J Surg Med. 2020;4(12):1108-1111.
DOI: 10.28982/josam.827657

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of the effects of antiepileptic drugs on complete blood count parameters

Antiepileptiklerin kan sayımı üzerine etkilerinin değerlendirilmesi

Haticenur Kırar [1], Emine Türkkan [1], Tuğçe Aksu Uzunhan [1], Alper Kaçar [1], Soner Sazak [1], Okan Dikker [2], Hüseyin Dağ [1]

[1] University of Health Sciences, Istanbul Prof.Dr. Cemil Taşçıoğlu City Hospital, Department of Pediatrics, Istanbul, Turkey
[2] University of Health Sciences, Istanbul Prof.Dr. Cemil Taşçıoğlu City Hospital, Department of Medical Biochemistry, Istanbul, Turkey

ORCID ID of the author(s)
HK: 0000-0002-7549-6886
ET: 0000-0002-5126-7843
TAU: 0000-0003-0596-2690
AK: 0000-0001-7577-5386
SS: 0000-0003-0233-6950
OD: 0000-0002-9153-6139
HD: 0000-0001-7596-7687

Corresponding author/Sorumlu yazar:
Hüseyin Dağ
Address/Adres: Sağlık Bilimleri Üniversitesi, İstanbul Prof.Dr. Cemil Taşçıoğlu Şehir Hastanesi, Çocuk Sağlığı ve Hastalıkları Bölümü, Darülaceze sokağı, No: 27, Sisli, İstanbul, Türkiye
E-mail: huseyindag2003@gmail.com

Ethics Committee Approval: The study was approved by the Ministry of Health Okmeydani Training and Research Hospital Ethics Committee (date: 07.02.2018 and number: 4396). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Sağlık Bakanlığı Okmeydanı Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından onaylandı (tarih: 07.02.2018 ve sayı: 4396). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: The incidence of pediatric epilepsy ranges between 1-3%, and various anticonvulsant drugs are used in its treatment. Seizure type, effectiveness and side effects are important in drug selection. Various hematological side effects of anticonvulsants have been reported. This study aims to determine the hematological side effects of the anticonvulsants used in our clinic.

Methods: A total of 87 epilepsy patients between the ages of 1 and 15 years, who were diagnosed and followed up in the Pediatric Neurology Outpatient Clinic of Health Sciences University, Okmeydanı Training and Research Hospital between January 2017-2018 and who received anticonvulsant medication for at least 3 months were included in this study. The blood values and hematological side effects of the anticonvulsants were noted from the patient files. The statistical analyses were performed with IBM SPSS Statistics v.22 (SPSS IBM, Turkey).

Results: Among all, 44.8% of the patients were using Valproic acid (VPA), 28.7%, Levetiracetam (LEV), 12.6%, Oxcarbazepine (OXC), 8%, Phenobarbital (PB), and 4.6%, Carbamazepine (CBZ). Platelet values were below 150,000/ul in 7.6% of VPA users and 14.2% of PB users. The hemoglobin value fell below 10 g/dl in 2.5% of VPA users, 14.2% of PB users, and 8% of LEV users. Absolute neutrophil count fell below 1500/ul in 9% of the patients using OXC and 14.2% of those using PB. The decrease in platelet values before and after anticonvulsant use was statistically significant (P=0.039), while the decrease in hemoglobin and neutrophil values were not.

Conclusion: In patients using antiepileptic drugs, complete blood count may be affected. Periodic monitoring of blood parameters is important in the close follow-up of patients. It is not known exactly how and how often the hematological side effects of antiepileptic drugs take place. Future studies on this subject are necessary.

Keywords: Antiepileptic drug, Child, Complete blood count

Öz

Amaç: Çocukluk çağında epilepsi görülme oranı %1-3 arasındadır. Epilepsi tedavisinde çeşitli antikonvülzan ilaçlar kullanılmaktadır. İlaç seçiminde nöbet tipi, ilacın etkinliği ve ilacın yan etkileri önemlidir. Antikonvülzan kullanımının çeşitli hematolojik yan etkileri bildirilmiştir. Bu çalışmanın amacı kliniğimizde kullanılan antikonvülzanlara bağlı hematolojik yan etkileri ve bu etkilerin sıklığını saptamaktır.

