**Scholars Journal of Applied Medical Sciences**
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

**Medicine**

# Biochemical Side Effect of Antiepileptic Drugs on Liver Enzymes, Lipid Profile and Haematological Profile in Epileptic Pediatric Patients

Fadwah Altayf Amhimmid[1*], Fawzia S. Khalifa Alfazzani[1], Salima M. M. Alzehawi[1], Salimah S. Alabeedi[1], Waraeda Saad Bashoon[1], Salah Abdusalam Alhasi[1]

[1]Faculty of Medicine, Benghazi Universty, Libya

**DOI:** https://doi.org/10.36347/sjams.2024.v12i08.005 | **Received:** 04.07.2024 | **Accepted:** 09.08.2024 | **Published:** 13.08.2024

***Corresponding author:** Fadwah Altayf Amhimmid
Faculty of Medicine, Benghazi Universty, Libya

**Abstract** **Original Research Article**

Antiepileptic drugs are large group of medications with variable mechanisms of action. There are various effects have been reported with long-term antiepileptic therapy. To assess the effects of the antiepileptic drugs on blood indices, liver function and lipid enzymes in epileptic pediatric age group. A comparative case-control study was performed in which 50 epilepsy cases were matched with 50 controls for age and sex. The mean age of the cases was 9.1(± 3.7) years, 86% from Benghazi. The 68% were primarily generalized seizure, 64% tonic clonic convulsion. The age at diagnosis between 2 months - 13 years. The 74% used Na-valproate as a single or a combined therapy and Carbamazepine was prescribed as a single medication in 18%. No statistical significant differences in the means of CBC indices and liver function profiles (AST and ALT) in the treatment groups compared to the control. Alkaline phosphatise was highly significant difference in the mean between the two groups (P=0.007). Mean of serum Cholesterol level showed higher in the cases than controls with highly statistical significant difference (P<0.001). HDL mean level is higher for cases on carbamazepine and Na-valproate group compared to controls with statistical significant difference (P=0.011). Cases on carbamazepine and Na-valproate group as well showed higher mean LDL level compared to the controls with statistically significant (P=0.006). No any statistical significant difference in means of CBC indices between epileptic patient treated with AED and control. Carbamazepine group expressed higher mean HDL level as compared to Na-valproate group, this difference is highly significant. Key words: Antiepileptic drugs, liver enzymes, lipid profiles.
**Keywords**: Pediatric, antiepileptic drugs, antiepileptic therapy, Alkaline phosphatise.

**Copyright © 2024 The Author(s):** This is an open-access article distributed under the terms of the Creative Commons Attribution **4.0 International License (CC BY-NC 4.0)** which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

## INTRODUCTION

Epilepsy is a neurological disease common in childhood and characterized by aperiodic and unpredictable seizure occurrence and requires long-term treatment. Their frequency is highly variable, which necessitated an effective treatment with good control [1]. As per WHO, epilepsy is one of the most common serious brain disorder disturbs the family and the society and estimates that 8 / 1000 population worldwide have epilepsy with higher prevalence in developing countries [2]. In 2014 the ILAE the practical clinical definition of epilepsy [2], by:

1. At least two unprovoked seizure occurring > 24 hours apart
2. One unprovoked seizure and a probability of further seizures similar to the general recurrence risk

The ILAE classification seizures into 4 groups based on clinical and EEG data: focal, generalized, unclassified and unknown (e g. epileptic spasms) [3].

A. Diagnosis: based on the identification of recurrent seizures., recognize during:

1. Dysmorphic feature and cutaneous abnormalities [4].
2. CBC, liver and thyroid function tests, blood glucose, LP [2].
3. EEG-differentiating between partial and generalized seizure) [5].
4. CT and MRI [2].

**B. AEDs action:**

(i) reducing cell membranes electrical excitability; (ii) enhancing GABA inhibition; (iii) inhibiting T-type calcium channels [6].

In pediartic epilepsy still lack of knowledge and understanding long-term effects of AEDs on growth and development, liver functions, lipid metabolism and

blood profile [7, 8]. There are > 900 drugs are known to be hepatotoxic [9, 10], Clinicians should be aware of the different therapeutic options available for patients with liver disease and recognize the hepatotoxic of different AEDs [10], in patients undergoing liver transplantation between 1990 and 2002, AEDs were the third most common cause [11], AEDs commonly cause asymptomatic or transient enzyme elevations, upto 75% to 95% of patients exposed to carbamazepine and phenobarbital [12]. The mechanism of hepatic injury is heterogeneous. Hypersensitivity in 70% of the individuals related to phenytoin, only 30% associated with carbamazepine [13, 14]. Valproic acid is the third common cause reported by the WHO [15] mild to severe hepatotoxicity, other side effects on gastrointestinal, vision hormonal hair loss [16], rare ray syndrome can be happened [17]. The risk factors: younger age and polytherapy, febrile illness, and status epileptics [18]. Pre-treatment testing for POLG mutations may be useful in some children with refractory seizures and developmental regression [19-22].

