Original research

Hematological consequences of antiepileptic drug therapy among children with epilepsy

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Abstract: Epilepsy is a chronic neurologic disease that comes third after cerebrovascular and Alzheimer's disease. Anti-epileptic drugs may affect certain hematological parameters of epileptic patients. Few researches investigated hematological adverse effects of antiepileptic drugs in Libya. Thus, the aim was to evaluate hematological parameters in epileptic children who are on antiepileptic drugs. This retrospective study included 83 pediatric patients with epilepsy recruited from Benghazi Children Hospital, Department of Neurology, from December 2017 to April 2018. Data collected included demographic characteristics, types of epilepsy, anti-epileptic drugs and serum hematological parameters. Hematological parameters recorded included: hemoglobin, hematocrit, platelet, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration and white blood cell count. In all treated patients, regardless of the number of antiepileptic drugs therapy used, the average levels of hematological parameters were significantly lower in treated group compared to control group (11.64 gm per dl, 34.53%, 27.74 pg and 33.13 gm per dl, respectively). A significant increase (12.1210^9 per l) in white blood cell counts in treated group was found. Average hemoglobin, hematocrit and mean cell hemoglobin concentration levels were significantly lower in patients on poly-therapy compared to mono-therapy and control groups. Average white blood cell counts were significantly increased in patients on anti-epileptic drugs. In sodium valproate users, levels of hematological parameters were significantly decreased but significantly increased in white blood cell counts. In diazepam users, significant increases in white blood cells and platelet but no difference in other parameters observed. There were no differences in all hematological parameters among patients using carbamazepine except for platelet counts (significantly decreased). In conclusion, there is substantial effect of the anti-epileptic drugs, especially sodium valproate, on hematological parameters of children despite the effects were not critical as the changes were still in the normal range.

Keywords: Anti-epileptic, child, drug therapy, hematological parameters, Libya

Introduction

Epilepsy is a chronic neurologic disease that is considered the most common neurological diseases in the world and comes third after cerebrovascular and Alzheimer's disease [1]. Epilepsy is a disorder characterized by a long-term tendency to cause epileptic seizures due to abnormal electrical activity in the brain with neurological, cognitive, psychological and social consequences [2]. However, it is not a single disease entity but it is a collection of different kinds of seizures resulting

from several mechanisms and different causes [1, 2]. According to Fiest and associates, the raw global prevalence of lifetime epilepsy was 7.60 per 1 000 persons; the point prevalence of active epilepsy was 6.38 per 1 000 persons, while the global incidence rate was 61.44 per 100 000 person-years [3]. While, the median lifetime prevalence of epilepsy in Arabic countries was found to be 6.9 per 1000 and the median incidence was 89.5 per 10 0000 [4]. The prevalence of epilepsy in North America was 5 - 10 per 100, where the children (under five years of age) and elderly were at high risk to have epilepsy [5]. However, in Libya, there is no updated information regarding epilepsy prevalence since 1986, the prevalence of epilepsy in Benghazi and northeastern cities of Libya was 2.3 per 1000 in the adult population according to a prospective study that has been done over two years from January to December, 1983 1984 [6]. In children, there is no epidemiological study done in this region yet, but world widely studies estimated that more than 10 million children below 15 years have active epilepsy [7]. Furthermore, the prevalence of this neurological disorder in developing countries is more than that in developed countries, also the incidence of epilepsy is high especially in low- and middle-income countries because these countries are not capable to treat all epileptic patients successfully [2, 8]. In the middle of the ninth-century potassium bromide was used as treatment of epilepsy [9], then, the serendipitous discovery of phenobarbital [10] followed by phenytoin, troxidone, valproate, lamotrigine, carbamazepine and other benzodiazepines [11].

Some of the anti-epileptic drugs (AEDs) have their own pharmacological action at the $GABA_A$ receptor's level, either by optimizing the response to synaptically released GABA (barbiturates, benzodiazepines) or by changing its synthesis, metabolism or reuptake at the synapse like sodium valproate, vigabatrin and tiagabine, respectively [12]. Therefore, using anti-epileptic drugs may result in life-threatening side effects such as severe hypersensitivity reactions, serious hematological disorders or hepatic failure [13]. Nevertheless, hematological side effects of anti-epileptic medications are well known such as aplastic anemia, megaloblastic anemia, leukopenia, etc. [14]. Moreover, according to Kırar and his colleagues [15], AEDs may affect the hematological parameters of epileptic patients younger than 15 years old. There are few researches investigating the hematological adverse effects of AEDs specifically in Libya. Therefore, investigating these effects is required. In this study, it is interested to evaluate the hematological parameters in epileptic children who were treated with mono-therapy and/or poly-therapy of anti-epileptic drugs.

