ORIGINAL ARTICLE

The Risk of Development of Thrombocytopenia during Valproic Acid Therapy in Children Attending Aswan University Hospitals

Hanan Mohammed Abd El-Moneim[1], Mohammad Bahaa-Eldeen Alameer[1], Ahmed Mohammad Nour Eldeen Elgalaan[1]*

[1] Pediatrics' Department, Faculty of Medicine, Aswan University

ABSTRACT

Keywords: Thrombocytopenia, Valproic Acid Therapy, Children

***Corresponding author:** Ahmed Mohammad Nour Eldeen, **Mobile:** (+20) 01111273231, **E-Mail:** ahmed.nou1992@gmail.com

Background: Thrombocytopenia reported to be the most frequent adverse event nevertheless, hematologic toxicity was never severe enough to discontinue therapy and it always improved after small decrements of Valproic acid (VPA) doses.**Objective:** To determine the relationship between valporic acid treatment and incidence of thrombocytopenia in epileptic children attending Aswan university hospital.**Patients and methods:** This study is an observational cross-sectional study, conducted in 6 months duration from September 2019 to February 2020 on 73 epileptic children attending Aswan university hospital in neurological out clinic or admitted to PICU or pediatric department estimating the prevalence of thrombocytopenia during Valproic acid treatment. **Results:** A total of 73 pediatric patients on VPA therapy, fourteen (19.1%) patients had thrombocytopenia. There was statistical significant difference (p- value 0.008) to incidence of thrombocytopenia according to family history and developmental history of studied cases. There was no statistical significant of incidence of thrombocytopenia as regard to duration of Valproic acid treatment. There was high statistical significant difference in platelets between primary valproic acid dose and after 2 weeks of decreasing or increasing of VA dose (P-value < 0.001). **Conclusion:** Our findings underline the importance of monitoring platelet counts on patients treated with VPA, as advised in the product label, before the onset and during the therapy.

INTRODUCTION

Now international guidelines recommend use of VPA for acute and long-term treatment of bipolar disorder (BD). VPA monotherapy has showed the same effectiveness as lithium and atypical antipsychotics for the treatment of acute mania, but with a better tolerability [(1)].

Valproic acid poisoning in childhood frequently develops due to overdosing or suicidal use. Central nervous system (CNS) depression, cerebral edema, hyperammoniemia, hepatotoxicity, hemorrhagic pancreatitis, bone marrow suppression and death are among the clinical

findings it causes [2]. Hematological disorders are seen in children treated with VPA, including thrombocytopenia, platelet dysfunction, Von Willebrand disease, Factor XIII deficiency, hypofibrinogenemia and vitamin K-dependent factor deficiency [3].

Thmbocytopenia is defined as a platelet count of < 150,000/uL (2.5^{th} lower percentile); however, emergency treatment is required in case of a count < 50,000/uL [4].

Thrombocytopenia reported to be the most frequent adverse event; nevertheless, hematologic toxicity was never severe enough to discontinue therapy and it always improved after small decrements of VPA doses [5]. VPA therapy is also known to produce thrombocytopenia in pediatric patients as a result of marrow suppression [6]. Children seem to be affected more frequently than adults. This may be because children are treated more often with VPA and frequently with higher doses compared with adults [7].

The aim of the present study was to investigate the relationship between valporic acid treatment and incidence of thrombocytopenia in epileptic children attending Aswan University Hospital.

PATIENTS AND METHODS

This study is an observational cross-sectional study, conducted in 6 months duration from September 2019 to February 2020 on 73 epileptic children attending Aswan university hospital in neurological out clinic or admitted to PICU or pediatric department.

Ethical consent:

An approval of the study was obtained from Aswan University academic and ethical committee. Parents was be given free choice to refuse or enroll in the study. Verbal & written consent were obtained from all patients' parents before getting them involved in the study.

Inclusion criteria: Diagnosed epileptic children who use valproic acid treatment only, and age of 1 to 18 years old.

Exclusion criteria: Epileptic children using antiepileptic drugs other than Valproic acid, and children with definitive evidence of thrombocytopenia for other reasons.

Data Collection:

All included patients were interviewed and data were collected in the form of structured questionnaire (was filled from parents or care givers of the included children) which includes the following data:

1. **Full history taking**

Age, child sex, residency, consanguinity of parents, family history of epilepsy, natal, postnatal history, developmental history (mental @ motor history), vaccination history, history of purpura or bleeding tendency, history of associated diseases, age of onset of epilepsy, type of epilepsy, presenting symptoms, history of hospital admission and Valproic acid dose, and duration of Valproic acid therapy.

