapy for children with idiopathic epilepsy, on hematological indices after six months of its use **[6].**

METHODS

This prospective cohort study was carried out at Zagazig University Hospital's pediatric department neurology unit between July 2024 to December 2024. Our study involved fifty-eight participants divided in two groups; the first one (the case group) included children who were newly diagnosed idiopathic epilepsy on levetiracetam as monotherapy with six months follow up. Our cases were 75% compliant on levetiracetam orally by the dose of 40mg/kg/day. The other group (the control group) had healthy children who had been attending pediatric clinic, of the same age range as cases.

All participants' families provided written informed consent and the study was accepted by Zagazig university's faculty of medicine's research ethics council (ZU-IRB# 287-12-5-2024). The work was conducted in compliance with the World Medical Association's Code of Ethics (Declaration of Helsinki) for human subjects' research.

On one hand, our inclusion criteria were any child between one and fourteen years old, of both genders, diagnosed as idiopathic epilepsy on levetiracetam as monotherapy, followed up six months later, after levetiracetam initiation. Diagnosis was based on sound neurological examination interictally with lack of history of previous hypoxia or trauma .Also, the absence of any brain lesions on magnetic resonance imaging (MRI) eliminates most of the etiological groups. EEG findings, matching ILAE criteria, can be elicited by hyperventilation or photic stimulation. **[16].** On the other hand, our exclusion criteria were any epileptic child with structural brain anomalies or underlying hematological disorders. Also, any epileptic child who received or on medications known to affect blood parameters was eliminated.

All patients were subjected to full history taking including; age of seizure onset, relevant family history of similar condition, levetiracetam compliance and tolerance with frequency and seizure duration prior to treatment. Patients were examined thoroughly with specific emphasis on neurological assessment. Furthermore, evaluation of anthropometric measurements of all enrolled children and adolescents (height, weight, body mass index (BMI) and head circumference was made to rule out other causes of seizures like hydrocephalus, microcephaly or chromosomal anomalies. Moreover, both idiopathic epilepsy and obesity can be attributed to genetic basis. Additionally, seizures can disturb ghrelin, leptin, and adiponectin levels, which will finally cause obesity **[19].**

For the pre-treatment period patients' data were collected including seizure frequency, seizure type, electroencephalogram results, magnetic resonance imaging (MRI) findings, CBC (Hb, MCV, MCH, platelet count, total leucocytic count, absolute neutrophilic count and lymphocyte count) and coagulation profile (pT, pTT, INR). These laboratory results were compared six months after levetiracetam therapy. This analysis was done, according to manufacturer instructions at Zagazig University clinical pathology department, by the Automated Cell Counter (Sysmex Xn1000 corporation , Kobe, Japan) and the Automated Blood Coagulation Analyzer (Sysmex CS5100 corporation, Kobe, Japan) for both complete blood count and coagulation profile respectively.

Statistical analysis

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 27. Categorical variables were described using their absolute

frequencies and were compared using chi square test, and Fisher exact test when appropriate. To compare ordinal data between two groups, chi square for trend test was used. Shapiro-Wilk test was used to verify assumptions for use in parametric tests. Quantitative variables were described using their means and standard deviations or median and interquartile range according to type of data. To compare quantitative data between two groups, independents sample t test (for normally distributed data) and Mann Whitney test (for not normally distributed data) were used. Spearman rank correlation coefficient was used to measure strength and association of correlation between two continuous not normally distributed variables. To compare quantitative data between more than two groups, Kruskal Wallis test (for not normally distributed data) was used when the difference is significant, pairwise comparison was used to detect difference between each individual group. Percent change in outcome parameters was calculated as [(postoperative value – preoperative value)/preoperative value *100]. The level statistical significance was set at $P<0.05$. Highly significant difference was present if $p\leq0.001$.