Martials and methods

Study Design: This retrospective study included eighty three patients younger than 17 years old with known history of epilepsy. Patients were recruited from Department of Neurology of Benghazi Children Hospital, Benghazi, Libya from December 2017 to April 2018.

Inclusion criteria were:

a) Child's patients of both genders aged < 17 years who diagnosed with epilepsy.

b) Children subjects on mono- and poly-therapy anti-epileptic drug therapy.

c) Epileptic children who were on treatment for at least six months.

d) Control subjects who were matched for age and gender.

Exclusion criteria were:

a) Children were on treatment for less than six months.

b) Children had other conditions besides epilepsy that could affect blood parameters.

The ethical approval for data collection of the patient from hospital health records was obtained from the medical administration of Benghazi Children Hospital, Benghazi (2/2020). Data collected included demographic characteristics, types of epilepsy, anti-epileptic drugs prescribed and hematological parameters. The hematological parameters recorded included: hemoglobin, hematocrit, platelet counts, mean corpuscular

volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and white blood cells.

Statistical analysis: Statistical Package for Social Sciences (version 22; SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Data were tested for normality distributed. Non-parametric independent sample test (Mann-Whitney *U*-test) was used for the analysis of continuous variables, comparing patients on mono-therapy and poly-therapy with controls. A two-sided $p < 0.05$ was considered statistically significant.

Results

Patient's demographics data and distribution according to the treatments: The descriptive analyses findings of the epileptic patients as well as comparable control characteristics were presented in **Table 1**. The sample consists of 83 epileptic patients under treatment by either one or more AED drugs, and were 65 control subjects (healthy children without treatment). Among the patient sample, 43 patients were females (51.8%), while 40 patients were males (48.2%). Patient sample' age range from one year to 17 years old. More than half of the treated patients, n = 45 were between the age of one to five years old (54.2%), 22 were between six and ten years old (26.5%) and 16 patients were aged between 11 -17 years old (19.3%). The distribution of the control group according to age was equal in the age group from one to five years and 11 - 17 years representing 23 patients (35.4%) for each. Meanwhile, the number of the control group was nearly comparable to the other age groups representing 19 cases (29.3%). The patients were also divided into three groups according to the number of AEDs treatment, the first group was the control (n = 65, 43.9%), they were healthy children with no treatments, the second group was patients on one AED (mono-therapy) (n = 29, 19.6%) and the third group of the patients was on more than one AEDs (poly-therapy) (n = 54, 36.5%). In total, among these groups, the number of anti-epileptic drugs prescribed for each patient was ranged from one to five drugs. Among the studied sample of patients, the most frequently prescribed anti-epileptic drug was sodium valproate in 62 patients and diazepam in 45 patients however, carbamazepine was the third in 15 patients. Then, levetiracetam in 15 patients, phenytoin in 15 patients, clonazepam in six patients, phenobarbital in five patients and lamotrigine in four patients.

Table 1: Demographic distribution of the patients and AEDs therapy

	Control n (%)	Treated patients n (%)
Gender		
Male	28 (43.1%)	40 (48.2%)
Female	37 (56.9%)	43 (51.8%)
Age (years)		
1 - 5	23 (35.4%)	45 (54.2%)
6 - 10	19 (29.2%)	22 (26.5%)
11 - 17	23 (35.4%)	16 (19.3%)
Sample distribution according to treatments		
Control group (no treatment)	65 (43.9%)	----------
Group one (AEDs mono-therapy)	----------	29 (19.6%)
Group two (AEDs poly-therapy)	----------	54 (36.5 %)