The majority of cases are associated with hypersensitivity reactions [23-26]. Fever in 75% of these patients, rash in 62%, eosinophilia in 89%. The mortality rate is 13 % with multiple AEDs and about 25% with hepatotoxicity [27, 28]. Severe hepatotoxicity is not dose dependent in the first 12 months of therapy. The hepatic death appears higher in children when exposed to multiple AEDs [28]. The 61 Liver biopsies show inflammatory reactions, cholestasis, or hepatic necrosis in lethal cases [25]. Granulomatous hepatitis and ductopenia other liver injury. A rare condition, loss of small bile ducts and jaundice, associated with valproic acid and lamotrigine [29, 30]. Oxcarbazepine is a newer-generation sodium channel blocker. Hepatotoxicity is rare if cases exposure to another AED [31, 32]. Phenobarbital produce elevation in liver enzymes, hypersensitivity reactions, hepatitis, and acute liver failure [33-36]. Topiramate can produce hyperammonemia when combined with valproic acid, severe hepatotoxicity with carbamazepine [37]. Lamotrigine can produce liver toxicity in status epilepticus and poly therapy, reversible on discontinuation [38]. All AEDs significantly impaired lipid and hematological profile of the epileptics. Platelet count was significantly reduced in epileptics treated with carbamazepine, phenytoin, and valproate as compared to newer AEDs combination therapy [39]. Leucopenia in phenytoin and carbamazepine treated monotherapy group patients. Hepatotoxic, decreased hemoglobin, RBC and WBC counts after long term AEDs, some AEDs do not have any effect [26]. Some of the AEDs diphenylhydantoin, sodium valproate and CBZ are implicated in pure (RBC) aplasia [40]. Fever, transient skin rash, eosinophilia and lymphadenopathy associated with carbamazepine and phenytoin [40]. Several studies reported, common AEDs increase serum HDL-C levels, some researchers observed, newer AEDs has no influence.

## II. OBJECTIVE

Study was conducted on a sample of epileptic patients of pediartic age group attending the neurology clinic at Benghazi children hospital to assess and evaluate the effects of antiepileptic drugs on: Liver enzymes and Haematological, Lipid profiles.

## III. MATERIALS AND METHODS

***WAS THE CASE CONTROL STUDY***

***Cases:*** 50 patients with epilepsy on regular AEDs as Na-valproate (37 patients) and Carbamazepine (13 patients) for at least one year, they are registered and on regular follow up to the Neurology Clinic.

***Controls*****:** 50 children from other clinics such as nutrition and GIT clinics at Benghazi Children Hospital, from March 2018 to December 2019.

## IV. RESULTS

**= *Distribution according to age groups*:**

The (Table 1) showed that, for young age group (0-5 years) the cases were double frequency of control (6 controls: 12 cases) and only one case above 15 years, For the cases, age ranged 2 -15 year with mean 9.1(± 3.7) years. Compared to the control, age ranged 4 -14 years with mean was 9.7 (±2.7) years. The mean age of cases and controls groups does not show statistical significant difference (P = 0.357).

**Table 1: Distribution of cases and controls according to socio-demographic characteristics**

| Characteristics | Subgroups | Cases Control 50 50 | | | |
|---|---|---|---|---|---|
| | | No | % | No | % |
| **Age / year** | >1 – 5 yrs | 12 | 24 | 6 | 12 |
| | >5 – 10 | 24 | 40 | 23 | 46 |
| | >10 | 18 | 36 | 21 | 42 |
| **Gender** | Male | 33 | 66 | 40 | 80 |
| | Female | 17 | 34 | 10 | 20 |

**= *Distribution according to gender cases and controls:***

The 66% of the cases were male compared to 80% of controls, this not statistically significant (P = 0.177).