RESULTS

This study enrolled a total of 58 children; 29 of them were healthy as the control group with similar demographic characteristics to the case group. The cases were 19 (65.5%) male and 10 (34.5%) female with age ranging between 1 to 14 years. About 38% (n=11) of cases had generalized tonic and same percentage had generalized tonic clonic seizures. Regarding levetiracetam compliance, approximately 76% (n=22) of patients have achieved compliance while all the studied group tolerated levetiracetam. The pretreatment EEG findings was found to be normal for 34.5% (n=10) of the cases however, EEG revealed generalized epileptogenic activity in 34.5% (n=10) and 31% (n=9) had focal epileptogenic discharge. Each attack of seizure ranged from 1 to 10 minutes before starting treatment **(Table 1).**

Comparing the cases' pretreatment laboratory findings to the control group's data, MCV and MCH were significantly lower among patient group while they had significantly higher ANC and PT. Whereas, there is a non-significant difference regarding hemoglobin, total leucocytic count, platelet count, lymphocyte count, INR or partial thromboplastin time. **(Table 2)**

On one hand, about 48%, 63%, 69% and 52% of the studied group showed a decrease in hemoglobin level, total leucocytic count, ANC and lymphocytes 6 months after levetiracetam treatment respectively. Also, about 52% of them had a decrease in PTT and 48.2% had lower INR. On the other hand, about 52% and 55% of the studied group showed higher levels of platelet count and PT after same period of levetiracetam treatment. **(Table 3)**

Compared to pretreatment counts, after six months of levetiracetam, absolute neutrophilic count was found to be decreased in all patients while the other hematological parameters (hemoglobin, MCV, MCH, PT, PTT, INR, total leucocytic count, lymphocyte count and platelet count) are statistically non-significantly changed. **(Table 3)**

The relationship between the pretreatment EEG and changes in hematological parameters in the post-treatment period was also evaluated separately. Statistically, we can assume that there is a non-significant relation between EEG pattern and percent change in hemoglobin, total leucocytic count, ANC, lymphocytes, MCV, MCH, PT, PTT, platelet count or INR. **(Table 4)**

Table 1: Disease-specific data of studied patients before LEV treatment

	N=29	%
Gender		
Female	**10**	**34.5%**
Male	**19**	**65.5%**
Age group:		
Preschool	**24**	**82.7%**
School age	**5**	**17.2%**

	N=29	%
Type of seizures		
Generalized tonic	**11**	**37.9%**
Generalized tonic clonic	**11**	**37.9%**
Focal	**5**	**17.2%**
Absence seizures	**1**	**3.4%**
Atonic	**1**	**3.4%**
Frequency of attack before LEV treatment per day		
2 attacks	**3**	**10.3%**
3 attacks	**9**	**31%**
4 attacks	**9**	**31%**
5 attacks	**6**	**20.7%**
6 attacks	**1**	**3.4%**
Present as status	**1**	**3.4%**
LEV compliance		
Non-compliant	**7**	**24.1%**
Compliant	**22**	**75.9%**
LEV tolerance		
Tolerated	**29**	**100%**
EEG (Electroencephalography)		
Normal	**10**	**34.5%**
Focal epileptogenic discharge	**9**	**31%**
Generalized epileptogenic activity	**10**	**34.5%**
MRI (Magnetic resonance imaging) brain		
Normal	**29**	**100%**
	Median (IQR)	**Range**
Age at onset (month)	**18(8 – 45)**	**1.67 – 132**
Disease duration (month)	**6(2 – 6)**	**0 – 84**
Duration of attack / min.	**5(2 – 6)**	**1 – 10**

Table 2: Comparison between the studied groups regarding laboratory data before levetiracetam treatment

	Case group [n=29]	Control group [n=29]	t	P
	Mean ± SD	Mean ± SD		
Hemoglobin(g/dl)	**10.54 ± 1.19**	**10.61 ± 0.91**	**-0.335**	**0.789**
MCV (fL)	**73.19 ± 6.27**	**78.78 ± 7.28**	**-3.13**	**0.003***
MCH (pg)	**23.76 ± 2.87**	**26.32 ± 2.85**	**-3.407**	**0.001****
PT (second)	**11.66 ± 1.79**	**10.85 ± 0.73**	**2.225**	**0.03***
PTT (second)	**33.58 ± 7.36**	**31.72 ± 6.07**	**1.047**	**0.299**
INR	**1.06 ± 0.18**	**1.0 ± 0.07**	**1.935**	**0.061**
	Median (IQR)	**Median (IQR)**	**Z**	**P**
TLC (10^3/ml)	**10.9(7.95 – 15)**	**9.2(6.1 – 12.65)**	**-1.82**	**0.069**
ANC (10^3/ml)	**5.5(3.2 – 8.7)**	**3.5(2.55 – 4.9)**	**-2.373**	**0.018***
Lymph (10^3/ml)	**3.4(2.5 – 5.5)**	**3.4(2 – 5.8)**	**-0.226**	**0.822**
Platelet (10^3/ml)	**317(272 – 399)**	**345(274 – 509)**	**-1.376**	**0.169**

*Hb: Hemoglobin; MCV: Mean corpuscular volume; TLC: total leucocytic count; MCH: Mean corpuscular hemoglobin; PLT: Platelet count; ANC: Absolute Neutrophilic count; Lymph: Lymphocyte count; PT: Prothrombin time; PTT: Partial thromboplastin time; INR: international normalized ratio.