2. **Full physical examination**.
3. **Some anthropometric measurements** (according to growth charts)
4. **Laboratory investigations include:**
    a. **Complete blood count**: to screen for any one of a variety of diseases and conditions that affect blood cells.
        - **Anemia:** children aged 6 months to 6 years are considered anemic at hemoglobin value of less than 11 gm/dl and children aged 6 years to 14 years are considered anemic at hemoglobin value of less than 12 gm/dl**.**

- **Leucopenia**: decrease in the number of White Blood Cells below 3500/mcl.
- **Thrombocytopenia**: decrease in the number of platelets below 150000/mcl.

b. Serum Valproic acid level: To determine the concentration of valproic acid in patients' blood.

c. Electroencephalogram (EEG) finding :A non-invasive way to look into brain of patients

These children are reviewed at least once every three months.

Statistical Analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). The data were tested for normality using the Kolmogorov-Smirnov test and for homogeneity variances prior to further statistical analysis. Categorical variables were described by number and percent (N, %), where continuous variables described by mean and standard deviation (Mean, SD, Median). Chi-square test and fisher exact test used to compare between categorical variables. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

A total of 73 pediatric patients on VPA therapy, fourteen (19.1%) patients had thrombocytopenia.

Socio-demographic characteristics of the studied cases including the Mean ± SD of age was (5.53±3.33) years, male represent 53.4 % of cases, 24.7% of cases had positive consanguinity, and 69.9% of cases had normal developmental history. Percentage of residency distribution showed that Aswan, Draw, Edfo, Elkhatara, Komombo, Kous and Nasr-elnouba are 67.1%, 8.2%, 5.5%, 1.4%, 15.1%, 1.4% and 1.4%, respectively, and only 16.4 % of cases had positive family history of epilepsy **(Table 1).**

There was statistical significant difference **(p- value 0.008**) between thrombocytopenic and all cases regarding family history and developmental history of studied cases as 12 (85.7%) of cases with thrombocytopenia had positive family history and delayed developmental history. There was no statistical significant difference **(p- value > 0.05)** to incidence of thrombocytopenia regarding age, gender, residency and consanguinity in studied cases **(Table 2).**

Twelve (85.7%) cases with thrombocytopenia did not have associated diseases, 1(7.1%) had cerebral palsy and 1(7.1%) of cases had Hydrocephalus with VP shunt. There was statistical significant difference **(p- value 0.001)** between cases of thrombocytopenia and all cases regarding presence of associated disease **(Table 3).** There was statistical significant difference (**p- value 0.001)** between incidence of thrombocytopenia and Type of epilepsy (Table 4). There was no statically significant of incidence of thrombocytopenia as regard to duration of Valproic acid treatment. In addition, all cases of thrombocytopenia had high Valproic acid daily dose and high serum valproic acid level **(Table 4).**

6 (55.5%) of anemic cases had high serum level of Valproic acid. 5(45.5%) of anemic cases had normal serum Valproic acid level**.** All cases of leucopenia had high serum level of Valproic acid **(Table 5).** There was high statistical significant difference in platelets between primary valproic acid dose and after 2weeks of modulation of VA dose (P-value < 0.001) **(Table 6).**

Table (1): Socio-demographic data of studied cases.

Variables	Total sample (n=73)
Age	
• Mean ± SD	5.53±3.33
• Range	1.5_16
Age categories	
• 1-6 years	51 (69.9) %
• 6-12 years	18 (24.7) %
• 12-18 years	4 (5.5)%
Gender	
• Male	39 (53.4) %
• Female	34 (46.6) %
Residency	
• Aswan	49 (67.1) %
• Draw	6 (8.2) %
• Edfo	4 (5.5) %
• Elkhatara	1 (1.4) %
• Komombo	11 (15.1) %
• Kous	1 (1.4) %
• Nasrelnoba	1 (1.4) %
Consanguinity of parents	
• Cousins	18 (24.7) %
• No	55 (75.3) %
Vaccination history	
• Yes	73 (100%)
• No	0 (0%)
Motor developmental history	
• Normal	51 (69.9) %
• Delayed	22 (30.1)%
Family history of epilepsy	
• Yes	12 (16.4) %
• No	61 (83.6) %
Age at onset of epilepsy (month)	
• Range	0.5 – 84
• Mean ± SD	16.92±16.57
Valproic acid dose	
• Mean ± SD	46.1±15.27
• Range	20 – 80
Duration of VA treatment levels	
• Mean ± SD	3.45±2.84
• Range	0.25-12
CBC results	
• Anemia	11(15 %)
• Leucopenia	3 (4.1 %)
• Thrombocytopenia	14 (19.2 %)

Table (2): Incidence of thrombocytopenia according to socio-demographic data of studied cases.