Yöntemler: Ocak 2017 - Ocak 2018 tarihleri arasında Sağlık Bilimleri Üniversitesi Okmeydanı Eğitim ve Araştırma Hastanesi Çocuk Nöroloji polikliniğinde epilepsi tanısı almış ve en az 3 aydır antikonvülzan tedavi verilmiş, 1 - 15 yaş arasındaki 87 hastanın dosyalarından kan değerleri ve ilaçların hematolojik yan etkileri kaydedildi. Çalışmada elde edilen bulgular değerlendirilirken, istatistiksel analizler için IBM SPSS Statistics 22 (IBM SPSS, Türkiye) programı kullanıldı.

Bulgular: Çalışmamızda hastaların %44,8'i Valproik asit (VPA), %28,7'si Levatiresetam (LEV), %12,6'sı Okskarbazepin (OXC), %8'i Fenobarbital (PB), %4,6'sı Karbamazepin (CBZ) kullanıyordu. VPA kullananların %7,6'sında, PB kullananların %14,2'sinde trombosit değerinin 150.000/ul altına düştüğü saptandı. VPA kullananların %2,5'inde, PB kullananların %14.2 'sinde, LEV kullananların %8'inde hemoglobin değerinin 10 g/dl altına düştüğü saptandı. OXC kullanan hastaların %9'unda, PB kullananların %14,2'sinde mutlak nötrofil sayısının 1500/ul altına düştüğü saptandı. İlaç öncesi ve sonrası değerler karşılaştırıldığında, hemoglobin ve nötrofil değerlerindeki düşüş anlamlı bulunmazken, trombosit değerlerindeki düşüş istatistiksel olarak anlamlı bulundu (P=0,039).

Sonuç: Anti epileptik ilaç kullanan hastaların kan sayımı etkilenebilmektedir. Hastaların takibinde kan parametrelerinin periyodik olarak yakından izlenmesi önemlidir. Antiepileptik ilaçların hematolojik yan etkisinin nasıl ve ne sıklıkta olduğu tam olarak bilinmemektedir. Bu konuda yapılacak çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Antiepileptik ilaç, Çocuk, Kan sayımı

How to cite/Atıf için: Kırar H, Türkkan E, Uzunhan TA, Kaçar A, Sazak S, Dikker O, Dağ H. Evaluation of the effects of antiepileptic drugs on complete blood count parameters. J Surg Med. 2020;4(12):1108-1111.

Introduction

Epilepsy is associated with persistent dysregulation of brain functions and a predisposition to recurrent seizures. The International League Against Epilepsy (ILAE) defines epilepsy as having at least two unprovoked seizures, at least 24 hours apart. It can be caused by various genetic, structural, metabolic, immune, and infectious reasons [1,2]. It is a common neurological problem in children and adolescents, whose frequency varies between 1-3%. There are few studies on the side effect profile of antiepileptic drugs used in the treatment of epilepsy in children, and their safety profile is not completely known. Only 13 of the 34 drugs used have the Food and Drug Administration (FDA) approval for children [3].

Most epileptic seizures can be treated with antiepileptic drugs (AEDs). When choosing an AED, physicians should pay attention that it is a highly effective, safe, and well-tolerated drug for the seizure type. The main goal in epilepsy treatment should be monotherapy. However, if seizures cannot be controlled despite the first two monotherapy treatments, drug combinations should be tried. The list of drugs used in epilepsy is gradually increasing. Drugs are primarily used in partial seizures in adults and, when effective, they can be used in other seizure types and children [4,5].