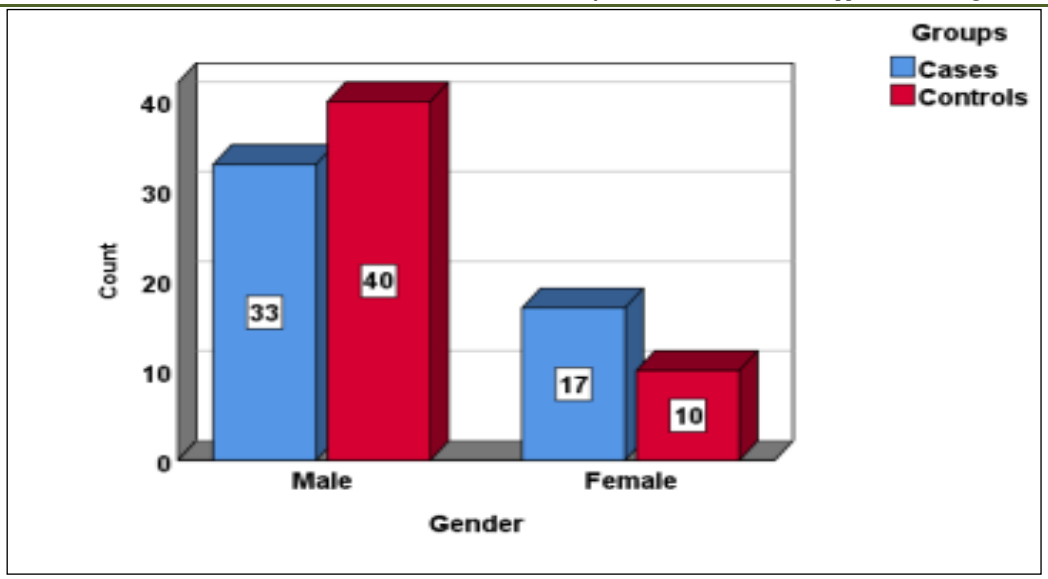


**Figure 1: Gender distribution of the cases with matched controls**

**= *Distribution according to epilepsy type in the cases*:**

Showed that, 68% (34/50) were primarily generalized seizure, 64% (32 case of them) tonic clonic convulsion. The 32% is focal partial seizure, 26% were simple partial seizure.

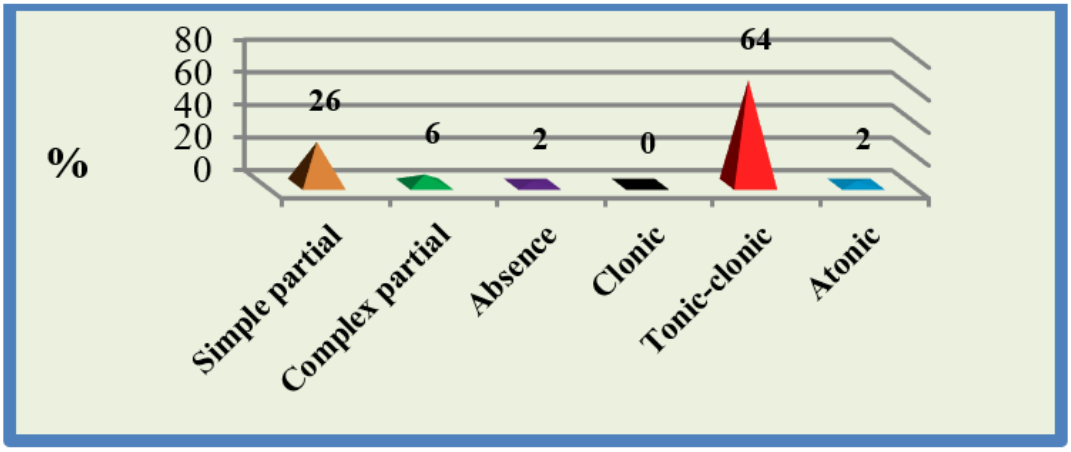


**Figure 2: Distribution according to epilepsy type in the cases**

**= *Distribution according to age at the time of diagnosis of epilepsy:***

Ranged 2 months - 13 years, The 64% at 1-5 years, while 22% were at 6-10 years,

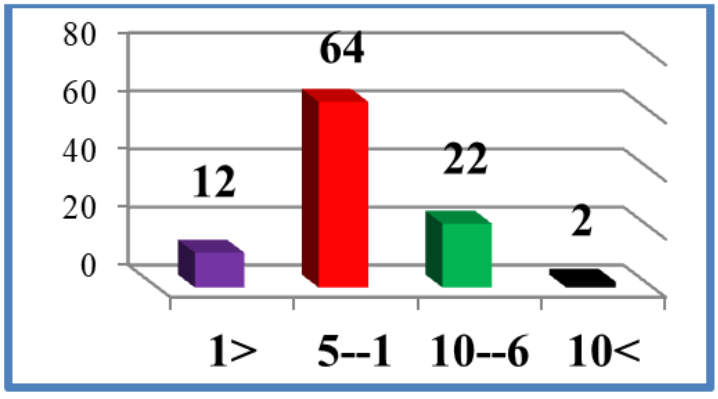


**Figure 3: Distribution according to age at the time of diagnosis**

***= Distribution according to epilepsy Control of the cases:***

Showed in (Figure 4).