		Total sample (n=73)	Thrombocytopenia (n=14)	P value
Age categories	• 1-6 years • 6-12 years • 12-18 years	51 (69.9) % 18 (24.7) % 4 (5.5)%	7 (50%) 6 (42.9%) 1 (7.1%)	0.109
Gender	• Male • Female	39 (53.4) % 34 (46.6) %	8 (57.1%) 6 (42.9%)	0.593
Residency	• Aswan • Draw • Edfo • Elkhatara • Komombo • Kous • Nasrelnoba	49 (67.1) % 6 (8.2) % 4 (5.5) % 1 (1.4) % 11 (15.1) % 1 (1.4) % 1 (1.4) %	7 (50%) 2 (14.3%) 2 (14.3%) 0 (0.0%) 2 (14.3%) 0 (0.0%) 1 (7.1%)	0.192
Consanguinity of parents	• Cousins • No	18 (24.7) % 55 (75.3) %	5 (35.7%) 9 (64.3%)	0.064
Developmental history	• Normal • Delayed	51 (69.9) % 22 (30.1)%	12 (85.7%) 2 (14.3%)	0.008**
Family history of epilepsy	• Yes • No	12 (16.4) % 61 (83.6) %	2 (14.3%) 12 (85.7%)	0.008**

* Statistically significant difference (p<0.05) ****** Highly statistically significant difference (p<0.01)

Table (3): Incidence of thrombocytopenia according to history of associated diseases of studied cases.

	Total sample (n=73)		Thrombocytopenia (n=14)		P value
	No.	%	No.	%	
History of associated diseases					0.001**
No	51	69.9%	12	85.7%	
CP	7	9.6%	1	7.1%	
Holoprosencephaly	2	2.7%	0	0.0%	
Hydrocephalus with VP shunt	5	6.8%	1	7.1%	
Metachromatic leukodystrophy	1	1.4%	0	0.0%	
Neurofibromatosis	1	1.4%	0	0.0%	
Postmeningitic epilepsy	3	4.1%	0	0.0%	
Sturge weber syndrome	1	1.4%	0	0.0%	
Tay sachs dis	1	1.4%	0	0.0%	
Van der knaap dis	1	1.4%	0	0.0%	

* Statistically significant difference (p<0.05) ****** Highly statistically significant difference (p<0.01)

Table (4): Type of epilepsy and Valproic acid (duration of treatment, daily dose, serum levels) in studied cases.

	Total sample (n=73)	Thrombocytopenia (n=14)	P.value
Type of epilepsy • Generalized tonic convulsions • Generalized tonic clonic convulsions • Focal tonic clonic convulsions • Myoclonic convulsions	 13 (17.8) % 54 (74) % 4 (5.5) % 2 (2.7) %	 1 (7.1%) 12 (85.7%) 1 (7.1%) 0 (0.0%)	0.001**
Duration of VA treatment levels • 0 – 2 • 3 – 4 • 5 – 6 • 7 – 8 • 9 - 10 • 11 – 12	 35 (47.9%) 19 (26.0%) 10 (13.7%) 3 (4.1%) 3 (4.1%) 3 (4.1%)	 3(21.4%) 4(28.6%) 5(35.7%) 0(0.0%) 1(7.1%) 1(7.1%)	0.334
Categories of Valproic acid daily dose • Cut of point • Low • High	 51 (69.8)% 5 (6.8)% 17 (23.3)%	 0(0.0%) 0(0.0%) 14(100%)	-
Categories of serum Valproic acid level • **Cut of point** • **Low** • **High**	 18 (24.7)% 5 (6.8)% 50 (68.5)%	 14(100%) 0(0%) 0(0%)	-

Chi-square test Independent samples T Test and Chi-square test

* Statistically significant difference ($p<0.05$) ****** Highly statistically significant difference ($p<0.01$)

Table (5): Anemia and Leucopenia according to serum Valproic acid level.

Categories of serum Valproic acid level	Total sample	Anemia (n=11)	Leucopenia (n=3)
• Cut of point • Low • High	18 (24.7)% 5 (6.8)% 50 (68.5)%	5 (45.5%) 0 (0.0%) 6 (55.5%)	3 (100%) 0 (0.0%) 0 (0.0%)
P. value	-	0.998	-

Table (6): Follow up of Serum valproic acid and platelets after 2 weeks of modulation of Valproic acid dose.