Many side effects of antiepileptic drugs have been described, and their hematological side effects are given particular attention in the literature. Many AEDs are associated with hematological disorders ranging from mild thrombocytopenia or neutropenia to anemia, from red cell aplasia to bone marrow failure. Fortunately, potentially fatal hematological disorders such as aplastic anemia are exceedingly rare. Children are more frequently affected by the side effects of AEDs than adults because they are treated more frequently and at higher doses. Although there are many studies and publications on the side effects of AEDs, there is no consensus on which drug causes which hematological side effect and how often [6].

In this study, we aimed to discuss the hematological side effects of AEDs in children, which are rarely seen, in light of the literature by evaluating our patients who were followed up in our clinic.

Materials and methods

Research method and study population

Patients diagnosed with epilepsy who were admitted to the Pediatric Neurology outpatient clinic of Health Sciences University Okmeydanı Training and Research Hospital between January 2017 and January 2018 were included in our study. The study was approved by the Ministry of Health Okmeydani Training and Research Hospital Ethics Committee (date: 07.02.2018 and number: 4396) and carried out in accordance with the Helsinki Declaration. Patients aged between 1-15 years who were given anticonvulsant therapy for at least 3 months, and whose hospital records were complete, were included in the study. The hospital records of patients with an infection or known hematological disease, using drugs other than antiepileptic therapies, and having any other systemic diseases were excluded. Gender, date of birth, age, diagnosis date, drugs used, drug initiation date, drug doses, duration of use, hemoglobin in blood count (HGB), hematocrit (HCT), leukocyte (WBC), thrombocyte (PLT), absolute neutrophil count (ANC), absolute lymphocyte count (ALC) and absolute monocyte count (AMC) were recorded on patient forms. How often and which anticonvulsant was causing hematological side effects were evaluated. This information was then transferred to the electronic program to analyze the statistical data.

Statistical analysis

When evaluating the findings obtained in the study, IBM SPSS Statistics 22 (SPSS IBM, Turkey) program was used. The normality of distribution of the parameters was evaluated with the Shapiro Wilks test. Descriptive statistical methods (mean, standard deviation, frequency), as well as One-way ANOVA test were used to compare normally distributed parameters between groups for quantitative data. Kruskal Wallis test was used for intergroup comparisons of non-normally distributed parameters. Paired Sample t-test and Wilcoxon Signed Ranks test were used to compare the normally and non-normally distributed quantitative data, respectively, before and after drug use. $P<0.05$ was considered statistically significant.

Results

The study was conducted with 87 patients, 50 (57.5%) males and 37 (42.5%) females, aged between 1 and 15 years. The mean age of the patients was 8.51 (4.09) years. Among them, 44.8% (n=39) were using VPA, 28.7% (n=25) were using LEV, 12.6% (n=11), OXC, 8% (n=7), phenobarbital, 4.6% (n=4) CBZ and 1.1% (n=1) was using ethosuximide.

In this study, the most used anti-epileptic drug was VPA. In 7.6% (n=3) of VPA users, the PLT value fell below 150,000 /ul, and in 2.5% (n=1), the HGB value fell below 10 g/dl. In 8% of the patients using LEV (n=2), HGB value was below 10 g/dl. Nine percent of OXC (n=1) users had ANC below 1500 /ul. In 14.2% of the patients using PB (n=1), the HGB value fell below 10 g/dl, in 14.2% (n=1), PLT count fell below 150,000 /ul, and in 14.2% (n=1), neutrophil count was <1500 /ul. When the pre- and post-drug values summarized in Table 1 were compared, the decrease in HGB and ANC values were not statistically significant, while the decrease in PLT count was ($P=0.039$). No statistically significant difference was found among the drug groups in terms of percentage change in blood count values measured during the pre- and post-drug periods ($P>0.05$) (Table 2).

