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Hematological changes in adult patients on valproic acid therapy

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Abstract
Introduction: Valproic acid (VPA) is one of the commonly used anti-epileptic drugs. It is also an effective mood stabilizing drug. Despite its therapeutic benefits, hematological toxicity of valproic acid is increasingly encountered. Therefore, this study was carried out to evaluate the various hematological changes in adult patients on VPA and to closely monitor them so as to prevent the life threatening side effects of VPA.
Aims and Objectives: (1) To study the spectrum of hematological changes in adult patients on VPA therapy and its distribution in different age groups and sex. (2) To establish a correlation between the dosage and duration of VPA therapy and its hematological effects.
Materials and Methods: The present study was a prospective study done over a period of one year. A total of 50 adult patients on VPA therapy for atleast six months duration and attending the out -patient department (OPD) in General hospitals under the Bangalore rural district were included in the study.
Results: A total of 50 adult patients on VPA therapy were included in the study. The patients were categorized into different age groups and sex. Female to male ratio was 2.6:1. Females constituted 72% of the total number of cases. The majority of the patients were in the age group of 26-35 years constituting 36% of the total number of cases. The spectrum of hematological changes were isolated anemia (8%), isolated leucopenia (4%), isolated thrombocytopenia (28%), bicytopenia (28%) and pancytopenia (24%). A direct correlation was established between the dosage as well as the duration of VPA therapy and the hematological changes observed especially in the elderly females. A significant negative correlation was found between the dosage of VPA therapy and the platelet and leucocyte counts.
Conclusion: The study helps in identifying the potential risk factors, closely monitoring the patients on VPA and preventing life-threatening side effects. It also helps the clinicians in dose adjustments and sensitizes them to be cautious while prescribing VPA in higher doses and for longer duration.

Keywords: Hematological toxicity, monotherapy, thrombocytopenia, valproic acid

Introduction
Valproic acid is the single most commonly used antiepileptic drug, and it is also indicated for multiple other uses, such as bipolar and mood disorders [1]. Despite its therapeutic benefits, hematological toxicity of valproic acid is increasingly encountered. VPA has a wide spectrum of hematological toxicity, including thrombocytopenia, anemia, leucopenia, pancytopenia, macrocytosis, and the presence of Pelger-Huet abnormality [2, 3]. Pure red cell aplasia, Aplastic anemia, Myelodysplastic syndrome and acute leukemia have also been reported [2, 4]. Most of these changes are dose-related [5, 6]. Advanced age, female gender, and high doses were found to be risk factors for the development of thrombocytopenia during the treatment with valproate [7]. Therefore, this study was carried out to evaluate the spectrum of hematological changes in adult patients on VPA therapy, to study its distribution in different age groups and sex and to establish correlation between the dosage and duration of VPA therapy and its hematological effects.

Materials and Methods
- **Place of study:** Out-patient department (OPD) in General hospital under the District Mental Health Program (DMHP), Bangalore Rural District.
- **Duration of study:** One year **(**January 2018 to January 2019)
- **Type of study:** Prospective study

- **Sample size:** 50
- **Sampling method:** Purposive sampling

Inclusion criteria

1. Patients on monotherapy with VPA for neuro-psychiatric disorders.
2. Patients above 18 years of age.
3. Patients on VPA therapy for atleast 6 months duration.
4. Patients whose relevant clinical history and definitive diagnosis is available.

Exclusion criteria

1. Patients on multidrug therapy for neuro-psychiatric disorders.
2. Pregnant women.

Sample collection method: A total of 50 adult patients of either sex on VPA therapy for atleast 6 months duration and attending the OPD in General hospital under the District Mental Health Program (DMHP), Bangalore Rural District were included in the study. The old investigation reports of atleast 6 months duration of the hematological parameters in the patients who were already on the VPA therapy were obtained as the baseline records. These were compared with the parameters recorded at the time of enrollment. Investigations were carried out on the day of enrollment for the patients who had no old reports and for the freshly diagnosed cases. These results were considered as the baseline records. These patients were followed up atleast for the next 6 months, the investigations were repeated and compared with the baseline reports. The blood samples were collected in the EDTA tubes for complete blood count (CBC) and peripheral smear (PS) examination. The hematological parameters obtained from the automated analyzer were correlated and confirmed with the peripheral smear examination. The various morphological changes in the blood cells were noted on peripheral smear examination. The data obtained was analyzed using the Microsoft Excel 2007 and SPSS statistical tool.

