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Evaluation of Extra and Intra Cerebral Blood Vessels by Ultrasonographic Studies in Epileptic Patients on Valproic Acid in Comparison to Patients on Levetiracetam

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ABSTRACT

Background: This study aims to evaluate the extra and intra cerebral blood vessels in epileptic patients on valproic acid versus patients on levetiracetam

Methods: One hundred participants were diagnosed with idiopathic epilepsy in accordance with ILAE standards and were categorized into Group A (VPA - 50 patients) and Group B (levetiracetam - 50 patients). A control group of 50 healthy individuals was also included. Participants underwent a comprehensive clinical assessment, Anthropometric Measurements (weight, height, BMI) , serum lipid profile, EEG, and cerebral blood vessels were evaluated through Extracranial carotid duplex sonography for Carotid Intima-Media Thickness (CIMT) measurements and Transcranial Color-Coded Duplex (TCCD).

Results: there was an increase in Body Mass Index (BMI) and weight in the VPA group, which were significantly higher in comparison to both the levetiracetam and control groups ($p \leq 0.001$). Also, VPA treatment therapy corresponded with markedly elevated triglyceride levels and significantly lower HDL levels compared to both levetiracetam and control groups ($p \leq 0.001$ and $p \leq 0.05$, respectively). CIMT measurements were significantly increased in the VPA group (0.08 ± 0.02 cm) compared to the levetiracetam (0.05 ± 0.01 cm) and control groups (0.05 ± 0.01 cm) ($p \leq 0.001$). However, TCCD parameters (PSV, EDV, MFV, and PI) showed no significant differences among the studied groups.

Conclusion: Our study points out that VPA may contribute to weight gain, increased BMI, altered lipid profiles, and increased CIMT, suggesting the need for careful clinical monitoring and cerebral blood vessel ultrasound assessment in these patients.

Keywords: *Valproic acid, levetiracetam, lipid profile, cerebral hemodynamics, Carotid Intima-Media Thickness, Transcranial Color-Coded Duplex.*

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1. INTRODUCTION

Antiseizure medications are the principal therapeutic approach used to achieve seizure control. Seizure remission is expected to reduce morbidity and the likelihood of early mortality **(1)**.

The prolonged use of antiseizure medications leads to enduring consequences, including mental diseases, metabolic disorders, endocrine abnormalities, idiosyncratic responses, and potential drug interactions in some instances (**2)**.

Valproic acid (VAP) is a comprehensive anticonvulsant used in the treatment of epilepsy. The prolonged use of valproic acid is linked to metabolic problems, including hyperinsulinemia, insulin resistance, weight gain, dyslipidemia, hyperandrogenism, and polycystic ovarian syndrome **(1)**.

VPA therapy may indicate an underlying risk factor for systemic vascular disorders, including atherosclerosis. VPA has been linked to metabolic and endocrine issues such as weight gain, hyperinsulinemia, and insulin resistance, which may elevate cardiovascular risk in individuals with epilepsy. Furthermore, it potentially affects atherothrombotic risk variables, including blood lipids, lipoprotein , uric acid levels, and homocysteine **(3)**.

Research indicates that insulin resistance may elevate atherosclerosis-related risks by directly modulating proinflammatory activity, affecting endothelial function, and facilitating macrophage recruitment (**4)**.

Levetiracetam (LEV) is a novel broad-spectrum, non-enzyme-inducing antiseizure medication characterized by good effectiveness and a high safety profile in the treatment of epilepsy. Research indicates that levetiracetam has less effect on serum lipid profile compared to old antiseizure medications, along with a reduced risk of atherosclerosis or cardiovascular incidents (**5)**.

Carotid intima-media thickness (CIMT) is a non-invasive, straightforward, and cost-effective method used for the identification of early preclinical atherosclerosis **(3)**.

Transcranial Doppler (TCD) ultrasonography assesses cerebral perfusion in patients with cerebrovascular illness by tracking changes in hemodynamic parameters. Timely identification of cerebral atherosclerotic disease may enhance the treatment approach while the condition remains asymptomatic **(6)**.

This research aims to assess the hemodynamics of extra- and intracerebral blood arteries in epileptic patients treated with valproic acid compared to those receiving levetiracetam, using ultrasonography for the early diagnosis and treatment of cerebral atherosclerosis.