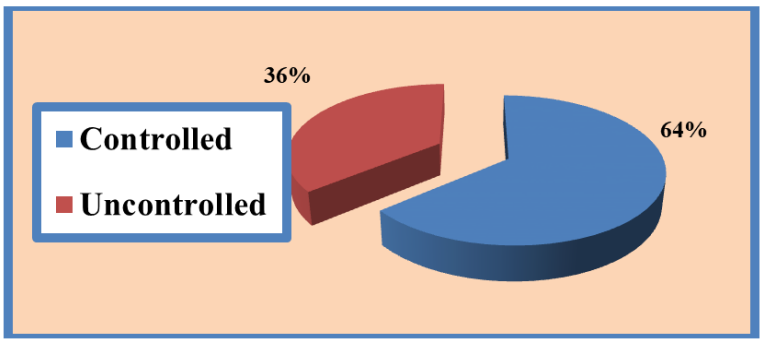


**Figure 4: Distribution according to epilepsy Control**

***= Distribution according to EEG finding*:**

The 66% showed generalized discharge,

**Table 2: Distribution according to EEG finding**

| EEG mode of Discharge | Frequency | % |
|---|---|---|
| **Generalized discharge** | **33** | **66.0** |
| **Centro-temporal discharge** | **11** | **22.0** |
| **Centro-parietal discharge** | **5** | **10.0** |
| **Others** | **1** | **2.0** |
| **Total** | **50** | **100** |

***= Distribution according to Type of AEDs*:**

The 74% of cases used Na-valproate either as a single or with Carbamazepine and 26% of the cases used carbamazepine as single or combined.

**Table 4: Type of antiepileptic age n**

| AEDs | No | % |
|---|---|---|
| Carbamazepine | 13 | 26 |
| Na-Valproate | 37 | 74 |
| Total | 50 | 10 |

**Haematological profile for cases compared to controls:**

The cases according to AEDs type …carbamazepine (13) or Na-Valproate (37) to assess the difference between cases and control group. In general no statistical significance difference between cases and controls (Table 5).

Mean haemoglobin for controls, cases on carbamazepine (P= 0.68), and Na-Valproate cases (P=0.84).

Red blood cell count for controls carbamazepine (P= 0.3), and Na-Valproate cases (P= 0.5).

Mean White blood cell count (WBC) for controls, carbamazepine cases (P= 0.6), and Na-Valproate cases (P= 0.4).

Platelets count for controls, carbamazepine (P=0.51), and for Na-Valproate group B (P=0.29).

**Table 5: Haematological profile for treatment groups compared to controls**

| Test variable | Pairs of comparison | Mean | Std. Deviation | P .value |
|---|---|---|---|---|
| **AST** | Carbamazepine | 18.35 | 7.25 | 0.34 |
| | Controls | 19.32 | 6.92 | |
| **AST** | Valproate | 25.71 | 13.1 | 0.018* |
| | Controls | 19.32 | 1.92 | |
| **ALT** | Carbamazepine | 17.43 | 6.2 | 0.76 |
| | Controls | 16.5 | 7.3 | |
| **ALT** | Valproate | 18.42 | 12.6 | 0.5 |
| | Controls | 16.5 | 7.3 | |
| **ALK.Ph** | Carbamazepine | 341.1 | 142.9 | 0.04* |
| | Controls | 228.0 | 57.2 | |
| **ALK.Ph** | Valproate | 236.74 | 95.9 | 0.9 |
| | Controls | 228.0 | 57.2 | |
| **Bilirubin** | Carbamazepin | 0.29 | 0.1 | 0.8 |
| | Controls | 0.28 | 0.14 | |
| **Bilirubin** | Valoproate | 0.34 | 0.16 | 0.02* |
| | Controls | 0.28 | 0.14 | |

**= Liver Function profiles of treatment groups compared to controls**:

(The AST mean for controls close to carbamazepine group (P=0.34), Na-Valproate group have significantly higher (P=0.018). Alkaline phosphates mean in carbamazepine group, compared to control (P=0.04), while no significant difference between controls and Na-Valproate group (P=0.5). Total Bilirubin mean significant higher than controls in Na-Valproate group (P=0.02) (Table 6).