Serum hematological parameters: Hematological parameters of the complete blood count of all the patients were analyzed and the results given in **Table 2**. It showed that the average blood parameters level of control was normal in comparison to standard blood parameters level. In addition, in all the treated patients regardless of the number of AEDs therapy used, the average levels of hemoglobin, mean cell hemoglobin and mean cell hemoglobin concentration were slightly but

significantly lower (11.64 gm per dl, 34.5%, 27.74 pg and 33.13 gm per dl, respectively) in the treated group in comparison to the average levels of controls with ($P < 0.05$; $P < 0.001$, $P < 0.01$, 0.001 and $P < 0.001$). There were also a statistically significant increase (12.1210^9 per l) in white blood cell counts ($P < 0.05$, $P = 0.001$). While there were no significant differences in platelet counts and mean cell volume in comparison with their average counts in controls respectively. In treated patients, the average hemoglobin level was significantly ($P < 0.05$) lower in females (11.33 gm per dl) than male patients (12.7 gm per dl). While the mean platelet counts were insignificantly lower in male group (308.910^9 per l) in comparison to the female group (328.410^9 per l). However, there are insignificant changes of all the hematological parameters in both genders of patients.

Serum hematological parameters of patient on mono and poly AEDs: The results of comparing controls with patients on mono- and poly- AEDs therapy are shown in **Table 3**. The average hemoglobin, hematocrit and mean cell hemoglobin concentration levels were significantly lower in patients on poly-therapy in comparison to mono-therapy and control groups ($P < 0.001$, $P < 0.05$ and $P < 0.001$). While the average white blood cell counts was increased significantly ($P < 0.001$) in patients on poly anti-epileptic therapy and mono-therapy in comparison to control. However, there were non-significant differences in red blood cells, platelets, mean cell volume and mean cell hemoglobin in patients on mono- and poly-therapy compared with that in the controls. Additionally, in **Figure 1**, linear regression analysis showed that there is a statistically significant linear relationship between the increases in the number of anti-epileptic drugs consumed by patients and the decreases in hemoglobin level ($P < 0.05$).

Table 2: Serum hematology parameters of the patients with AEDs therapy

Hematological parameters	Normal CBC range	Control (n = 65)	All patients (n = 83) ± SD	P Value
WBC (10^9 per l)	05.1 - 17.6	07.8 ± 2.71	12.12 ± 6.31	**0.001*** **
RBC (10^{12} per l)	3.22 - 5.55	04.56 ± 0.40	04.46 ± 0.39	0.177
HGB (gm per dl)	11.5 - 15.5	12.76 ± 1.03	11.64 ± 1.09	**0.001*** **
PLT (10^9 per l)	110 - 637	307.98 ± 81.71	317.58 ± 129.25	0.876
HCT (%)	24.4 - 38.8	40.05 ± 27.82	34.53 ± 3.98	**0.001*** **
MCV (fl)	56 - 87	80.45 ± 4.35	79.08 ± 5.90	**0.238**
MCH (pg)	16.9 - 29.7	28.60 ± 5.04	27.74 ± 8.35	**0.001****
MCHC (g per dl)	30.0 - 36.9	34.87 ± 1.69	33.13 ± 2.51	**0.001*** **

CBC: complete blood picture, HGB: hemoglobin concentration, WBC: white blood cell, RBC: red blood cell, PLT: platelets count, HCT: hematocrit, MCV: mean cell volume, MCH: mean cell hemoglobin, MCHC: mean cell hemoglobin concentration.

Serum hematological parameters of patients according to specific AED as mono-therapy: In this study, the number of patients who were on monotherapy are 29. The most used anti-epileptic drug as mono-therapy was sodium valproate (n = 20, 68.9%), followed by diazepam (n = 6, 20.7%) and then carbamazepine (n = 3, 10.3%). In sodium valproate users, the levels of hemoglobin (11.63 gm per dl), HCT (33.5%), mean cell volume (76.98 fl), MCH (30.65 pg) and mean cell hemoglobin concentration (33.04 g per dl) were significantly lower than controls ($P < 0.05$). While, there was a significant increase in white blood cell counts (13.2710^9 per l) and insignificant increase in the platelet counts (31710^9 per l). In diazepam users, there was insignificant difference in pure red cells parameters among patients using this medication. However, there were significant increases in the levels of white blood cells (12.8510^9 per l) and platelet counts (388.810^9 per l). In patients using carbamazepine, there were insignificant differences in all the hematological parameters among the patients using this medication except that for platelet counts, as there was a significant decreas ($P < 0.01$) in the platelet counts (188.510^9 per l) (**Table 5**).