2. PATIENTS AND METHODS

Study design: A case-control comparative study.

Ethical issues: - Ethical approval (No 1564) was obtained from the ethical committee of the Faculty of Medicine, Al-Azhar University. Participants were assured that all acquired data would be kept confidential. Additionally, each participant provided informed consent before participating in the study.

Participants: This research was done in two groups: a patient group that included 100 epileptic patients aged 18 to 45 years and 55 men and 45 females. They received a diagnosis of idiopathic epilepsy in accordance with the standards of the ILAE and were categorized into two categories. Group A (VPA - 50 patients) and Group B (Levetiracetam - 50 patients). Fifty people constituted the control group. Participants were chosen from the outpatient clinic of the neurology department at Al Zahraa University Hospital, and Damanhour medical national institute, the evaluation was conducted during the period between January 2024 and December 2024. at the neurosonology unit of neurology department and radiology department at Al Zahraa University Hospital.

Inclusion Criteria for patients' groups, included Patients diagnosed with idiopathic epilepsy according to the ILAE recommendations (2017), Ages 18 - 45 years old, and Patients on monotherapy valproic acid or levetiracetam for at least 6 months.

Regarding **exclusion Criteria.** Patients under 18 years or over 45 years, patients undergoing polytherapy with various antiepileptic medications, or non-compliant patients. Patients with acute or chronic illnesses can affect hormonal assessments, including metabolic syndromes, diabetes mellitus, thyroid dysfunction, cardiovascular diseases, and autoimmune disorders, as well as those who smoke or consume alcohol. Additionally, patients exhibiting atherosclerotic vascular diseases, such as cerebrovascular strokes or transient ischemic attacks, are also included.

Methodology

All subjects underwent comprehensive history taking with detailed epileptic history in addition to general and neurological examinations. Body mass index (BMI) calculation was done using the formula: BMI = Weight (Kg)/Height **(m^2) (7)**.

Electroencephalography (EEG)

A standard EEG for 30 minutes was done for all patients using a 10-20 system by a neurospectrum-5 machine (41 channel) in Russia.

Laboratory investigation

Fasting blood samples (4 mL) were collected from participants and centrifuged to isolate serum. Biochemical assays, including lipid profile (total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol), were performed using a fully automated chemistry analyzer (Cobas C 311, Roche, Germany).

Sonological investigations

Extracranial carotid duplex sonography was performed using a high-frequency linear array transducer (Samsung HS60) to measure the carotid intima-media thickness (CIMT). Patients underwent an examination in the supine position with neck extension, and a 45-degree head turn. The common carotid artery (CCA) bulb was identified, and CIMT measurements were obtained from the far wall of the CCA 1-2 cm proximal to the bulb. Measurements were taken in B-mode grayscale with a minimum resolution of 0.1 mm. The intima-media complex was identified, and the maximum thickness was measured at three locations, with the mean value reported. A CIMT value of 0.9 mm or greater was considered indicative of early atherosclerotic changes**(8).**

(figure 1&2)

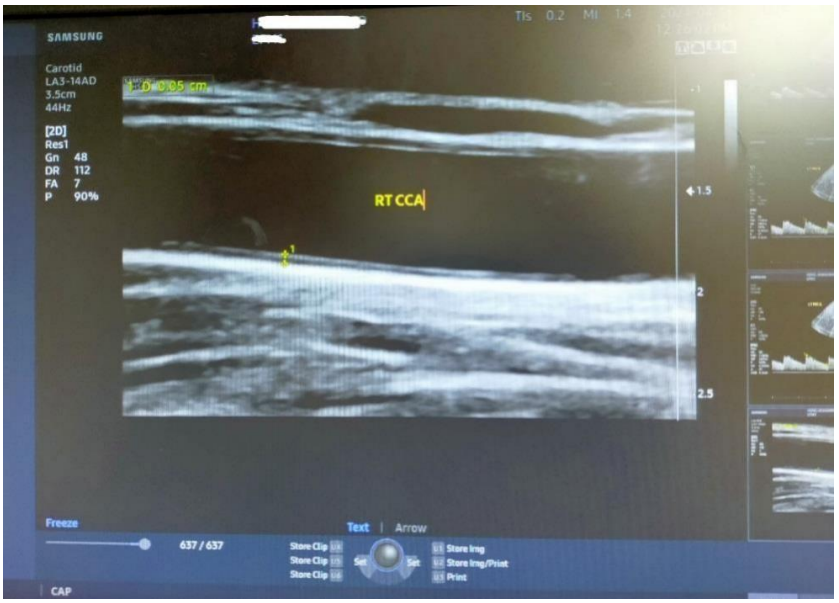


Figure (1): Carotid u/s B mode showing normal CIMT.