**Table 6: Liver Function profiles of treatment groups compared to controls (50)**

| Test variable | Pairs of comparison | Mean | Std. Deviation | P .value |
|---|---|---|---|---|
| Hb | Carbamazepin | 12.44 | 0.96 | 0.68 |
| | Controls | 11.8 | 0.99 | |
| Hb | Valoproate | 12 | 1.49 | 0.84 |
| | Controls | 11.8 | 0.99 | |
| RBCs | Carbamazepin | 4.57 | 0.38 | 0.3 |
| | Controls | 4.55 | 0.5 | |
| RBCs | Valoproate | 4.62 | 1.2 | 0.5 |
| | Controls | 4.55 | 0.5 | |
| WBC | Carbamazepin | 7.3 | 2.1 | 0.6 |
| | Controls | 8.1 | 2.97 | |
| WBC | Valoproate | 8.32 | 2.57 | 0.4 |
| | Controls | 8.1 | 2.97 | |
| HTC | Carbamazepin | 35.49 | 3.10 | 0.62 |
| | Controls | 34.13 | 2.99 | |
| HTC | Valoproate | 33.7 | 4.27 | 0.56 |
| | Controls | 34.13 | 2.99 | |
| PLTs | Carbamazepin | 258.62 | 64.04 | 0.51 |
| | Controls | 266.92 | 75.75 | |
| PLTs | Valoproate | 259.62 | 74.3 | 0.29 |
| | Controls | 266.92 | 75.75 | |

**= Lipid profile of treatment groups compared to controls (Table 7):**

Serum Cholesterol mean for controls was significantly lower than both cases groups: on carbamazepine was (P= 0.008), and for Na-Valproate group (P=0.01). HDL mean level is higher for cases on carbamazepine as compared to controls with statistical significant difference (P=0.03), for Na-Valproate compared to controls with P=0.06. Mean LDL level is significantly higher on carbamazepine than controls P.value = 0.009, similarly for Na-Valproate compared to controls (P=0.004). Triglyceride mean level higher for cases on carbamazepine and Na-Valproate groups than controls but no statistical significance (P= 0.055, and 0.75 respectively).

**Table 7: Lipid profile of treatment groups compared to controls (50)**

| Test variable | Pairs of comparison | Mean | Std. Deviation | P .value |
|---|---|---|---|---|
| **Cholesterol** | Carbamazepine | 160.38 | 40.76 | 0.008** |
| | Controls | 103.23 | 26.25 | |
| **Cholesterol** | Valproate | 130.86 | 40.04 | 0.01* |
| | Controls | 103.23 | 26.25 | |
| **HDL** | Carbamazepine | 72.4 | 35.8 | 0.03* |
| | Controls | 40.6 | 10.8 | |
| **HDL** | Valproate | 48.7 | 14.4 | 0.06* |
| | Controls | 40.6 | 10.8 | |
| **LDL** | Carbamazepine | 78.6 | 27.93 | 0.009** |
| | Controls | 58.1 | 28.41 | |
| **LDL** | Valproate | 75.05 | 24.31 | 0.04* |
| | Controls | 58.1 | 28.41 | |
| **TG** | Carbamazepine | 102.12 | 43.52 | 0.55 |
| | Controls | 88.73 | 16.35 | |
| **TG** | Valproate | 93.67 | 30.95 | 0.75 |
| | Controls | 88.73 | 16.35 | |

**= Comparison in mean values of significant investigations between two main treatment groups of epileptic cases**:

The results showed that Na-valproate group have significant higher mean serum bilirubin (0.34) than carbamazepine group (0.3). while carbamazepine group have much higher mean HDL level (72.4) as compared to Na-valproate group (48.7), this difference is highly significant (P=0.00). Other parameters which were higher in cases compared to controls showed no significant difference across the two treatment groups (Table 8).

**Table 8**

| Lab investigation | Carbamazepine group (13) | Na-valproate group (37) | P. value |
|---|---|---|---|
| **Alkaline phosphatase** | 319.5 | 248.5 | 0.76 |
| **Bilirubin** | 0.3 | 0.34 | 0.04* |
| **Cholesterol** | 160.4 | 130.9 | 0.4 |
| **HDL** | 72.4 | 48.7 | 0.00** |
| **LDL** | 78.6 | 75.1 | 0.5 |

## V. DISCUSSION

Antiepileptic medications are used for the prevention and treatment of seizures, these medications have adverse drug reactions due to their complex pharmacological properties and narrow therapeutic index. Most clinicians would starting after a cluster of seizures or an unprovoked status epileptics [1].