Table 3: Hematological parameters of patients on anti-epileptic drugs

Hematological parameters	Patients' therapy			P Value
	Control (n = 65)	Mono-therapy (n = 29)	Poly-therapy (n = 54)	
WBC (10^9 per l)	07.8 ± 2.71	12.94 ± 7.16	11.68 ± 5.82	**0.001*** **
RBC (10^{12} per l)	04.56 ± 0.40	04.49 ± 0.46	04.45 ± 0.36	0.400
HGB (gm per dl)	12.76 ± 1.03	11.82 ± 1.01	11.55 ± 1.137	**0.001*** **
PLT (10^9 per l)	307.98 ± 81.71	325.00 ± 139.95	313.44 ± 124.14	0.987
HCT (%)	40.05 ± 27.82	33.97 ± 4.62	34.87 ± 3.59	**0.05***
MCV (fl)	80.45 ± 4.35	77.90 ± 3.61	79.75 ± 6.84	0.179
MCH (pg)	28.60 ± 5.04	29.75 ± 12.78	26.47 ± 3.23	0.064
MCHC (g per dl)	34.87 ± 1.69	33.47 ± 2.87	32.93 ± 2.30	**0.001*8***

CBC: complete blood picture, HGB: hemoglobin concentration, WBC: white blood cell, RBC: red blood cell, PLT: platelets count, HCT: hematocrit, MCV: mean cell volume, MCH: mean cell hemoglobin, MCHC: mean cell hemoglobin concentration. Data presented as mean ± SD, P < 0.05.

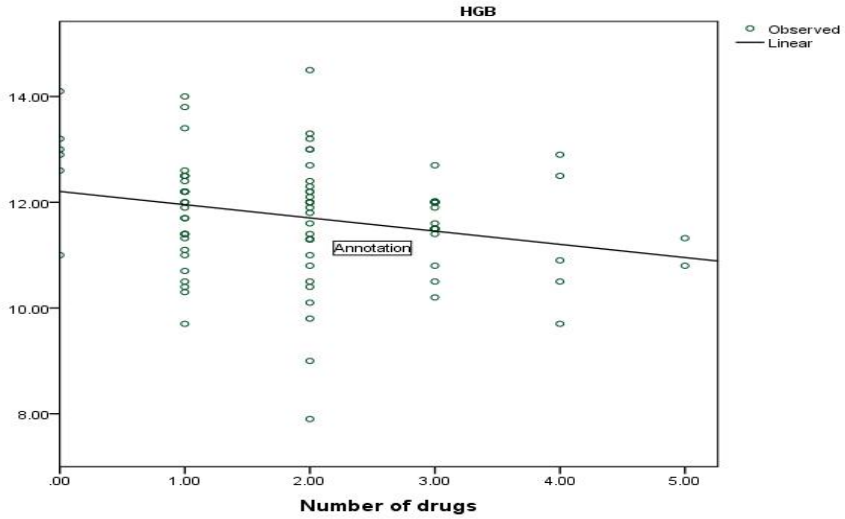

Figure 1: Number of anti-epileptic drugs correlated with HGB level

Table 5: Hematological parameters in patients on mono-therapy

Drugs	Valproate (n = 20)			Diazepam (n = 6)			Carbamazepine (n = 3)		
Hematological parameters (Mean ± SD)	Control	Treated	P value	Control	Treated	p value	Control	Treated	P value
WBC (10^9/L)	7.8 ± 2.71	13.27 ± 7.89	**0.000*** **	7.8 ± 2.71	12.85 ± 5.64	**0.05***	7.8 ± 2.71	12 ± 8.48	0.611
RBC (10^{12}/L)	4.56 ± 0.405	4.51 ± 0.541	0.478	4.56 ± 0.405	4.49 ± 0.2	0.766	4.56 ± 0.405	4.52 ± 0.02	0.924
HGB (g/dl)	12.76 ± 1.030	11.63 ± 0.94	**0.000*** **	12.76 ± 1.030	12.3 ± 1.09	0.338	12.76 ± 1.030	13.05 ± 0.49	0.655
PLT (10^9/L)	307.98 ± 81.71	317.68 ± 152.78	0.586	307.98 ± 81.71	388.3 ± 92.95	**0.05***	307.98 ± 81.71	188.5 ± 45.96	**0.01****
HCT (%)	40.05 ± 27.82	33.51 ± 5.44	**0.05***	40.05 ± 27.82	34.57 ± 2.25	0.171	40.05 ± 27.82	38.1 ± 0.00	0.656
MCV (fl)	80.45 ± 4.35	76.98 ± 3.57	**0.01****	80.45 ± 4.35	79.2 ± 3.39	0.668	80.45 ± 4.35	83 ± 0.00	0.508
MCH (pg)	28.60 ± 5.04	30.65 ± 15.29	**0.05***	28.60 ± 5.04	27.56 ± 1.71	0.848	28.60 ± 5.04	29.2 ± 0.00	0.476
MCMC (g/dL)	34.87 ± 1.69	33.04 ± 3.295	**0.05***	34.87 ± 1.69	34.8 ± 1.11	0.941	34.87 ± 1.69	35.2 ± 0.00	0.667