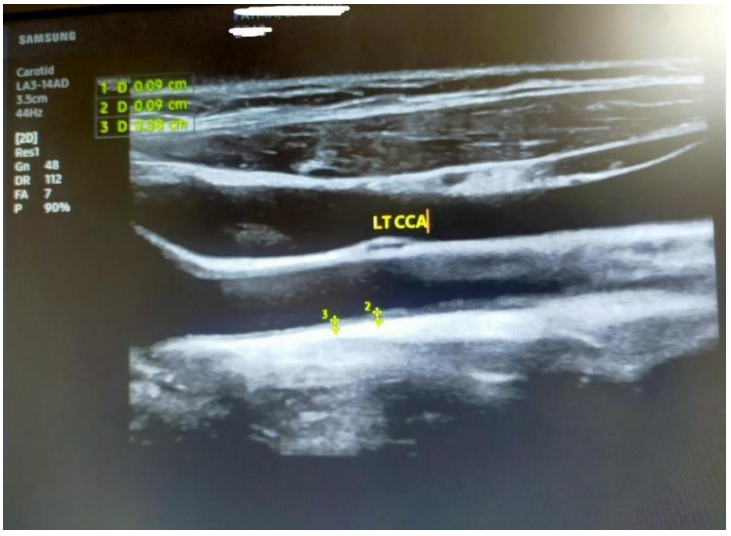


Figure (2): B Mode showing increase IMT of left CCA in epileptic patients on VA

Transcranial Color-Coded Duplex (TCCD) sonography was performed using a low-frequency phased array transducer (Samsung HS60) to assess the middle cerebral artery (MCA) through the transtemporal window. Patients were examined in the supine position, with the head maintained in a neutral position. Transcranial Doppler ultrasound was performed through the temporal window, anterior to the ear and superior to the zygomatic arch. B-mode imaging was used to localize the midbrain and the circle of Willis. Color Doppler imaging was employed to visualize and assess the direction of MCA blood flow. Peak systolic velocity (PSV), end-diastolic velocity (EDV), and pulsatility index (PI) were measured. The obtained hemodynamic parameters were interpreted according to the Baumgartner criteria (**9). (figure 3).**

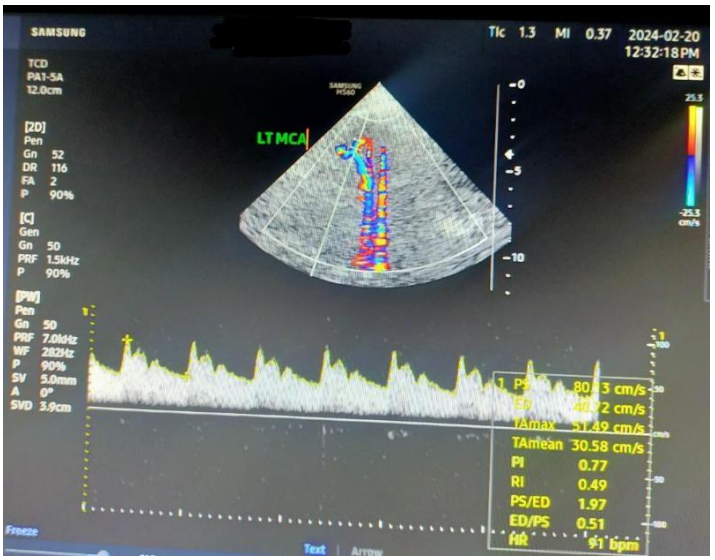


Figure (3): TCCD showing blood flow velocity of left MCA.

Statistical analysis- :

Data analysis used SPSS v20.0. Categorical data were compared with chi-square and quantitative data were analyzed using ANOVA or Kruskal-Wallis, based on normality (Shapiro-Wilk test). Correlations used Pearson's or Spearman's coefficients. Significance: $p < 0.05$; highly significant: $p \leq 0.001$.