Results

A total of 50 adult patients on VPA therapy for atleast six months duration and attending the out -patient department (OPD) in General hospitals under the Bangalore rural district were included in the study. The patients were categorized into different age groups and sex. The number of female patients were more than that of the males with the female to male ratio being 2.6:1. The female patients constituted 72% of the total number of cases (Table 1). The majority of the patients were in the age group of 26-35 years constituting 36% of the total number of cases (Table 1).

Table 1: Distribution of the cases according to different age groups and sex

Age Groups (in years)	No. of Males	No. of females	No. of Cases	percentage
18-25	02	06	08	16%
26-35	02	16	18	36%
36-45	04	06	10	20%
46-55	06	04	10	20%
56-65	00	04	04	08%
Total	14 (28%)	36 (72%)	50	100%

The spectrum of hematological changes were cases with no abnormality, isolated anemia, isolated leucopenia, isolated thrombocytopenia, bicytopenia and pancytopenia (Table 2). Majority of the cases were isolated thrombocytopenias (28%) and bicytopenias (28%) followed by pancytopenias (24%). A total of 10 (27.7%) female patients had pancytopenia, and most of the pancytopenia cases (8/10) were seen among the female patients in the age group of 26-35 years (Table 3).

Table 2: Spectrum of hematological changes in patients on Valproic acid

Hematological spectrum		No. of Cases	Percentage
1	No Abnormality	04	08%
2	Anemia	04	08%
3	Leucopenia	02	04%
4	Thrombocytopenia	14	28%
5	Bicytopenia	14	28%
6	Pancytopenia	12	24%
	Total	50	100%

Table 3: Distribution of the spectrum of hematological changes in different age groups and sex

Age Group	Males							Females						
	Hematological Changes							Hematological Changes						
	NO	AN	LP	TP	BC	PC	Total	NO	AN	LP	TP	BC	PC	Total
18-25	-	-	-	-	-	02	02 (4%)	-	02	-	04	-	-	06 (12%)
26-35	-	-	-	-	02	-	02 (4%)	02	02	-	-	04	08	16 (32%)
36-45	-	-	-	02	02	-	04 (8%)	-	-	-	02	04	-	06 (12%)
46-55	02	-	02	02	-	-	06(12%)	-	-	-	02	-	02	04 (8%)
56-65	-	-	-	-	-	-	00	-	-	-	02	02	-	04 (8%)
Total	02		02	04	04	02	14(28%)	02	04		10	10	10	36 (72%)

Abbreviations: NO- No abnormality, AN- Anemia, LP- Leucopenia, TP- Thrombocytopenia, BC- Bicytopenia, PC- Pancytopenia.

Table 4: Table showing the correlation between the dosage of VPA and the hematological changes

Dosage OF VPA (in mg/day)	Hematological Changes						
	NO	AN	LP	TP	BC	PC	TOTAL
400	04	04	02	08	06	00	24 (48%)
600	-	-	-	06	04	02	12 (24%)
800	-	-	-		02	04	6 (12%)
1000	-	-	-	-	02	02	4 (8%)
1500	-	-	-	-	-	04	4 (8%)
Total	04	04	02	14	14	12	50 (100%)

Abbreviations: NO- No abnormality, AN- Anemia, LP- Leucopenia, TP- Thrombocytopenia, BC- Bicytopenia, PC- Pancytopenia

A direct correlation was established between the dosage of VPA and the hematological changes observed. The majority of the cases (48%) were given a dosage of 400mg/day of VPA. Among them, the commonest hematological finding was thrombocytopenia (8/24) followed by bicytopenia (6/24). Out of 12 cases of pancytopenias, 10 (83.3%) cases were put on a dosage of VPA ranging from 800-1500 mg/day **(**Table 4).