CBC: complete blood picture, HGB: hemoglobin concentration, WBC: white blood cell, RBC: red blood cell, PLT: platelets count, HCT: hematocrit, MCV: mean cell volume, MCH: mean cell hemoglobin, MCHC: mean cell hemoglobin concentration. Data presented as mean ± SD, p < 0.05.

Discussion

In diagnosis of epilepsy, hematological investigation becomes important to determine the cause and guiding management. As many studies have indicated that different AEDs were associated with a variety of adverse effects including hematological side effects. Unfortunately, a small number of research was done in regard to the hematological side effects of AEDs in children as well as in adults. The most frequently prescribed drug in this study was sodium valproate (valproic acid) and the less frequently prescribed drug was lamotrigine. Comparably, the majority of the patients in a study by Kırar and others [15] used valproic acid as an AED. Similarly, Kaushik et al. [16] studied the adverse drug reactions of AEDs among children and found that the majority of patients were on mono-therapy and the commonly prescribed drug was valproic acid then phenytoin after that carbamazepine, levetiracetam and clopazam. While, another study carried out in 2015 evaluated the prevalence of side effects of AEDs in epileptic children and identified carbamazepine as the most frequently used drug then valproic acid [17]. However, carbamazepine was identified to be the most frequently used in adult patients [6, 18].

In the present study, the hematological parameters were not significantly changed in children treated with diazepam or carbamazepine as a mono-therapy in comparison to the control group. While white blood cells and platelet count increased significantly in children treated with diazepam compared to the control group. However, platelet count was significantly declined in carbamazepine treated group compared with controls. Comparable to this study, Al-kazzaz and his colleagues [19] found that all blood parameters were insignificantly different in patients on carbamazepine as compared to the control group for both genders except for hemoglobin, which was significantly decreased. In addition, the platelet count showed a non-significant decline in the patients compared with controls [19]. Not compatible with the present findings, Pottoo et al. [20] studied the hematological adverse effects in adult patients using carbamazepine, the findings showed that they had lower mean cell hemoglobin, mean cell volume, white blood cells and mean cell hemoglobin concentration levels in comparison to controls [20]. An another study was done in 2011 showed that hemoglobin level is slightly, but significantly lower in patients taking carbamazepine compared with that in controls [21]. A case report study by Özkaya et al. [22] concluded that carbamazepine-induced red blood cell aplasia in which hemoglobin below the normal value. Additionally, Mathur and others [23] presented a case report study of women on carbamazepine admitted to hospital with severe anemia, thrombocytopenia and decreased white blood cell count, after drugs' cessation the blood parameters showed a significant improvement.

However, the present results showed that patients on valproic acid/valproate mono-therapy had significantly lower hematological parameters compared to control. Comparably, a study by Yilmazbas and Şenbil found that at least one hematological side effects developed in about half of the patients who used valproate as a single antiepileptic drug [24]. Moreover, other study showed that 12 weeks of sodium valproate treatment significantly down regulate hemoglobin and hematocrit [25]. While, previous published study found that the hemoglobin value fell below 10 g/dl in valproic acid users but the difference with control was not significant [15]. On the other hand, several studies investigated the effect of valproic acid on the patients' blood parameters reported that there were no differences between cases and controls concerning hemoglobin level [21, 26, 27]. Furthermore, a case-control study of a 13-year-old patient on a standard dose of valproic acid showed no abnormalities in blood parameters except for mild macrocytic anemia [28]. Regarding platelet counts, some studies indicated that the mean platelet count was diminished significantly after valproate treatment which is not compatible