Table3: Change in laboratory data of case group before and 6 months after LEV treatment

	Pretreatment	6 months Posttreatment		t	P
	Mean ± SD	Mean ± SD	Median percent change		
Hemoglobin(g/dl)	10.54 ± 1.19	10.49 ± 1.08	0(-2.87, 4.23%)	0.223	0.825
MCV (fL)	73.19 ± 6.27	73.39 ± 6.46	-0.53(-2.26, 2.59)	-0.295	0.77
MCH (pg)	23.76 ± 2.87	23.77 ± 2.84	0(-3.75, 2.44)	-0.024	0.981
PT (second)	11.66 ± 1.79	11.21 ± 1.0	0.95(-10.14, 5.29)	1.371	0.181
PTT (second)	33.58 ± 7.36	32.41 ± 8.32	-6.23(-12.55, 15.57)	0.631	0.533
INR	1.06 ± 0.18	1.02 ± 0.08	0(-13.46, 4.13)	1.385	0.177
	Median (IQR)	Median (IQR)		Wx	P
TLC (10^3/ml)	10.9(7.95 – 15)	9.5(7 – 12.8)	-13.33(-37.14, 20.46)	-1.763	0.078
ANC (10^3/ml)	5.5(3.2 – 8.7)	3.5(2.45 – 7.15)	-36.36(-58.3, 12.91)	-2.433	0.015*
Lymph (10^3/ml)	3.4(2.5 – 5.5)	3.5(2.55 – 7.6)	-1.22(-26.92, 91.17)	-0.735	0.462
Platelet (10^3/ml)	317(272 – 399)	334(279.5 – 460.5)	0.33(-19.16, 38.69)	-0.616	0.538

Wx Wilcoxon signed rank test t paired sample t test *p<0.05 is statistically significant

Table4: Relation between EEG pattern and change in laboratory data before the start of LEV therapy and 6 months after

	Focal epileptogenic form	Generalized epileptogenic activity	Normal EEG	KW	p
	Median (IQR)	Median (IQR)	Median (IQR)		
Hemoglobin	-2.59(-10.48, 6.14%)	2.87(-2.69, 5.61%)	-0.42(-1.53, 4.1%)	1.737	0.419
TLC	-12.96(-40.97, 22.25%)	8.01(-22.8, 20.81%)	-22.37(-36.96, 9.94%)	0.523	0.77
ANC	-16.87(-51.04, 4.39%)	-11.73(-57.85, 44.47%)	-38.7(-74.03, -10.58%)	1.9	0.387
Lymphocyte	-19.05(-41.11, 56.67%)	-15.38(-30.1, 55.72%)	44.22(-17.1, 152.24%)	2.255	0.324
Platelet	4.16(-33.22, 30.25%)	-3.25(-20.49, 50.53%)	-2.3(-15.51, 76.93%)	0.389	0.823
MCV	-0.91(-1.93, 2.98%)	2.33(-1.2, 3.03%)	-1.55(-3.69, 0.99%)	3.198	0.202
MCH	-1.32(-5.13, 2.08%)	0.39(-1.78, 2.95%)	-0.44(-5.65, 3.29%)	0.976	0.614
PT	1.96(-3.18, 9.92%)	1.95(-7.56, 6.29%)	-6.48(-14.25, 1.7%)	4.483	0.106
PTT	-6.77(-11.65, 19.18%)	4.01(-16.88, 15.36%)	-7.46(-18.08, 16.23%)	0.054	0.973
INR	2.22(-4.62, 16.59%)	0.5(-12.5, 5.05%)	-5.84(-20.03, 1.69%)	2.902	0.234