Table 1: The Effects of Antiepileptics on Complete Blood Count

	Pre-drug		Post-drug		
	Min-Max	Mean (SD)	Min-Max	Mean (SD)	*P*-value
HGB	10.2-14.6	12.32 (0.99)	9.4-15.8	12.33 (1.28)	[1]0.884
HCT	30.2-43.1	36.54 (2.79)	29.5-46.7	36.71 (3.11)	[1]0.488
WBC	3760-17450	7976.43 (2309.36)	4680-16600	8019.42 (2289.81)	[1]0.886
PLT	156000-478000	296206.90 (74858.8)	125000-489000	279678.16 (76622.22)	[1]0.039*
ANC (median)	1210-13020	4087.24 (2154.70) (3380)	550-11580	3982.64 (1899.65) (3540)	[2]0.906
ALC (median)	890-7400	3035.75 (1234.62) (2870)	1130-7200	3181.61 (1254.91) (2960)	[2]0.349
AMC (median)	220-1880	621.49 (282.61) (580)	250-1710	597.70 (218.89) (600)	[2]0.942

[1] Paired samples t-test, [2] Wilcoxon sign test, * $P<0.05$

Table 2: Percentage Changes in Complete Blood Count Parameters by Antiepileptic Drug Group

Percentage Changes	Medications used					*P*-value
	Levetiracetam	Oxcarbazepine	Valproic acid	Phenobarbital	Carbamazepine	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
HGB	0.31 (7.29)	1.58 (6.24)	-0.28 (5.67)	-1.79 (10.22)	2.59 (5.71)	[1]0.832
HCT	0.85 (7.26)	1.93 (6.08)	0.45 (5.94)	-1.24 (6.88)	-0.44 (6.75)	[1]0.936
WBC	10.63 (47.59)	-3.29 (30.21)	4.61 (29.03)	18.48 (45.29)	9.76 (31.03)	[1]0.813
PLT	2.59 (26.38)	7.22 (22.57)	-9.46 (23.62)	-1.24 (38.43)	1.83 (8.55)	[1]0.253
ANC (median)	18.22 (86.68)	-0.57 (56.03)	8.73 (50.66)	75.33 (107.58)	45.43 (79.7)	[2]0.382
	(-12.23)	(-19.85)	(-0.51)	(36.96)	(22.93)	
ALC (median)	29.72 (75.37)	5.38 (25.8)	18.27 (68.46)	-1.86 (48.82)	-4.67 (40.98)	[2]0.727
	(8.73)	(4.56)	(6.7)	(-25.58)	(-13.02)	
AMC (median)	-7.12 (38.96)	1.66 (38.23)	22.01 (51.65)	12.41 (73.98	12.96 (50.3)	[2]0.191
	(-5.19)	(0)	(16.13)	(7.14)	(27.45)	

[1] One-way ANOVA test, [2] Kruskal Wallis test, Note: It was excluded from the analysis due to 1 child using ethosuximide

Discussion

Epilepsy is a common neurological disorder seen in the pediatric age group and AEDs constitute the basis of treatment. The new generation AEDs are gradually added to the old generation antiepileptics [7, 8]. The choice of AEDs for epilepsy treatment in infants and children depends not only on the effectiveness of the agent, but also on its safety, toxicity potential, tolerability, its effect on behavior and learning, and existing patient comorbidities [9-11].

BDZs (Benzodiazepines), clonazepam, diazepam, and lorazepam, which have been used frequently in the treatment of epilepsy, act on the GABA (Gamma Amino Butyric Acid) -BDZ receptor complex [12,13]. Few cases of lorazepam and clonazepam-induced pancytopenia, thrombocytopenia caused by clonazepam, and acute granulocytopenia, acute thrombocytopenic purpura, and active antiplatelet antibodies during treatment with diazepam were reported [14-18]. In this study, we also had patients using BDZ, but these patients were not included in the study because they were using multiple AEDs.

CBZ is widely used as an antiepileptic, which rarely causes hematological diseases such as aplastic anemia, thrombocytopenia, and leukopenia [19,20]. The rate of aplastic anemia due to CBZ ranges between 1/50000 and 1/200.000 [21]. In a cohort study by Blackburn et al. among 29,357 patients receiving AED, the frequency of severe blood dyscrasias, including aplastic anemia was investigated. They found only one case of aplastic anemia and did not find any relationship between the use of antiepileptic agents and aplastic anemia [22]. However, cases of thrombocytopenia related to CBZ have been reported in the literature [23-26]. In our study, 4.6% of the patients (4 patients) were using CBZ. No hematological side effects were encountered due to this drug.