with the outcomes of this study, as there is a non-significant change in platelet counts in valproate treated group [15, 24, 29]. Various studies in children and adults showed a significant negative correlation between valproic acid and platelet [30 - 32]. Likewise, Ko et al. [33] suggested that children with a valproic level of > 450 µmol per L were more likely to develop mild thrombocytopenia. A previous study, however, reported that valproic acid causes thrombocytopenia in 60% of patients using this medication and children were more vulnerable than adults [20]. Currently, white blood cell count is significantly elevated in children treated with poly-therapy of AEDs and in patients treated with valproate/valproic acid and diazepam as a monotherapy. This is similar to the published study by Sarkis et al. [35] which concluded that high white blood cell count was present in patients with generalized epilepsy despite greater use of valproic acid. However, these findings dissimilar to the study on pediatric patients treated with valproate confirmed reports of decreased white blood cell associated with the use of valproate [24]. Furthermore, an analysis of the hematological data in the child and adolescent patients revealed an incidence of leukopenia of 26% in the valproate mono-therapy group [34]. Concerning the carbamazepine treated group, the finding showed that platelet counts considerably declined. Comparable results found that platelet counts reduced significantly in epileptic patients treated with carbamazepine as mono-therapy or poly-therapy. Other report mentioned that AEDs,specifically carbamazepine causes thrombo-cytopenia [13]. The present findings showed that the mean hemoglobin, hematocrit and mean cell hemoglobin concentration levels were significantly lower in patients on multi-therapy in comparison to mono-therapy and control groups. In addition, it showed that there is significant correlation between the increases in the number of drugs used by children and the decreases in hemoglobin levels. A supportive study in epileptic children stated that potential damage of AEDs combination (with more than three drugs) could be greater than that caused by the seizures themselves [37]. Another study also investigated hematological changes in adult epileptic patients and revealed a significant decrease in hemoglobin which was compatible with present study. A non-significant decrease in white blood cell and platelet among patients on poly-therapy in comparison to those on mono-therapy which is not in line with the current study outcome [38].

Conclusion: The average hematological levels are significantly lower in all epileptic pediatric patients regardless number of AEDs therapy used. A significant effect of the anti-epileptic drugs especially sodium valproate on hematological parameters of the epileptic children despite the effects being not critical as the changes are still within the normal range.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions: Both authors contributed equally.

Ethical issues: Including plagiarism, informed consent, data fabrication or falsification and double publication or submission have completely been observed by authors.

Author declarations: We confirm all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.