3. RESULTS

The research had 100 epileptic patients, separated into two subgroups of 50 each: the first group received valproic acid, while the second cohort was administered levetiracetam. A control group consisting of fifty healthy volunteer individuals, matched for age and sex with the epileptic group, was established. No statistically significant difference was seen among the valproic acid group, levetiracetam group, and control group for demographic data since all groups were matched in gender and age distribution. The chosen age group of 18 to 45 years was determined to minimize the influence of other risk variables that may impact our results. In our study, the weight and Body Mass Index (BMI) in the VPA group were significantly elevated compared to the levetiracetam group and control group ($p \leq 0.001$). No significant differences in BMI or weight were observed between the levetiracetam group and the control group ($p > 0.005$).

Additionally, there was no statistically significant difference between the Valproic acid group

and the levetiracetam group concerning the type of seizure, duration of illness, and duration of treatment **(Table 1).**

Table. 1. Demographic, clinical data, and anthropometric measurements for studied groups

Parameter	Valproic Acid (n=50)	Levetiracetam (n=50)	Control (n=50)	Test of Significance	p-value
Gender (Male/Female)	28/22	25/25	26/24	χ^2=1.158	0.571
Age (years)	29.27± 6.42 (19-40)	31.70 ± 5.79 (18-43)	27.97 ± 4.52 (19-40)	F=2.709	0.072
Type of Seizure	96.7% Generalized	90% Generalized	—	χ^2=1.071, FEp=0.612	
Seizure-Free (last 3 mo.)	94.3%	91%	—	χ^2=1.021, FEp=0.663	
Duration of Illness (y)	15.17 ± 9.04 (3-37)	12.43 ± 8.87 (2-36)	—	U=362.0	0.193
Duration of TTT (y)	6.30 ± 3.17 (1-11)	5.87 ± 2.14 (2-9)	—	U=447.0	0.964
Dose (mg/day)	1400 ± 454.86 (500-2000)	2220 ± 564.5 (1000-3000)	—	U=75.50	—
Weight (kg)	77.73 ± 9.63	67.0 ± 5.86	66.40 ± 7.18	F=20.495	<0.001**
Height (m)	1.67 ± 0.08	1.68 ± 0.08	1.68 ± 0.08	F=0.099	0.906
	27.78 ± 2.25	23.74 ± 1.11	23.44 ± 0.67	F=78.499	<0.001**

F: One-way ANOVA test,χ^2**:** Chi square test **, FE:** Fisher Exact test **, U:** Mann Whitney test. **p:** p value for comparing between the three studied groups ***:** Statistically significant at $p \leq 0.05$,****:** Highly statistically significant at $p \leq 0.001$.

The VPA group showed markedly elevated triglyceride levels and significantly lower HDL levels compared to both levetiracetam and control groups ($p \leq 0.001$ and $p \leq 0.05$, respectively), without a statistically prominent difference between the levetiracetam group and the control group in serum levels of triglycerides or HDL. Meanwhile, there was no statistically significant difference between the three studied groups regarding serum levels of cholesterol or LDL ($p > 0.005$) **(Table 2)**.

Table (2): Comparison between the three studied groups according to lipid profile.

	Valproic acid (n = 50)	Levetiracetam (n = 50)	Control (n = 50)	F	p
TGs .					
Mean ± SD.	135.4 ± 37.76	94.97 ± 21.52	88.73 ± 19.46	25.477*	<0.001**
Median (IQR)	124.5 (98.0 – 175.0)	97.50 (76.0 –113.0)	86.0 (72.0 103.0)		
Sig. bet. grps.	p_1<0.001**, p_2<0.001**, p_3=0.656				
Cholesterol					

Mean ± SD. Median (IQR)	118.0 ± 36.08 108.5 (90.0 –132.0)	122.0 ± 27.80 120.0 (97.0–147.0)	108.8 ± 20.79 102.5(91.0-126.0)	1.659	0.196
HDL Mean ± SD. Median (IQR)	50.53 ± 7.14 50.0 (46.0 –56.0)	54.37 ± 4.97 54.0 (51.0 –58.0)	55.0 ± 5.55 53.50 (50.0 – 58.0)	4.936*	0.009*
Sig. bet. grps.	p_1=0.038*, p_2=0.013*,p_3=0.911				
LDL Mean ± SD. Median (IQR)	77.53 ± 12.37 77.50 (68.0 – 89.0)	76.80 ± 9.44 76.50 (71.0 – 83.0)	77.80 ± 8.56 76.0 (70.0 84.0)	0.076	0.926