Out of 26 cases of anemia, isolated anemia was found in 4 cases. Out of 36 cases of thrombocytopenia, isolated thrombocytopenia was found in 14 cases and out of 22 cases of leucopenia, only 2 cases had isolated leucopenia. A significant negative correlation was found between the dosage of VPA therapy and the platelet and leucocyte count. Out of 22 cases of leucopenia, 15 (68%) cases had neutropenia.

The majority of the patients (48%) were on VPA therapy for 1 year duration. Isolated thrombocytopenias (8/24) and pancytopenias (8/24) were among the commonest findings in them. All the four patients (8%) who were on 1500 mg/day dosage of VPA therapy for more than 2 years duration were elderly females with refractory epilepsy and they had pancytopenia (Table 4 & 5). Therefore, a direct correlation was established between the dosage as well as the duration of VPA therapy and the hematological changes observed especially in the elderly female patients.

Table 5: Table showing the correlation between the duration of VPA therapy and the hematological changes

Duration of VPA therapy	Hematological Changes						
	NO	AN	LP	TP	BC	PC	TOTAL
6 Months	04	04	-	04	06	00	18 (36%)
1 Year	-	-	02	08	06	08	24 (48%)
1.5 Years	-	-	-	02	02	-	4 (8%)
2 Years	-	-	-	-	-	04	4 (8%)
Total	04 (8%)	04 (8%)	02 (4%)	14 (28%)	14 (28%)	12 (24%)	50 (100%)

Abbreviations: NO-No abnormality, AN- Anemia, LP- Leucopenia, TP- Thrombocytopenia, BC- Bicytopenia, PC- Pancytopenia

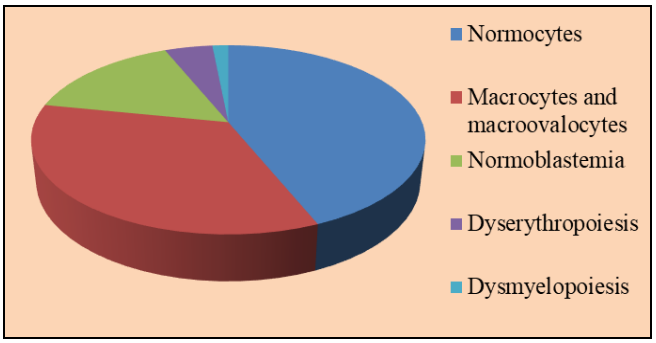

Fig 1: Pie diagram showing the peripheral smear findings in patients on VPA

The various peripheral smear findings observed were normocytes (28/50), macrocytes and macroovalocytes (22/50) (Figure 2), presence of nucleated RBCs (8/50) (Figure 2), dyserythropoietic features like nuclear budding in the nucleated RBCs (3/50) (Figure 3), dysmyelopoietic feature like presence of hyposegmented neutrophil resembling pseudo Pelger Huet anomaly (1/50) (Figure 4).

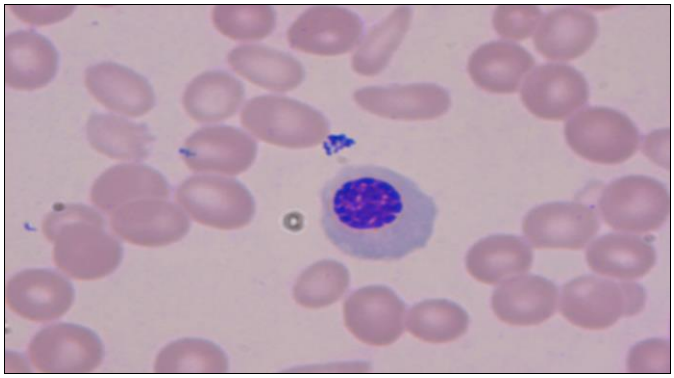

Fig 2: Peripheral blood smear of a case showing macrocytes, macro-ovalocytes and nucleated RBC. (PBS; Leishman's stain; 1000X)