When prescribing for infants and young children the selection of the most appropriate AED and account the safety profile of that drug with paucity of knowledge about long-term effects on growth and development, short-term effects on behaviour and patterns of sleep. Although the newer AEDs appear more safety. The present study showed that Na-valproate was the most common AEDs used, in 74% of the sample either as a single or combined with carbamazepine (CBZ) in 8%. (CBZ) was prescribed to 26% of the cases.

Also, AEDs have no statistical significance difference in means of CBC indices was found between cases and controls groups. However, some studied deduced a contradictory results, (CBZ) causes Pure Red Cell Aplasia (PRCA). Because of antibodies against erythroid precursor cells or erythropoietin, or T-cell mediated suppression of erythropoiesis. Further aplastic anaemia, leukopenia and thrombocytopenia are adverse effects of valproic acid therapy cited in the literature (69,70). A case report study published in 2017, described of sodium valproate induced PRCA in a 7 years old male child with Absence Seizure.

In a prospective study over one and half year duration on 142 patients < 12 years of age (72) microcytic anemia in one patient was on phenytoin. leucocytosis in another patient on VPA therapy, by the physician like stopping the drug in 8 cases, withholding in 6 cases, decreasing the dose in 4 cases and continuing the same dose in 50 cases.

This study showed that Na-valproate have higher mean serum bilirubin (0.34) than (CBZ) groups (0.3), although is statistically significant, but has no clinical relevance. Also revealed (CBZ) have higher mean HDL level (72.4) compared to Na-valproate groups (48.7), with significant difference (P=0.00). Other parameters showed no significant difference across the two treatment groups.

One study reported that AEDs responsible for 11% of overall ADRs. (lorazepam (3%) and valproate (3%) were associated most commonly with ADRs) (106). And an Indian hospital study, AEDs were responsible for 5% of ADRs among all of the prescribed drugs as (CBZ) and phenytoin.

A case control study was at Indian included (28 cases and 28 controls) to evaluate (CBZ) effect on serum lipids and liver function tests. Found that blood level of TC, LDL-C, HDL-C and alkaline phosphatise were increased (108), with significant increase in serum alkaline phosphatase in cases (P <0.03) compared to controls.

Epilepsy type in the current study was partial focal seizure in 16/50. And 34/50 were primarily generalized seizure, well controlled in 64% of the cases, alkaline phosphatise was significantly higher in controlled compared to uncontrolled groups (P. value 0.017).

A previous study included 22 patients with idiopathic epilepsy, 17 males and age range 3 -12 years. The 10 had localization and 12 patients had generalized epilepsy syndromes. The duration of the therapy range months - 6.5 years. The 9 patients on valproate), 13 on carbamazepine as initial monotherapy. Out of them (86.4%) were considered controlled in the last 6 months on AEDs. with normal liver and kidney function results.

When comparing patients on different antiepileptic drugs, levels of total cholesterol, low-density lipoproteins and high density lipoproteins cholesterol, and apolipoprotein AI, showed the lipids were significantly lower in patients receiving valproate compared with patients receiving carbamazepine. No significant difference was detected between the studied groups regarding triglycerides, apolipoprotein B levels,

or any of the atherogenic ratios [4]. The mechanism underlying the decreased serum lipid levels with valproate a suggested cause is the enzyme inhibitor property of valproate.

## VI. CONCLUSIONS

- The case control study was conducted on a sample of epileptic cases to investigate the effects of antiepileptic agents on CBC, LFT and lipid profile.
- Which showed no significant difference in the means of CBC indices as Hb. level, RBC, WBC, platelets and haematocrit, where means of Alkaline phosphates and Total Bilirubin were significantly higher in the cases than the controls, Lipid profile was significantly higher in children treated with AED compared to the control. Na-valproate associated with significant higher mean serum bilirubin than carbamazepine group while carbamazepine group expressed much higher mean HDL level as compared to Na-valproate group, this difference was highly significant.