References

1. Harvey RA, Clark M, Finkel R, Rey J, Whalen K (2019) Lippincott's illustrated reviews: Pharmacology (5th edition, pp. 530-541). Philadelphia. ISBN: 978-1496384133.
2. Fisher RS, Boas WVE, Blume W, Elger C, Genton P, Lee P, Engel Jr J (2005) Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 46 (4): 470-472. doi: 10.1111/j.0013-9580.2005.66104.x.
3. Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, Jetté N (2017) Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology. 88 (3): 296-303. doi: 10.1212/WNL.0000000000003509.
4. Idris A, Alabdaljabar, MS, Almiro A, Alsuraimi A, Dawalibi A, Abduljawad S, AlKhateeb M (2021) Prevalence, incidence, and risk factors of epilepsy in Arab countries: A systematic review. Seizure. 92: 40-50. doi.org/10.1016/j.seizure.2021.07.031.
5. Theodore WH, Spencer SS, Wiebe S, Langfitt JT, Ali A, Shafer PO, Vickrey BG (2006) Epilepsy in North America: a report prepared under the auspices of the global campaign against epilepsy, the International Bureau for Epilepsy, the International League Against Epilepsy, and the World Health Organization. Epilepsia. 47 (10): 1700-1722. doi: 10.1111/j.1528-1167.2006.00633.x.
6. Sridharan R, Radhakrishnan K, Ashok PP, Mousa ME (1986) Epidemiological and clinical study of epilepsy in Benghazi, Libya. Epilepsia. 27 (1): 60-65. doi: 10.1111/j.15281157.1986.tb03502.x.
7. Camfield P, Camfield C (2015) Incidence, prevalence and aetiology of seizures and epilepsy in children. Epileptic Disorders. 17 (2): 117-23. doi: 10.1684/epd.2015.0736.
8. Beghi E (2020) The epidemiology of epilepsy. Neuroepidemiology. 54 (2): 185-191. doi: 10.1159/000503831.
9. Korinthenberg R, Burkart P, Woelfle C, Moenting JS, Ernst JP (2007) Pharmacology, efficacy, and tolerability of potassium bromide in childhood epilepsy. Journal of Child Neurology. 22 (4): 414-418. doi: 10.1177/0883073807302758.
10. Yasiry Z, Shorvon SD (2012) How phenobarbital revolutionized epilepsy therapy: The story of phenobarbital therapy in epilepsy in the last 100 years. Epilepsia. 53 (S8): 26-39. doi: 10.1111/epi.12026.
11. Brodie MJ (2010) Antiepileptic drug therapy the story so far. Seizure. 19 (10): 650-655. doi: 10.1016/j.seizure.2010.10.027.
12. Sills GJ, Brodie MJ (2001) Update on the mechanisms of action of antiepileptic drugs. Epileptic Disorders. 3 (4): 165-172. PMID: 11844711.
13. Arroyo S, de la Morena A (2001) Life-threatening adverse events of antiepileptic drugs. Epilepsy Research. 47 (1-2): 155-174. doi.org/10.1016/s0920-1211(01)00306-0.
14. Son YR, Kim YS, Chu K, Lee SK (2013) Oxcarbazepine induced leukopenia. Journal of Korean Epilepsy Society. 17 (1): 22-23. ID: wpr-764818.
15. Kırar H, Türkkan E, Uzunhan TA, Kaçar A, Sazak S, Dikker, O, Dağ (2020) Evaluation of the effects of antiepileptic drugs on complete blood count parameters. Journal of Surgery and Medicine. 4 (12): 1108-1111. doi.org/10.28982/josam.827657.
16. Kaushik S, Chopra D, Sharma S, Aneja S (2019) Adverse drug reactions of anti-epileptic drugs in children with epilepsy: A cross-sectional study. Current Drug Safety. 14 (3): 217-224. doi: 10.2174/1574886314666190311112710.
17. Koliqi R, Polidori C, Islami H (2015) Prevalence of side effects treatment with carbamazepine and other antiepileptics in patients with epilepsy. Materia Socio-Medica. 27 (3): 167. doi: 10.5455/msm.2015.27.167-171.
18. Farooq N, Ali N, Ullah S (2019) Evaluation of hematological parameters in the genetic prospective in epileptic patients of Khyber Pakhtunkhwa. Pharmacogenomics and Personalized Medicine. 12, 377. doi.org/10.2147/PGPM.S223572.
19. KM Al-kazzaz, H, A Ahmed, F, K Alsamman, D (2011) The effect of carbamazepine monotherapy on full blood count in epileptic patients. Iraqi Journal of Pharmacy. 11 (1): 13-17. doi: 10.33899/iphr.2011.49576.
20. Pottoo FH, Al-Khalifa F, Al-Hassar F, Al-Muhanna S, Al-Ghamdi M, Aljaafari D, Joseph R (2019) Antiepileptic drugs: prescription pattern, hematobiochemical changes and adverse effects: A retrospective study in eastern