Levetiracetam is another commonly used AED, and there are a few case reports about thrombocytopenia associated with LEV use [27-29]. To estimate the rate of LEV-induced thrombocytopenia, Sahaya et al. published a retrospective study in 2010. Accordingly, the medical records of 758 patients aged 18 years and older who received LEV during their hospital stay from June 2006 to December 2008 were reviewed. Thrombocytopenia was detected in 29 of 758 patients during LEV treatment. A secondary factor causing thrombocytopenia was determined in 23 patients, pre-existing thrombocytopenia was detected in 4 patients, and a clear relationship between LEV therapy and thrombocytopenia was reported in one patient [30]. In our study, 28.7% of the patients (n=25) were using LEV, HGB value fell below 10 g/dl in 8% (n=2), and no patient developed thrombocytopenia. Changes in hemoglobin values were not statistically significant.

Oxcarbazepine (OXC) is used in monotherapy or combination therapy in adults and children with partial and secondary generalized tonic-clonic seizures. Although OXC treatment has rare hematological side effects, thrombocytopenia, neutropenia, pancytopenia, and hemolytic anemia have been reported, especially at higher doses [31-34]. In our study, 12.6% of the patients (11 patients) were using OXC, and ANC was below 1500 /ul in 9% (1 patient). However, this decrease was not statistically significant.

Phenobarbital (PB) acts through GABA-dependent chloride channels and is an effective anticonvulsant for many seizure types such as tonic-clonic and focal seizures, and some clinical epilepsy sub-syndromes [35]. Megaloblastic anemia, leukopenia, agranulocytosis, and thrombocytopenia were associated with PB treatment [36]. In our study, 8% of the patients (7 patients) were using PB and among those, 14.2% (n=1) had HGB values below 10 g/dl, 14.2% (n=1) had PLT counts below 150,000 /ul, and the neutrophil count of 14.2% (1 patient) fell under 1,500 /ul. Patients should be followed up in terms of side effects related to phenobarbital use.

Thrombocytopenia is observed in 12-18% of patients using VPA and it is the most common hematological side effect of this drug [37]. Studies in pediatric patients have shown that blood loss and administration of blood products during surgical procedures are significantly increased in children on VPA monotherapy. Patients who received VPA treatment had a 23-fold relative risk of increased blood loss compared to those who did not receive VPA treatment, and a significant difference was observed in bleeding times and PT/aPTT values. Generally, thrombocytopenia was not severe, and no bleeding symptoms were encountered. Platelets have been found to increase within a few days after VPA dosage adjustments or ceases. Nevertheless, very rarely, fatal subarachnoid and pulmonary hemorrhage and pancytopenia have been reported [38]. In our patient group, in 7.6% of the patients (3 patients) using VPA, the PLT value fell below 150,000/ul, but no patients had severe thrombocytopenia (PLT count <100,000/ul). Platelet depletion was significantly lower when other antiepileptics were considered. Besides, coagulation disorders were not observed. Very few cases of factor XIII deficiency were reported during VPA treatment in adults and children. The rarity of homozygous factor XIII deficiency and the return of factor XIII activity to the normal range after VPA dose reduction support the effect of VPA on factor XIII levels. It is especially important to evaluate the platelet count, PT, aPTT, TT, fibrinogen, vWF, and factor XIII before surgical procedures in patients using VPA. Bleeding, hematomas, petechiae, bruising and prolonged bleeding are the alarm signs for dose reduction or cessation of treatment [39].

Besides, there are also publications indicating that VPA use causes neutropenia, although it is not as common as thrombocytopenia [40]. In our study, this rare side effect of VPA use was not encountered. Neutropenia usually occurs during the

first weeks of drug exposure and resolves within the first days after stopping the drug. VPA should be discontinued if the absolute neutrophil count (ANC) drops to <500 cells/mm [41].