## REFERENCES


1. Fisher, R. S., Acevedo, C., & Arzimanoglou, A. (2014). An operational clinical definition of epilepsy. *Epilepsia*, 55, 475-482.
2. Minardi, C., Minacapelli, R., Valastro, P., Vasile, F., Pitino, S., Pavone, P., ... & Murabito, P. (2019). Epilepsy in children: from diagnosis to treatment with focus on emergency. *Journal of clinical medicine*, *8*(1), 39.
3. Trinka, E., Cock, H., Hesdorffer, D., Rossetti, A. O., Scheffer, I. E., Shinnar, S., ... & Lowenstein, D. H. (2015). A definition and classification of status epilepticus–Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*, *56*(10), 1515-1523.
4. Mountz, J. M., Patterson, C. M., & Tamber, M. S. (2017, March). Pediatric epilepsy: neurology, functional imaging, and neurosurgery. In *Seminars in nuclear medicine* (Vol. 47, No. 2, pp. 170-187). WB Saunders.
5. Kandar, H. K. M. C. C., Das, S. K., Ghosh, L., & Gupta, B. K. (2012). Epilepsy and its management: A review. *Journal of PharmaSciTech*, *1*(2), 20-26.
6. Ahmed, S. N., & Siddiqi, Z. A. (2006). Antiepileptic drugs and liver disease. *Seizure*, *15*(3), 156-164.
7. Tomoum, H. Y., Awadallah, M. M., Fouad, D. A., & Ali, A. H. (2008). Lipid profile, apolipoproteins A and B in children with epilepsy. *Journal of child neurology*, *23*(11), 1275-1281.
8. Pandit, A., Sachdeva, T., & Bafna, P. (2012). Drug-induced hepatotoxicity: a review. *Journal of Applied Pharmaceutical Science*, (Issue), 233-243.
9. Vidaurre, J., Gedela, S., & Yarosz, S. (2017). Antiepileptic drugs and liver disease. *Pediatric Neurology*, *77*, 23-36.
10. Russo, M. W., Galanko, J. A., Shrestha, R., Fried, M. W., & Watkins, P. (2004). Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transplantation*, *10*(8), 1018-1023.
11. Strolin Benedetti, M., Ruty, B., & Baltes, E. (2005). Induction of endogenous pathways by antiepileptics and clinical implications. *Fundamental & clinical pharmacology*, *19*(5), 511-529.
12. Björnsson, E., & Olsson, R. (2005). Outcome and prognostic markers in severe drug-induced liver disease. *Hepatology*, *42*(2), 481-489.
13. Robles–Diaz, M., Lucena, M. I., Kaplowitz, N., Stephens, C., Medina–Cáliz, I., González–Jimenez, A., ... & Safer and Faster Evidence-based Translation Consortium. (2014). Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. *Gastroenterology*, *147*(1), 109-118.
14. Star, K., Edwards, I. R., & Choonara, I. (2014). Valproic acid and fatalities in children: a review of individual case safety reports in VigiBase. *PLoS One*, *9*(10), e108970.
15. Akhondian, J., Kiani, M. A., Jafari, S. A., Beiraghi Toosi, M., Mirzaei Najm Abad, M., Ahanchian, H., & Kianifar, H. (2015). Evaluation of liver enzymes rising in patients treated with sodium valproate (VPA). *International Journal of Pediatrics*, *3*(3.2), 685-689.
16. Bűdi, T., Tóth, K., Nagy, A., Szever, Z., Kiss, Á., Temesvári, M., ... & Monostory, K. (2015). Clinical significance of CYP 2C9-status guided valproic acid therapy in children. *Epilepsia*, *56*(6), 849-855. Doi: 10.1111/epi.13011.
17. Ogungbenro, K., & Aarons, L. (2014). A physiologically based pharmacokinetic model for Valproic acid in adults and children. *European Journal of Pharmaceutical Sciences*, *63*, 45-52.
18. Stewart, J. D., Horvath, R., Baruffini, E., Ferrero, I., Bulst, S., Watkins, P. B., ... & Chinnery, P. F. (2010). Polymerase γ gene POLG determines the risk of sodium valproate-induced liver toxicity. *Hepatology*, *52*(5), 1791-1796.
19. Rust, R. S. (2013). Alpers-Huttenlocher syndrome: origins of clinicopathologic recognition. *Pediatric Neurology*, *48*(3), 165-166.
20. Stumpf, J. D., Saneto, R. P., & Copeland, W. C. (2013). Clinical and molecular features of POLG-related mitochondrial disease. *Cold Spring Harbor perspectives in biology*, *5*(4), a011395.
21. Burusnukul, P., & de los Reyes, E. C. (2009). Phenotypic variations in 3 children with POLG1 mutations. *Journal of child neurology*, *24*(4), 482-486.
22. Rajakulendran, S., Pitceathly, R. D., Taanman, J. W., Costello, H., Sweeney, M. G., Woodward, C. E., ... & Rahman, S. (2016). A clinical, neuropathological and genetic study of homozygous

A467T POLG-related mitochondrial disease. *PLoS One*, *11*(1), e0145500.