F: One-way ANOVA test, pairwise comparison bet. each 2 groups were done using Post Hoc Test (Tukey) **p:** p value for comparing between the three studied groups

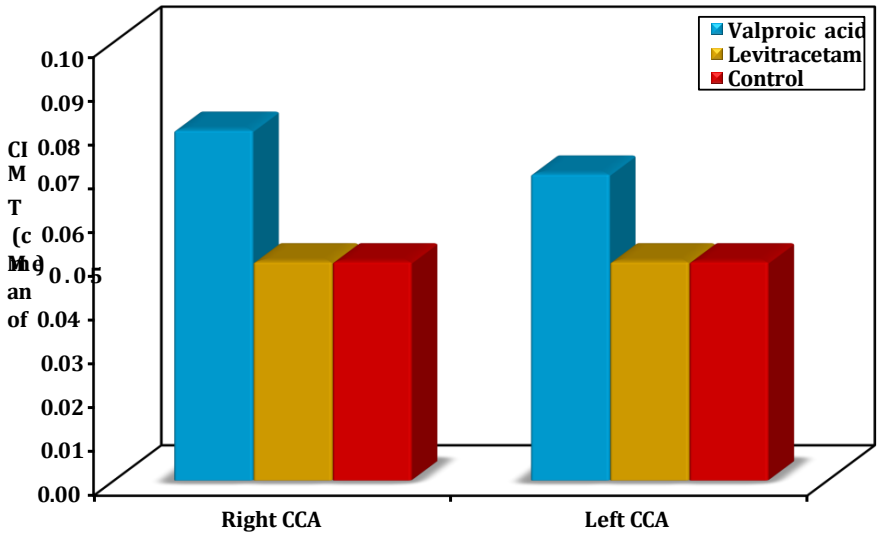
p_1: p value for comparing between valproic acid and levetiracetam

p_2: p value for comparing between valproic acid and control

p_3: p value for comparing between levetiracetam and control.

According to sonographic studies results, the VPA treatment group revealed a significant increase in CIMT of both sides of the common carotid arteries (RT 0.08 ± 0.02, LT 0.07 ± 0.02) compared t (RT 0.05 ± 0.01, LT 0.04 ± 0.02) o both levetiracetam group (RT 0.05 ± 0.01, LT 0.04 ± 0.02) and control group (RT 0.05 ± 0.01, LT 0.05 ± 0.01) ($p \leq 0.001$). No significant differences in CIMT were found between the levetiracetam and control groups ($p > 0.005$ **(Figure 4).**

Figure (4): Comparison between the three studied groups according to CIM



Concerning the TCCD characteristics of the middle cerebral artery (MCA), our investigation revealed no statistically significant differences among the three examined groups for the TCCD parameters (PSV, EDV, MFV, and PI) of the MCA **(Table 3)**.

Table (3): Comparison between the three studied groups according to TCCD parameters of middle cerebral artery (MCA).