Limitations

Our study is retrospective, and the number of our cases is relatively low, which are its two major limitations.

Conclusion

Considering the increasing number of pediatric patients diagnosed with epilepsy and the increasing use of AEDs, the hematological side effects of antiepileptic drugs should not be overlooked. It is seen in our study that the use of AEDs caused a significant decrease in the platelet value. In line with these results, blood count results of AED users must be followed up periodically. The mechanisms through which antiepileptic drugs cause hematological side effects and how often they occur are not known yet. There is a need for larger series and multi-center studies on this subject.

References

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014 Apr;55(4):475-82. doi: 10.1111/epi.12550. Epub 2014 Apr 14. PMID: 24730690.
2. Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017 Apr;58(4):531-42.
3. Cormier J, Chu CJ, Safety and efficacy of levetiracetam for the treatment of partial onset seizures in children from one month of age. Neuropsychiatr Dis Treat. 2013;9:295-306.
4. Bialer M, Johannessen SI, Koepp MJ, Levy RH, Perucca E, Tomson T, et al. Fourteenth Eilat Conference on new antiepileptic drugs and devices (EILAT XIV). I. Drugs in preclinical and early clinical development. Epilepsia. 2018;59:1811-41.
5. Perry MS. New and Emerging Medications for Treatment of Pediatric Epilepsy. Pediatr Neurol 2020;107:24.
6. Asadipooya AA, Sperling MR. Antiepileptic drugs and hematological disorders. Antiepileptic drugs: a clinician's manual. Oxford University Press, New York. 2009;165-170.
7. Guerrini R, Zaccara G, la Marca G, Rosati A. Safety and tolerability of antiepileptic drug treatment in children with epilepsy. Drug Saf. 2012;35(7):519-33.
8. Weijenberg A, Brouwer OF, Callenbach PM. Levetiracetam Monotherapy in Children with Epilepsy: A Systematic Review. CNS Drugs 2015;29(5):371–82.
9. Sankar R. Selecting appropriate pharmacotherapy for the child with epilepsy. Adv. Stud. Med 2005;5464–9.
10. Füsun Ferda Erdoğan. New Antiepileptic Drugs. Epilepsi. 2014; 20(Ek-1):56-8.
11. Sema saltık. Çocukluk Epilepsilerinde Tıbbi Tedavi. Epilepsi 2014;20(Ek 1):50-5.
12. Verrotti A, Coppola G, Parisi P. Bone and calcium metabolism and antiepileptic drugs. Clin Neurol Neurosurg. 2010;112:1-10.
13. Asadi-Pooya AA, Sperling MR. Mechanisms of actions and pharmacokinetic properties of antiepileptic drugs. Antiepileptic drugs: a clinician's manual. Oxford University Press, New York. 2009;69-148.
14. El-Sayed S, Symonds RP Lorazepam induced pancytopenia. Brit Med J. 1988;296:1332.
15. Bautista-Quach MA, Liao YM, Hsueh CT Pancytopenia associated with clonazepam. J Hematology Oncology. 2010;3:24.
16. Veall RM, Hogarth HC. Letter: Thrombocytopenia during treatment with clonazepam. Br Med J. 1975;4(5994):462.
17. Bussien R. Acute granulocytopenia after simultaneous administration of gentamicin and diazepam. Nouv Presse Med. 1974;3:1236.
18. Baumes RM. Drug induced cytopenia: acute thrombopenic purpura and active antiplatelet antibodies in the presence of valium. Maroc Med. 1971;546:321-4.
19. Handoko KB, Souverein PC, van Staa TP, Meyboom RH, Leufkens HG, Egberts TC, et al. Risk of aplastic anemia in patients using antiepileptic drugs. Epilepsia. 2006 Jul;47(7):1232-6.