23. Da Pozzo, P., Cardaioli, E., Rubegni, A., Gallus, G. N., Malandrini, A., Rufa, A., ... & Federico, A. (2017). Novel POLG mutations and variable clinical phenotypes in 13 Italian patients. *Neurological Sciences*, *38*, 563-570.
24. Björnsson, E., Kalaitzakis, E., & Olsson, R. (2007). The impact of eosinophilia and hepatic necrosis on prognosis in patients with drug-induced liver injury. *Alimentary pharmacology & therapeutics*, *25*(12), 1411-1421.
25. Sasaki, E., Matsuo, K., Iida, A., Tsuneyama, K., Fukami, T., Nakajima, M., & Yokoi, T. (2013). A novel mouse model for phenytoin-induced liver injury: involvement of immune-related factors and P450-mediated metabolism. *toxicological sciences*, *136*(1), 250-263.
26. Gökçe, S., Durmaz, Ö., Çeltik, C., Aydoğan, A., Güllüoğlu, M., & Sökücü, S. (2010). Valproic acid-associated vanishing bile duct syndrome. *Journal of Child Neurology*, *25*(7), 909-911.
27. Bhayana, H., Appasani, S., Thapa, B. R., Das, A., & Singh, K. (2012). Lamotrigine-induced vanishing bile duct syndrome in a child. *Journal of Pediatric Gastroenterology and Nutrition*, *55*(6), e147-e148.
28. Planjar-Prvan, M., Bielen, A., Sruk, A., Marusic, M., & Bielen, I. (2013). Acute oxcarbazepine-induced hepatotoxicity in a patient susceptible to developing drug-induced liver injury. *Collegium antropologicum*, *37*(1), 281-284.
29. Chait Mermelstein, A., Mermelstein, J., Adam, T., Brody, B. D., & Dubin, M. J. (2016). Oxcarbazepine-induced liver injury after sensitization by valproic acid: a case report. *Bipolar Disorders*, *18*(3), 307-309.
30. Bosdure, E., Cano, A., & Roquelaure, B. (2004). Oxcarbazepine and DRESS syndrome: a peddarticcause of acute liver failure. *Arch Pediatr*, 11, 1073–1077.
31. Li, A. M., Nelson, E. A., Hon, E. K., Cheng, F. W., Chan, D. F., Sin, N. C., ... & Fok, T. F. (2005). Hepatic failure in a child with anti-epileptic hypersensitivity syndrome. *Journal of paediatrics and child health*, *41*(4), 218-220.
32. Di Mizio, G., Gambardella, A., Labate, A., Perna, A., Ricci, P., & Quattrone, A. (2007). Hepatonecrosis and cholangitis related to long-term phenobarbital therapy: an autopsy report of two patients. *Seizure*, *16*(7), 653-656.
33. Santos, N. A. G., Medina, W. S. G., Martins, N. M., Rodrigues, M. C., Curti, C., & Santos, A. C. D. (2008). Involvement of oxidative stress in the hepatotoxicity induced by aromatic antiepileptic drugs. *Toxicology in vitro*, *22*(8), 1820-1824.
34. Fayad, M., Choueiri, R., & Mikati, M. (2000). Potential hepatotoxicity of lamotrigine. *Pediatric neurology*, *22*(1), 49-52.
35. Im, S. G., Yoo, S. H., Park, Y. M., Lee, S. J., Jang, S. K., Jeon, D. O., ... & Oh, M. J. (2015). Liver dysfunction induced by systemic hypersensitivity reaction to lamotrigine: case report. *Clinical and Molecular Hepatology*, *21*(2), 180-182.
36. Mecarelli, O., Pulitano, P., Mingoia, M., Ferretti, G., Rossi, M., Berloco, P. B., & Muda, A. O. (2005). Acute hepatitis associated with lamotrigine and managed with the molecular adsorbents recirculating system (Mars). *Epilepsia*, *46*(10), 1687-1689.
37. Flanagan, R. J., & Dunk, L. (2008). Haematological toxicity of drugs used in psychiatry. *Human Psychopharmacology: Clinical and Experimental*, *23*(S1), S27-S41.
38. Bhosale, U. A., Loharkar, N. R., Yegnanarayan, R., & Quraishi, N. (2014). Study of effects of antiepileptic therapy on various biochemical and hematological parameters patients suffering of epilepsy. *Int J Basic Clin Pharmacol*, *3*(1), 79-85.
39. Özkaya, H., Aydemir, G., Akcan, A. B., Kul, M., Karademir, F., Aydınöz, S., & Süleymanoğlu, S. (2012). Carbamazepine-induced red blood cell aplasia: A case report. *Turkish Journal of Hematology*, *29*(2), 195-196
40. Aliyu, H., Ayo, J., Ambali, S., Kawu, M., Aluwong, T., & Dzenda, T. (2016). Heamatobiochemical alterations induced by carbamazepine and phenytoin: mini review. *Biochem Pharmacol (Los Angel)*, *5*(219), 2167-0501.