		Valproic acid (n = 50)	Levetiracetam (n = 50)	Control (n = 50)	F	p
PSV	**Right MCA** Min. – Max. Mean ± SD. Median (IQR)	63.70 – 105.1 84.12 ± 9.27 81.70 (78.0 – 92.0)	65.80 – 95.60 79.41 ± 7.72 78.10 (74.90 – 86.70)	59.80 – 95.50 80.02 ± 10.82 80.40 (69.70 – 90.80)	2.249	0.112
	Left MCA Min. –Max. Mean ± SD. Median (IQR)	68.90 – 98.60 83.74 ± 7.56 82.50 (78.60 – 88.60)	69.40 – 89.00 79.80 ± 5.45 80.05 (75.40 – 83.60)	60.60 – 94.30 80.69 ± 9.48 81.00 (76.40 – 87.70)	2.178	0.119
ED	**Right MCA** Min. – Max. Mean ± SD. Median (IQR)	28.50 – 47.50 37.46 ± 5.86 38.50 (32.50 – 42.40)	32.40 – 50.00 40.25 ± 4.92 40.00 (36.10 – 44.30)	29.30 – 49.60 38.30 ± 5.70 38.10 (33.90 – 41.60)	2.022	0.139
	Left MCA Min. –Max. Mean ± SD. Median (IQR)	29.20 – 48.70 38.27 ± 5.54 37.15 (34.70 – 43.40)	32.30 – 48.70 40.56 ± 3.87 40.15 (38.0 – 43.0)	27.60 – 49.70 38.08 ± 5.51 37.35 (34.50 – 42.20)	2.245	0.112
MF	**Right MCA** Min. – Max. Mean ± SD. Median (IQR)	40.20 – 64.80 54.47 ± 5.91 54.35 (51.40 – 58.0)	43.90 – 62.50 51.64 ± 5.99 51.50 (45.50 – 55.90)	40.20 – 61.10 52.18 ± 6.15 52.75 (46.10 – 57.50)	1.870	0.160
	Left MCA Min.-Max. Mean ± SD. Median (IQR)	42.40 – 61.20 53.18 ± 4.24 52.70 (50.20 – 55.30)	44.70 – 61.90 50.67 ± 4.09 49.40 (48.0 – 53.80)	38.30 – 62.40 50.89 ± 6.60 50.20(45.20 – 55.10)	2.220	0.115
PI	**Right MCA** Min. – Max. Mean ± SD. Median (IQR)	0.60 – 1.20 0.81 ± 0.18 0.75 (0.70 – 1.0)	0.60 – 0.90 0.74 ± 0.08 0.70 (0.70 – 0.80)	0.60 – 0.90 0.75 ± 0.12 0.75 (0.60 – 0.90)	2.687	0.074
	Left MCA Min. –Max. Mean ± SD.	0.70 – 1.30 0.79 ± 0.12	0.60 – 0.90 0.73 ± 0.08	0.60 – 0.90 0.74 ± 0.11	2.564	0.083

		Valproic acid (n = 50)	**Levetiracetam (n = 50)**	**Control (n = 50)**	**F**	**p**
	Median (IQR)	0.80 (0.70 – 0.80)	0.70 (0.70 – 0.80)	0.75 (0.60 – 0.80)		

Notably, BMI showed a strong positive correlation with duration of illness (r=0.629, p<0.001), dose of valproic acid (r=0.553, p<0.005), and duration of VPA treatment (r=0,444, p<0.005). However, there was no statistically significant correlation in the valproic acid group between BMI and PSV, EDV, MFV, and PI of MCA (p > 0.005) **(Table 4).**

Table 4 Correlation between BMI and different parameters in Valproic acid group

	BMI (kg/m2)	
	R	**p**
Duration of illness (y)	0.629	<0.001**
Duration of TTT (y)	0.444	0.014*
Dose (mg/d)	0.553	0.002*
PSV		
Right MCA	0.162	0.391
Left MCA (no)	0.169	0.371
EDV		
Right MCA	-0.051	0.790
Left MCA	-0.227	0.228
MFV		
Right MCA	-0.069	0.718
Left MCA	0.176	0.353
PI		
Right MCA	0.008	0.968
Left MCA	0.159	0.402

r: Pearson coefficient **: Highly statistically significant at $p \leq 0.001$, *: Statistically significant at $p \leq 0.05$.

As regards CIMT correlation data, there was a statistically significant positive correlation in the valproic acid group between CIMT on both right and left sides and duration of illness, duration of treatment, VPA dose, BMI, and triglyceride ($p \leq 0.005$), and statistically significant negative correlation with HDL ($p \leq 0.005$). There was no statistically significant correlation between CIMT on both the right and left sides and cholesterol, LDL, and TCCD parameters (PSV, EDV, MFV, and PI) of MCA (p > 0.005) **(Table 5).**

Table 5: Correlation between CIMT and different parameters in Valproic acid group.

	CIMT			
	Right		**Left**	
	r	**P**	**r**	**p**
Duration of illness (y)	0.475	0.008*	0.625	<0.001**
Duration of TTT (y)	0.514	0.004*	0.508	0.004
Dose (mg/dL)	0.536	0.002*	0.476	0.008*

BMI (kg/m^2)	0.608	<0.001**	0.703	<0.001**
TGs	0.676	<0.001**	0.578	0.001**
Cholesterol	-0.179	0.344	-0.039	0.839
HDL	-0.698	<0.001**	-0.685	<0.001**
LDL	0.075	0.695	0.134	0.482
PSV	0.158	0.405	0.130	0.492
EDV	-0.071	0.711	-0.229	0.223
MFV	-0.147	0.437	0.096	0.613
PI	0.245	0.192	0.164	0.386

r: Pearson coefficient; *: Statistically significant at $p \leq 0.05$. **: Highly statistically significant at $p \leq 0.001$

4. DISCUSSION

Due to the fact that they have a wide range of action, valproic acid, and levetiracetam are the medications of choice for treating a wide range of epileptic seizures and syndromes ***(10)***.