20. Andres E, Maloisel F. Idiosyncratic drug-induced agranulocytosis or acute neutropenia. Curr Opin Hematol. 2008;15:15–21.
21. Zaccara G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. Epilepsia. 2007;48:1223–44.
22. Blackburn SC, Oliart AD, Garcia Rodriguez LA, Pérez Gutthann S. Antiepileptics and blood dyscrasias: a cohort study. Pharmacotherapy. 1998;18:1277–83.
23. Tichy E, Lam S, Militano U, Bessmertny O. A case of severe thrombocytopenia and antiepileptic hypersensitivity syndrome. J Pediatr Pharmacol Ther. 2003 Jan;8(1):29-33.
24. Tohen M, Castillo J, Cole JO, Miller MG, Heros R, Farrer RJ. Thrombocytopenia associated with carbamazepine: A case series. J Clin Psychiatry. 1991;52:496
25. Abate MV, Stocco G, Devescovi R, Carrozzi M, Pierobon C, Valencic E, et al. Carbamazepine-induced thrombocytopenic purpura in a child: Insights from a genomic analysis. Blood Cells Mol Dis. 2016 Jul;59:97-9.
26. Kumar R, Chivukula S, Katukuri GR, Chandrasekhar UK, Shivashankar KN. Carbamazepine Induced Thrombocytopenia. J Clin Diagn Res. 2017;11(9):OD12-3.
27. Kimland E, Höjeberg B, von Euler M. Levetiracetam-induced thrombocytopenia. Epilepsia. 2004;45:877–8.
28. Meschede A, Runge U, Sabolek M. Thrombocytopenia during levetiracetam therapy. Epilepsy. 2008;80:91–2.
29. Oghlakian R, Nock C, Koubeissi M. A case of levetiracetam-induced thrombocytopenia. Epileptic Disord. 2010;12:335–7.
30. Sahaya K, Goyal MK, Sarwal A, Singh NN. Levetiracetam-induced thrombocytopenia among inpatients: a retrospective study. Epilepsia. 2010;51(12):2492-5.
31. Mahmud J, Mathews M, Verma S, Basil B. Oxcarbazepine-induced thrombocytopenia. Psychosomatics. 2006;47:73-4.
32. Hsiao YT, Wei IH, Huang CC. Oxcarbazepine-related neutropenia: a case report. J Clin Psychopharmacol. 2010;30:94-5.
33. Calamaras MR, Stowe ZN, Newport DJ. Pancytopenia associated with the introduction of oxcarbazepine. J Clin Psychopharmacol. 2007;27:217-8.
34. Chaudhry MM, Abrar M, Mutahir K, Mendoza C. Oxcarbazepine-induced hemolytic anemia in a geriatric patient. Am J Ther. 2008;15:187-9.
35. Suddock JT, Cain MD. Barbiturate Toxicity. 2020 Jul 2. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. PMID: 29763050.
36. Asadipooya AA, Sperling MR. Antiepileptic drugs and hematological disorders. Antiepileptic drugs: a clinician's manual. Oxford University Press, New York. 2009;165-70.
37. Buoli M, Serati M, Botturi A, Altamura AC. The Risk of Thrombocytopenia During Valproic Acid Therapy: A Critical Summary of Available Clinical Data. Drugs R D. 2018;18(1):1-5.
38. Gerstner T, Teich M, Bell N. Valproate-associated coagulopathies are frequent and variable in children. Epilepsia. 2006;47:1136-43.
39. Teich M, Longin E, Dempfle CE, Konig S. Factor XIII deficiency associated with valproate treatment. Epilepsia. 2004;45:187-9.
40. Watts RG, Emanuel PD, Zuckerman KS, Howard TH. Valproic acid-induced cytopenias: evidence for a dose-related suppression of hematopoiesis. J Pediatr. 1990;117:495-9.
41. Curnutte JT, Coates TD. Disorders of phagocyte function and number. Hematology: basic principles and practice, 3rd edn. Churchill Livingstone, New York. 2000;743-5.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.