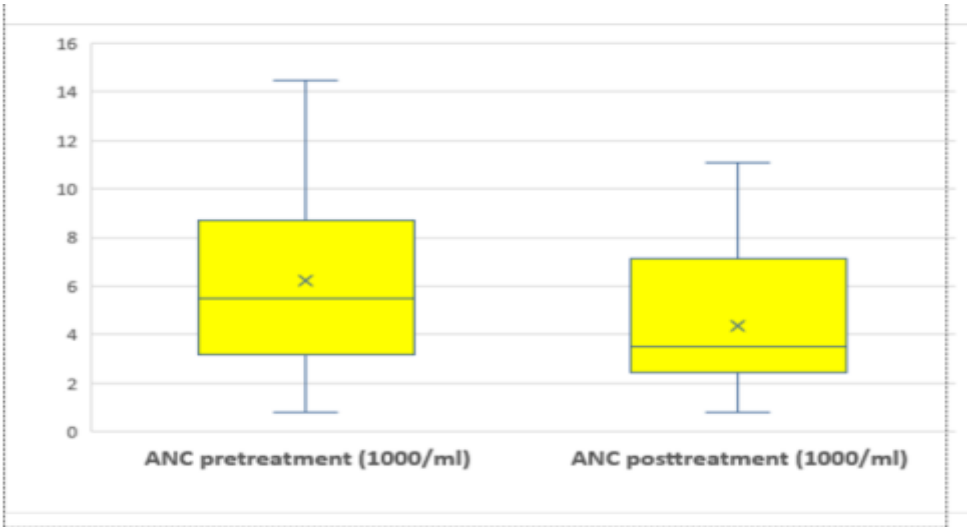

Figure (1): Boxplot showing ANC before and six months after LEV treatment.

DISCUSSION

Epilepsy is among the most common neurological disorders in children, with the highest incidence during early childhood. EEG and neuroimaging are key tools for identifying the cause, while genetic testing has become increasingly valuable in recent years [7].

Clinical trials have shown levetiracetam to be effective as both monotherapy and add-on therapy in a wide range of seizure types, including generalized epilepsies. It is increasingly used as an alternative to valproate, especially in children with idiopathic generalized epilepsy, due to its favorable safety profile [8]. However, studies have reported some hematologic effects, including doubled risk of infections (e.g., pharyngitis, rhinitis) when levetiracetam was used for one month as add-on therapy for adult focal epilepsy compared to placebo [17]. For pediatric population, fewer reports noted isolated cases of pancytopenia, thrombocytopenia, eosinophilia, and lymphopenia. For instance, after 3 weeks of levetiracetam monotherapy, a 9-year-old girl developed pharyngitis and skin rash with lymphocytosis, eosinophilia and thrombocytopenia [18].

Our prospective cohort study investigated the impact of levetiracetam on hematological parameters and coagulation profiles in children with idiopathic epilepsy following six months of treatment ,so it helps in the overall assessment of levetiracetam tolerability in pediatric population.

The study included 29 cases with idiopathic epilepsy from both sexes with age group from 1 to 14 years old on levetiracetam, with normal MRI brain with no structural anomaly, compared to 29 controls from Neurology Department at Children Hospital, Faculty of Medicine, Zagazig University.

Our study found a male predominance in the case group and no significant gender difference between case and control groups. Similar to our results, Uçar et al. [6] reported more boys (56%) than girls (44%) among children on levetiracetam monotherapy. On the contrary, Ibrahim et al. [9] actually found slightly more girls (54%) than boys (46%) in their cohort. This slight contrast can be attributed to demographic distribution and sample selection.

Regarding age, our study showed that the majority of the epileptic cases were preschool (82.7%) and school-age (17.2%) children while, Ibrahim et al. [9] had an older cohort (mean 8.5 years, range 2–15), with only 24% under age 5. Importantly, we found no difference in age distribution between cases and controls (p=0.163), suggesting age itself was not a confounder. The small discrepancies with other studies likely reflect different sample compositions.

In our study, the most common seizure types in cases were generalized (37.9% tonic, 37.9% generalized tonic-clonic) – totaling 75.8% generalized – followed by focal with secondary generalization (17.2%), and rare absence/atonic (3.4% each). In agreement with our results, Yıldırım et al. [10] found

that in a large pediatric epilepsy cohort (although mixed etiologies), 61.6% had primary generalized seizures and only 19.6% focal seizures.

According to our study, 75.9% of our cases were adherent which came along with Kolli et al. [11] who reported that the overall rate of adherence was 72% of prescribed doses taken. Our 24% non-compliance rate reflects real-world challenges. Since levetiracetam is generally well-tolerated and dosing is straightforward, compliance is usually high. We note our high compliance (three-quarters) and assume it did not differ markedly from other levetiracetam studies, like Li et al.[20], (which often have >70% compliance or retention).