Hyperinsulinemia, insulin resistance, weight gain, and dyslipidemia are some of the metabolic diseases that have been linked to the usage of valproic acid over an extended time. There have been several studies that have shown that valproic acid medication may cause weight gain, which is a frequent side effect that can occur in as many as 71% of patients **(11)**.

The pancreatic islet cells' insulin production is modulated by valproate, which results in an increase in appetite and the capacity to store energy. Those individuals who are receiving valproate medication for long time may have weight gain as a consequence of this. Similarly, it has the potential to raise the levels of leptin in the serum, perhaps leading to a change in the lipid profile **(12)**.

The illness known as atherosclerosis is classified as a chronic inflammatory condition. It starts at a young age and builds up gradually throughout one's lifetime. In order to undertake early aggressive vascular prophylaxis, it is necessary to identify people who have subclinical atherosclerosis **(13)**.

Atherosclerosis of the carotid artery is a significant and possibly avoidable cause of cerebral ischemia events. It is responsible for 15–20% of all ischemic strokes. Intima-media thickness of the carotid artery (CIMT) is a marker that may be identified at an early stage and is thus regarded to be a significant indicator of future severe atherosclerosis **(14)**.

When it comes to the primary or secondary prevention of cerebrovascular stroke, intracranial atherosclerotic disease (ICAD) continues to be a concern. There is a significant lack of knowledge on the pathophysiological changes that occur throughout the progression of ICAD from its asymptomatic beginnings **(15)**.

The purpose of this research was to compare the hemodynamics of intra and extra-cerebral blood vessels in patients who were treated with VPA to those of individuals who were treated with LEV.

. The 100 epileptic patients who participated in our study were divided into two groups, the first group was on valproic acid and the second group was on levetiracetam. As an alternative, there was a control group that consisted of fifty healthy volunteer participants whose ages and genders were matched with those of the individual patients.

The selection of age group range that was selected as the young adult population was between the ages of 18 and 45 years. This age group was selected in order to reduce the impact of other risk variables that may potentially have an impact on our findings.

Our study demonstrated that patients treated with VPA exhibited significantly higher BMI in comparison to levetiracetam and control groups ($p \leq 0.001$). Our findings align with previous research by ***Dimitrijević et al. (2021) and Drokov et al. (2020***), which indicated that VPA therapy could lead to significant weight gain and metabolic disturbances in both adult and pediatric populations **(16) (17).**

On the other hand, it was established by ***Espinosa et al. (2008)*** that the beginning of VPA treatment before the age of 12 years was not connected with an increase in weight **(18)**. Additionally, in the research conducted by ***ElKhayat et al. (2004)***, it was shown that females who were given VPA at various phases of puberty saw considerable weight gain. However, this was only noticed in those who were in the post-pubertal stage **(19)**.

The fact that these trials were conducted on children who had limited sex hormones, which may have a role in weight gain in adults, as well as the difference in the gender that was selected, the difference in the length of therapy, and the difference in follow up, may all be discussed as possible explanations for this phenomenon.

Our study demonstrated that VPA treatment was associated with significantly elevated serum triglyceride levels and decreased HDL levels compared to both levetiracetam and control groups. This is consistent with previous research by ***Sidhu et al. (2017***), who found that VPA monotherapy was linked to unfavorable lipid profiles, including decreased HDL and increased triglyceride levels ***(11)***. Similarly, ***Zuberi et al. (2017***) found that VPA treatment in epileptic patients was associated with increased triglyceride, cholesterol, and LDL levels, as well as decreased HDL levels, compared to lamotrigine and control groups **(20)**. However, our results disagree with those of ***Nisha et al. (2018),*** who found no significant differences in triglyceride and HDL levels between newly diagnosed untreated epileptic patients and those treated with VPA for over 12 months **(2).**

There has not been a complete understanding of the connection that exists between valproic acid and alterations in lipid profiles. Valproic acid may exert its influence on lipid profiles via a variety of very complicated processes. The differences in ethnicity, age, gender, and technique of each research, as well as the likelihood of a genetic predisposition to dyslipidemia, are the factors that explain the disagreement that exists across the studies.