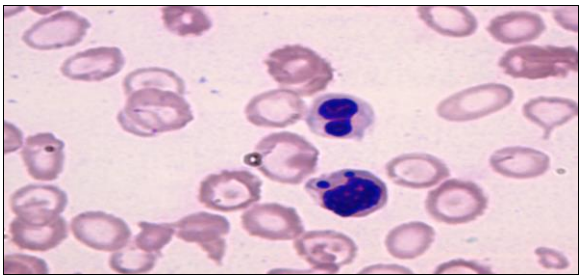

Fig 3: Peripheral blood smear in a case showing nuclear budding in nucleated RBCs. (PBS; Leishman's stain; 1000X)

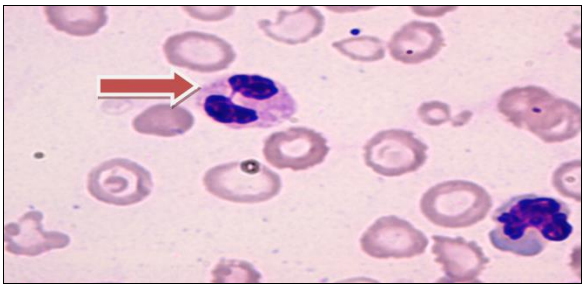

Fig 4: Peripheral blood smear of a case showing Pseudo-Pelger-Huet anomaly in neutrophils. (PBS; Leishman's stain; 1000X)

Discussion

Valproic acid is the single most commonly used antiepileptic drug, and it is also indicated for multiple other uses, such as bipolar and mood disorders [1]. Despite its therapeutic benefits, hematological toxicity of valproic acid is increasingly encountered. The present study was carried out to evaluate the spectrum of hematological changes in adult patients on VPA therapy, to study its distribution in different age groups and sex and to establish correlation between the dosage and duration of VPA therapy and its hematological effects.

In a study conducted by May RB *et al*., 60 patients receiving long-term VPA monotherapy were studied for hematologic side effects. The patients ranged in age from 2 to 29 years

[8]. In the present study 50 adult patients were studied. The patients were in the age group between 18 to 65 years and the majority of the patients were in the age group of 26-35 years constituting 36% of the total number of cases.

The spectrum of hematological changes observed in our study were cases with no abnormality, isolated anemia, isolated leucopenia, isolated thrombocytopenia, bicytopenia and pancytopenia. Majority of the cases were isolated thrombocytopenias (28%) and bicytopenias (28%) followed by pancytopenias (24%). Thrombocytopenia is the most common hematologic toxicity while aplastic anemia, pure red cell aplasia (PRCA), macrocytosis, neutropenia and bleeding disorders are some of the other hematological adverse reactions to VPA therapy cited in the literature [9-14].

A survey with 264 psychiatric patients reported a 12% prevalence of thrombocytopenia, with the elderly having the highest risk, especially with a VPA dosage >1 g/day [15]. Trannel *et al* [10] confirmed in a small sample of 39 psychiatric patients that elderly patients experienced thrombocytopenia more frequently than younger ones during VPA treatment (54 vs 13%). In addition, Nasreddine and Beydoun [11] reported that about 17.7% of epileptic patients experience at least one episode of thrombocytopenia during VPA treatment, and the risk was significantly increased in case of VPA plasma levels > 100 microg/ mL for women and 130 microg/mL for men. In our study, out of 12 cases of pancytopenias, 10 (83.3%) cases were put on a dosage of VPA ranging from 800-1500 mg/day. The majority of the patients (48%) were on VPA therapy for 1 year duration. Isolated thrombocytopenias (8/24) and pancytopenias (8/24) were among the commonest findings in them. All the four patients (8%) who were on 1500 mg/day dosage of VPA therapy for more than 2 years duration were elderly females with refractory epilepsy and they had pancytopenia. Therefore, a direct correlation was established between the dosage as well as the duration of VPA therapy and the hematological changes observed especially in the elderly female patients.