Our study reported that pre-treatment EEG was abnormal in 65.5% of patients (31% focal discharges, 34.5% generalized discharges); 34.5% had normal EEGs. In agreement with our results, Uçar et al. [6] found EEG abnormalities in 76.6% of their patients but with more focal (64.1%) than we reported (31%). Differences may come from patient selection as we included all idiopathic cases regardless of EEG, while Uçar's sample might have had more focal epilepsy. Importantly, both studies report a substantial fraction with normal EEG (23% in Uçar vs. 34.5% in ours), reflecting that a normal EEG is common in pediatric epilepsy.

Our study included all 29 patients with normal brain MRI. Similarly, Ibrahim et al. [9] required and reported normal brain MRI in their idiopathic epilepsy cohort. By definition, idiopathic epilepsy implies no structural pathology, our uniform normal MRI is thus in line with the criteria and literature.

Regarding hematological parameters, we compared the cases' pretreatment laboratory findings to the control group's data, MCV and MCH were significantly lower among patient group whereas, there is a non-significant difference regarding hemoglobin, TLC, platelet count, lymphocyte count, INR or partial thromboplastin time. Baseline factors like iron or nutritional status, ethnicity, or laboratory methods may also affect MCV and MCH, contributing to variation across studies.

Furthermore, our study showed that PT was significantly longer in patients than controls at baseline with no significant difference in PTT or in INR. Our study also has found that patients had significantly higher absolute neutrophil counts (ANC) at baseline than controls This might arise from differences in study populations or co-morbidities. For example, subtle baseline clotting factor differences, vitamin K status, or concomitant illnesses could prolong PT.

We set pretreatment hematological values side by side to them after 6 months of levetiracetam. There is only statistically significant decline in ANC after 6 months of levetiracetam with median percent change by 63%. Meanwhile, the other hematological parameters (hemoglobin, MCV, MCH, PT, PTT, INR, total leucocytic count, lymphocyte count and platelet count) remained statistically unchanged.

Regarding coagulation profile, our study found no significant difference in (PT) or (PTT) after 6 months of levetiracetam therapy. In favor to our results Ibrahim et al. [9] and Dilber et al. [12] noted no meaningful alteration in PT after 6 months of levetiracetam. None of the comparison studies specifically reported INR, but given the unchanged PT and PTT results, an unchanged INR is expected. In Ibrahim et al. [9], the focus was on PT and PTT and no abnormal coagulation was detected, implying INR (which is derived from PT) was unaffected. Likewise, Dilber et al. [12] reported no INR alteration. Therefore, our finding aligns with the consensus, Mbizvo et al. [21], that no disturbance in coagulation metrics had been detected with levetiracetam.

Similar to our results, Ibrahim et al. [9] similarly reported no significant change in Hb after levetiracetam therapy, while Dilber et al. [12] found a significant Hb rise in their long-term follow-up. Our finding of unchanged Hb agrees with Ibrahim et al. [9] and suggests levetiracetam monotherapy alone does not typically cause anemia in children. Variations in hydration, iron status, or assay calibration between studies could underlie the different Hb trends reported.

Our study found no significant difference in total leukocyte count (TLC) or in lymphocyte count after levetiracetam, which agrees with Dilber et al. [12] and Ibrahim et al. [9]. In

contrast, Uçar et al. [6] reported a significant decrease in total WBC and lymphocytes over 12 months of levetiracetam (notably in older children). Differences in study duration likely explain this: Uçar's follow-up was 12 months, capturing a gradual lymphopenia, whereas we reported only baseline vs 6-month data. It is possible that a lymphocyte decrease would emerge with longer treatment. Variation might also be due to differing viral exposure or baseline immune status in the cohorts.

Our study has not detected any significant change in platelet count with levetiracetam consisting with Ibrahim et al. [9] and Dilber et al. [12]. However, Uçar et al. [6] reported a modest but statistically significant decrease in platelet count over 12 months. The discrepancy may be due to Ucar's longer follow-up or the lack of a control group.