The carotid intima-media thickness (CIMT) method is not only simple and inexpensive but also non-invasive. Due to the fact that an increased CIMT is one of the earliest detectable symptoms of subclinical atherosclerosis, this ultrasonographic approach is an essential for diagnosing preclinical atherosclerosis **(21)**.

The results of our work revealed that the CIMT was higher in the group that received valproic acid as compared to the groups that received levetiracetam and the control group ($p < 0.001$). No statistically significant difference was seen between the group that received levetiracetam and the group that served as the control.

Our results were in agreement with ***(Chuang et al., 2012) and*** (***Mehrpour et al., 2014.*** They found that long-term monotherapy with older-generation AEDs, including CBZ, PHT, and VPA, caused significantly increased common carotid artery (CCA) intima-media thickness in patients with epilepsy compared to the control group and concluded that patients with epilepsy on either enzyme-inducing AED or valproic acid are at higher risk for development of atherosclerosis ***(22)(23).***

Karatoprak and Tosun (2020) also found increased CIMT in epileptic patients on VPA or levetiracetam monotherapy compared to controls **(3).** However, they did not observe significant differences in CIMT between the VPA and levetiracetam groups, suggesting that both drugs may contribute to increased subclinical atherosclerosis risk, with VPA potentially exerting a stronger effect.

According ***to Tokgoz et al. (2012)***, who established that there was no increase in the risk for early atherosclerosis determined by CIMT in children with epilepsy who were treated with VPA **(24)**, our findings regarding CIMT are in disagreement with their findings.

In reviewing published papers and studies till the time of writing of this study, the relationship between valproic acid-influenced insulin resistance and intracranial atherosclerotic burden in young adult epileptic patients has not been studied before.

As far as the TCCD parameters of the middle cerebral artery (MCA) are concerned, our research revealed that there was no statistically significant difference between the three groups that were investigated in terms of the TCCD parameters (PSV, EDV, MFV, and PI) of the MCA.

Our outcomes agreed with ***(Wang et al., 2021),*** who concluded that elevated triglyceride glucose index was significantly associated with a higher risk of extracranial artery stenosis but not with intra-cranial artery stenosis in Chinese adults ***(25).***

As regards CIMT correlation data, there was a statistically significant positive correlation in the valproic acid group between CIMT on both right and left sides and duration of illness, duration of treatment, dose, BMI, triglyceride, and statistically significant negative correlation with HDL.

According to the findings of ***Lai et al. (2017)***, who recorded that the use of CBZ and VPA was seen to exhibit substantial impacts on CCA-IMT, our results indicated that this occurred. It was also noted that the CCA IMT was discovered to have positive correlation with the length of time that AED treatment was administered. Neurologists and epileptologists who prescribe antiepileptic drugs (AEDs) should be aware of the possible adverse effects of these medications, particularly in patients who are at a high risk of experiencing vascular events, according to the results ***(26).***

Additionally, our findings were in accordance with the findings of **Luo et al. (2015)**, who indicated that the length of disease and the duration of the VPA treatment were positively correlation with the average CA-IMT. The average CA-IMT of epileptic patients who had a disease course that lasted for more than three years was significantly greater than the CA-IMT of epileptic patients who had a disease duration of three years or less ***(27).***

5. CONCLUSION

High-resolution B-mode ultrasonography assessment of CIMT is used as an early predictor of subclinical atherosclerosis. The length of therapy, the dosage, and the abnormal laboratory results were all positively connected with the rise in CIMT that was noticed in epileptic patients who had valproic acid administered to them. It has been shown via TCCD research that the parameters of the middle cerebral artery do not exhibit any discernible changes that might aid in the early diagnosis of subclinical atherosclerosis or early vascular alterations, particularly in young persons. On the other hand, the results of the treatment of epileptic patients with levetiracetam did not show any significant abnormalities in terms of weight gain, lipid profile, or ultrasonographic parameters. These results suggest that levetiracetam may not play any role in the insulin resistance or atherosclerotic process in young adult epileptic patients.

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