In a study by Jharna Sahu *et al*., out of 72 patients on VPA, total percentage of thrombocytopenia was found to be 12.5%; among that females constituted 19.04% and males constituted 9.8% [16]. Even in our study out of a total of 14 patients presenting with thrombocytopenia, 10 (71.4%) cases were females. A direct correlation was established between the dosage of VPA and the hematological changes observed. The majority of the cases (48%) were given a dosage of 400mg/day of VPA. Among them, the commonest hematological finding was thrombocytopenia (8/24) followed by bicytopenia (6/24).

Vasudev K *et al*., analyzed the data from 126 patients. The prevalence of thrombocytopenia was found to be approximately 5%. In female subjects, a significant negative correlation was found between serum valproate level and platelet count [9]. Twenty out of sixty patients treated with valproic acid were reported to have significant hematological abnormalities, with thrombocytopenia and macrocytosis being the most common in a study by May RB *et al*. [8].

Valproic acid has a wide spectrum of hematologic toxicity, including thrombocytopenia, anemia, leukopenia, macrocytosis, and the presence of the Pelger- Huet abnormality [17]. Many of these toxicities appear to be dose-related [5]. Twenty of 60 patients treated with valproic acid were reported to have significant hematological abnormalities, with thrombocytopenia and macrocytosis being the most common [8]. Serious, but reversible, hematologic toxicity resembling a myelodysplastic syndrome (MDS) has also been reported. Four patients were reported to have thrombocytopenia, macrocytosis, the Pelger-Huet abnormality, and trilineage dysplasia in the bone marrow associated with valproic acid [18]. Hongeng *et al*. reported a case of anemia, thrombocytopenia, and myelodysplastic changes in the marrow, which resolved with a decrease in valproic acid dose [19].

The various morphological findings observed in our study were normocytes (28/50), macrocytes and macroovalocytes (22/50), presence of nucleated RBCs (8/50), dyserythropoietic features like nuclear budding in the nucleated RBCs (3/50), dysmyelopoietic feature like presence of hyposegmented neutrophil resembling pseudo-Pelger Huet anomaly (1/50). In a case series by Chi-chiu so, dysmyelopoiesis was reported in two elderly patients on sodium valproate [20]. Neutrophils with pseudo-Pelger-Huet anomaly were found on peripheral smear examination. Dysmyelopoiesis was also seen on bone marrow aspirate smears.

Conclusion

The present study helps in identifying the potential risk factors, closely monitoring the patients on VPA therapy and preventing any life-threatening side effects. It also helps the clinicians in dose adjustments and sensitizes them to be cautious while prescribing VPA in higher doses and for longer duration, especially in patients with potential risk factors.

Abbreviations VPA- Valproic acid, CBC- Complete blood count, PS- Peripheral smear, EDTA- Ethylenediaminetetraacetic acid, OPD- Out-patient department, DMHP-District Mental Health Program, NO- No abnormality, AN- Anemia, LP- Leucopenia, TP- Thrombocytopenia, BC- Bicytopenia, PC- Pancytopenia**.**

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References

1. Perucca E. Pharmacological and therapeutic properties of valproate: a summary after 35 years of clinical experience. CNS Drugs. 2002; 16(10):695-714.
2. Coyle TE, Bair AK, Stein C, Vajpayee N, Mehdi S, Wright J. Acute leukemia associated with valproic acid treatment: a novel mechanism for leukemogenesis? Am J Hematol. 2005; 78(4):256-60.
3. Suchitra A, Bussel JB. Hematologic toxicity of sodium valproate. J Pediatr Hematol Oncol. 2000; 22:62-5.
4. Ganick DJ, Sunder T, Finley JL. Severe hematologic toxicity of valproic acid. Am J Pediatr Hematol Oncol. 1990; 12:80-5.
5. Watts RG, Emanuel PD, Zuckerman KS, Howard TH. Valproic acid induced cytopenias; evidence for a dose related suppression of hematopoieses. J Pediatr. 1990; 11:494-9.