Importantly, our study showed that absolute neutrophil count (ANC) significantly declined after 6 months of levetiracetam monotherapy, while other parameters (hemoglobin, MCV, MCH, PT, PTT, INR, TLC, lymphocytes, and platelets) remained statistically unchanged. Thankfully, this ANC decline range (2.45 – 7.15) is still above neutropenic standard. In agreement with our study, Uçar et al. [6] reported a statistically significant reduction in neutrophil count after 12 months of levetiracetam, without leukopenia. Similar to our results, Dilber et al. [12] also noted ANC reduction with long-term levetiracetam use, though still within safe ranges. Moreover, Ibrahim et al. [9] found slight (though statistically non-significant) falls in ANC after 6 months of levetiracetam. This variation might be due to the duration of follow-up (our 6 months vs others' 12 months), baseline neutrophil values, and patient immune status. Levetiracetam is generally well-tolerated but may induce mild neutropenia in a subset of patients.

In agreement with our study, Uçar et al. [6] also reported modest declines in TLC, ANC, and PTT and a slight increase in platelet count, although most values remained within normal clinical ranges. These percent changes suggest a subclinical effect of levetiracetam whereas, Dilber et al. [12] noted a statistically significant rise in hemoglobin and MCV after long-term levetiracetam unlike ours. Meanwhile, Erol et al. [15] has stated no significant alterations in the ANC, Lymph and Hb after one year of levetiracetam .

Regarding the association between compliance and hematological parameters, we found that medication non-compliance was associated with lower platelet counts at both baseline and six months, but no other laboratory value differed by compliance status. Similarly, Ibrahim et al. [9] reported no significant alterations in any complete blood count parameter or coagulation index after 6 months of levetiracetam. No prior studies have explicitly linked adherence to blood counts; in fact, levetiracetam monotherapy is generally hematologically benign. In contrast, older AEDs like valproate are well known to reduce platelets, but levetiracetam has minimal effect on platelets or clotting. Thus, aside from the isolated platelet finding, our results – no significant compliance effects on Hb, WBC, ANC, lymphocytes, MCV/MCH, PT/PTT/INR – are consistent with levetiracetam's generally stable hematology profile.

In our study the neutrophil drop reached significance only among compliant patients suggesting a drug effect rather than measurement variability. Importantly, these neutropenic episodes are typically mild; levetiracetam's label does list rare cases of neutropenia but severe agranulocytosis is not well documented. This aligns with recent evidence that levetiracetam can cause mild neutropenia over time. For example, Uçar et al. [6] found significant reductions in WBC, platelet, neutrophil, and monocyte counts at 12 months of levetiracetam therapy.

Regarding the association between EEG pattern and laboratory changes, we found no significant association between EEG findings (normal vs. epileptiform, focal vs. generalized discharges) and any percent change in labs. The study by Elkholy [13] demonstrated that EEG epileptiform discharges were significantly related to clinical outcomes in epilepsy, but did not report any concomitant blood abnormalities. Consistent with that, our analysis found no evidence that interictal EEG features influence hematological parameters. On the contrary, Özkale et al. [14] has not found neither neutropenia nor

lymphopenia after one year of levetiracetam, however the CD4/CD8 ratio was lower in children with focal seizures.

Limitations of the study:

Our single‑center study included only 29 patients in each group, limiting statistical power and generalizability. We also followed them for just six months, which may not capture long‑term hematologic or coagulation changes. Moreover, levetiracetam dose variation was not assessed, limiting dose–response interpretation.

Recommendations:

We recommend clinicians to obtain baseline and periodic complete blood counts (including differential) when initiating levetiracetam in children, with special attention to absolute neutrophil count. Moreover, we encourage studies examining dose–response relationships, levetiracetam serum levels, and impact on hematology in diverse populations.

Conclusion:

After six months of levetiracetam monotherapy, the idiopathic epilepsy cohort experienced a 36 % reduction in absolute neutrophil count specifically in fully compliant children, while hemoglobin, total leukocytes, lymphocytes, platelets, MCV, MCH, pT, pTT, and INR all remained statistically unchanged compared both to baseline and to the control group. These hematologic results were not influenced by neither seizure type nor EEG pattern, disease duration, nor seizure length. Thus, reduction in ANC emerges as the sole consistent hematologic effect of levetiracetam in this pediatric idiopathic epilepsy cohort.

Conflict of Interest: There are no conflicting interests, according to the authors.

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Availability of the data: Upon reasonable request, the associated author will make the datasets created and/or examined during the current work available.

Authors contribution: In addition to writing and getting the paper ready for publication, the writers were in charge of gathering and analyzing the data. The final version was examined and approved by all authors.

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