province of Saudi-Arabia. International Journal of Pharmaceutical Science and Research. 10 (11): 5146-5153. doi: 10.13040/IJPSR.0975-8232.10(11).5146-53.
21. Bachmann T, Bertheussen KH, Svalheim S, Rauchenzauner M, Luef, G, Gjerstad, L, Taubøll, E (2011) Haematological side effects of antiepileptic drug treatment in patients with epilepsy. Acta Neurologica Scandinavica. 124: 23-27. doi: 10.1111/j.1600-0404.2011.01539.x.
22. Özkaya H, Aydemir G, Akcan AB, 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. doi: 10.5505/tjh.2012.52296.
23. Jain A, Mathur P, Gupta D, Moolrajani K, Saxena GN, Mishra V (2020) Carbamazepine-induced pancytopenia: A rare entity. Journal of Mahatma Gandhi University of Medical Sciences and Technology. 3 (3): 97-98. doi: 10.5005/jp-journals-10057-0082.
24. Yilmazbas P, Şenbil N (2021) Hematological side effects of valproate used for the treatment of epilepsy. Namık Kemal Medical Journal. 9 (1): 39-42. doi: 10.4274/nkmj.galenos.2020.800497.
25. Lu RB, Chang YH, Lee SY, Wang TY, Cheng SL, Chen PS, Chen SL (2020) Dextromethorphan protects the valproic acid-induced down regulation of neutrophils in patients with bipolar disorder. Clinical Psychopharmacology and Neuroscience. 18 (1): 145. doi:10.9758/cpn.2020.18.1.145.
26. Maksoud HMA, El-Shazly SM, El Saied MH (2016) Effect of antiepileptic drug (valproic acid) on children growth. Egyptian Pediatric Association Gazette. 64 (2): 69-73. doi. 10.1016/j.epag.2016.04.001.
27. Carman KB, Özdemir ZC, Kar YD, Gunduz E, Teke HÜ, Arslantas D, Özcan, BÖR (2018) The effect of valproic acid on fetal hemoglobin synthesis in children with epilepsy. Osmangazi Journal of Medicine. 40 (3): 8-12. doi.org/10.20515/otd.411757.
28. Kaczorowska-Hac B, Matheisel A, Maciejka-Kapuscinska L, Wisniewski J, Alska A, Adamkiewicz-Drozynska E, Balcerska A, Reszczynska I (2012) Anemia secondary to valproic acid therapy in a 13-year-old boy: a case report. Journal of Medical Case Reports. 6, 239. doi.org/10.1186/1752-1947-6-239.
29. Choi JW, Oh KS (2000) The effects of antiepileptic drugs on hematologic parameters and liver enzymes according to antiepileptic plasma concentrations in epileptic children. Journal of the Korean Child Neurology Society. 8 (1): 70-79.
30. Nasreddine W, Beydoun A (2008) Valproate-induced thrombocytopenia: a prospective monotherapy study. Epilepsia. 49 (3): 438-445. doi.org/10.1111/j.1528-1167.2007.01429.x.
31. Verrotti A, Greco R, Matera, V, Altobelli, E, Morgese, G, Chiarelli, F (1999) Platelet count and function in children receiving sodium valproate. Pediatric Neurology. 21 (3): 611-614. doi.org/10.1016/S0887-8994(99)00060-0.
32. Kurahashi H, Takami A, Murotani K, Numoto S, Okumura A (2018) Decreased platelet count in children with epilepsy treated with valproate and its relationship to the immature platelet fraction. International Journal of Hematology. 107 (1): 105-111. doi.org/10.1007/s12185-017-2323-0.
33. Ko CH, Kong CK, Tse PW (2001) Valproic acid and thrombocytopenia: cross-sectional study. Hong Kong Medical Journal. 7 (1): 15-21. PMID: 11406671.
34. Rahman A, Mican LM, Fischer C, Campbell AH (2009) Evaluating the incidence of leukopenia and neutropenia with valproate, quetiapine, or the combination in children and adolescents. Annals of Pharmacotherapy. 43 (5): 822-830. doi.org/10.1345/aph.1L617.
35. Sarkis RA, Jehi L, Silveira D, Janigro D, Najm I (2012) Patients with generalized epilepsy have a higher white blood cell count than patients with focal epilepsy. Epileptic Disorders. 14 (1): 57-63. doi.org/10.1684/epd.2012.0493.
36. Bhosale UA, Loharkar NR, Yegnanarayan R, Quraishi N (2014) Study of effects of antiepileptic therapy on various biochemical and hematological parameters patients suffering of epilepsy. International Journal of Basic and Clinical Pharmacology. 3 (1): 79-85. doi: 10.5455/2319-2003.ijbcp20140207.
37. Oliva CF, Gangi, G, Marino S, Marino L, Messina, G, Sciuto S, Pavone P (2021) Single and in combination antiepileptic drug therapy in children with epilepsy: how to use it. AIMS Medical Science. 8 (2): 138-146. doi: 10.3934/medsci.2021013.
38. Dwajani S, Ranjana G, Sarma GRK, Kulkarni C, Ganapathi B (2014) Influence of anti-epileptic drugs on hematological and biochemical parameters in patients with epilepsy. International Journal of Basic and Clinical Pharmacology. 3 (4): 692. doi: 10.5455/2319-2003.ijbcp20140827.