6. Honeng S, May W, Christ WM. Transient myelodysplasia due to valproic acid. Clin Pediatr. 1997; 36:361-4.
7. Buoli M, Serati M, Botturi A, Altamura AC. Valproic acid therapy: A critical summary of available clinical data. Drugs R D. 2018; 18:1-5. Doi: https://doi.org/10.1007/s40268-017-0224-6.
8. May RB, Sunder TR. Hematologic Manifestations of Long-Term Valproate Therapy. Epilepsia. 1993; 11:494-9. Doi: https://doi.org/10.1111/j.1528-1157.1993.tb02139.x
9. Vasudev K, Keown P, Gibb I, McAllister-Williams RH. Hematological effects of valproate in psychiatric patients: what are the risk factors? J Clin Psychopharmacol. 2010; 30(3):282-5. Doi: https://doi.org/10.1097/JCP.0b013e3181db2684
10. Trannel TJ, Ahmed I, Goebert D. Occurrence of thrombocytopenia in psychiatric patients taking valproate. Am J Psychiatry. 2001; 158(1):128-30. Doi: https://doi.org/10.1176/appi.ajp.158.1.128
11. Nasreddine W, Beydoun A. Valproate-induced thrombocytopenia: a prospective monotherapy study. Epilepsia. 2008; 49(3):438-45. Doi: https://doi.org/10.1111/j.1528-1167.2007.01429.x
12. Chen Li, Lei Su, Minxi Lao, Shaofang Zhu, Meilin Ding. Anemia secondary to the use of sodium valproate for preventing postoperative seizures in a 79-year-old man: A case report. Medicine. 2018; 97:50.
13. Handoko KB, Souverein PC, van Staa TP, Egberts TC, van den Bemt PM. Risk of aplastic anaemia in patients using antiepileptic drugs. Epilepsis. 2006; 47:1232-6. Doi: https://doi.org/10.1111/j.1528-1167.2006.00596.x
14. Kanada J, Chonabayashi K, Watanabe M, Arima N, Tsudo M. Successful treatment with cyclosporine of sodium valproate indiced pure red cell aplasia. Rinsho Ketsueki. 2005; 46:1114-7.
15. Conley EL, Coley KC, Pollock BG, Dapos SV, Maxwell R, Branch RA. Prevalence and risk of thrombocytopenia with valproic acid: experience at a psychiatric teaching hospital. Pharmacoherapy. 2001; 21:1325-30
16. Sahu J, Hishikar R, Sahu MK, Raut P, Bharti AK, Agrawal S. Occurrences of thrombocytopenia with valproic acid used for psychiatric indication. Int J Basic Clin Pharmacol. 2015; 4:765-9. Doi: http://dx.doi.org/10.18203/2319-2003.ijbcp20150388.
17. Suchitra A, Bussel JB. Hematologic toxicity of sodium valproate. J Pediatr Hematol Oncol. 2000; 22:62-65.
18. Ganick DJ, Sunder T, Finley JL. Severe hematologic toxicity of valproic acid. Am J Pediatr Hematol Oncol 1990; 12:80-5.
19. Honeng S, May W, Christ WM. Transient myelodysplasia due to valproic acid. Clin Pediatr. 1997; 36:361-4.
20. Chi-chiu So, Kit-fao Wong. Valproate-associated dysmyelopoiesis in elderly patients. Am J Clin Pathol. 2002; 118:225-8.