	Total sample (n=73)	**Pre-modulation of VA dose (n=14)**	**Follow up after 2 weeks**	**P. value**
Serum valproic acid level (normal 50 - 100 micgm / ml)				
High	18 (24.7%)	18 (100%)	0 (0%)	-
Platelets (normal 150000 - 450000)				
Normal	59 (80.8%)	0 (0.0%)	14 (100%)	<0.001**
Low	14 (19.1%)	14 (100%)	0 (0.0%)	

Fisher exact test * Statistically significant difference (p<0.05)
** Highly statistically significant difference (p<0.01)

DISCUSSION

Our study revealed that the age of patients range from 1.5 years to 16 year with Mean ± SD of age is 5.53 ± 3. 33 years, which was agree with **Mehmood et al.** [8] study, of the eighty eight patients**,** where the age of the children ranged from 2 to 12 years with a mean age of 7.28±2.46 years. The median and mode ages were 7 and 8 years respectively. Also in line with **Koenig et al.** [9]**,** of twenty three patients, as their mean age of their patients 7.3±4.7 years. While, in contrast to our study **Fidanci et al.** [10], 114 patients, found that their Mean age was 9.91±4.69 years, this difference may be due to different sample sizes and different study which were retrospectively.

The studied group include 53.4% males and 46.6% females, this is similar to **Sahu and Dubey** [11] as their 72 patients (51 male and 21 female) ,While this is disagree with **Nasereddine and Beydoun** [12] where their patients were 46% males and 54% were females, also it is in contrast with **Koenig et al.** [9], 23 patients study, as their patients were 47.8% males and 52.2% females, also in contrast with **Fidanci et al.** [10] study where their patients were female (57.9%) and (42.1%) were male. This difference may be due to different age categories between studies as in our study were pediatrics mainly in early age before their hormonal changes and its consequences.

In our study the mean duration of valproic acid treatment ± SD among our cases was 3.45 ± 2.84 years which is close to that in **Rehman et al.** [13] study as they found that the mean duration of valproic acid treatment ± SD was 2.25 ±1.48 years.

In our study, VPA dose (normal dose 20_60 mg l kg l day) range from 5-80 mg/kg/day, which close to the mean VPA dose in **Mehmood et al.** [8] as it was ranged from 30.3-76.9 mg/kg/day in divided doses with a mean dose of 41.86 ± 9.37 mg/kg/day. Also close to the mean dose of valproic acid treatment in **Kanwal et al.** [14] as it was 38.40±6.07mg/kg. In contrast, some patients benefit from considerably larger doses of the drug with a dosage from 50 to 100 mg/kg/day, especially in seizure disorders that were difficult to control [15].

The spectrum of hematological changes observed in our study varies from cases with no abnormality, isolated anemia, isolated leucopenia, isolated thrombocytopenia, bicytopenia and pancytopenia. This is similar to **Shubha et al.** [16], 50 patients, but we found that majority of the cases were isolated thrombocytopenias (19.2%) followed by

anemias (8.2%) followed by leucopenia and bicytopenia (4.1%) followed by pancytopenia (1.4 %), and **Shubha et al.** [16] found that majority of the cases were isolated thrombocytopenias (28%) and bicytopenias (28%) followed by pancytopenias (24%)**,** also **Buoli et al.** [4] reported thrombocytopenia to be the most frequent adverse event; nevertheless and it always improved after small decrements of VPA doses.

Our study described thrombocytopenia in 19.2% of cases treated with valproate. Cases with no thrombocytopenia was 80.8% of sample, which were close to **Buoli et al.** [4]**, Delgado et al.** [17]**, Fidanci et al.** [10] **and Mehmood et al.** [8] studies as they found the prevalence of thrombocytopenia with Valproic acid treatment in their cases was 12-18%, 21 %, 16% and 19.3% respectively. Results of study of **Vasudev et al.** [18] reported slightly lower prevalence rate of 5% of thrombocytopenia among their cases. While, **Zighetti et al.** [19] study failed to find a significant association between VPA treatment and risk of thrombocytopenia. The frequency of valproate-induced thrombocytopenia varied widely in previous studies, due to methodological differences, one of the reasons for this is the definition of thrombocytopenia, another reason that in most of the studies, thrombocytopenia has been found to be mild to moderate and transient that resolves spontaneously.

We found that there was statistical significant relation between high serum valproic acid level and valprioc acid daily dose and the decrease in the platelets count, WBCs and HB, also which agree with almost the majority of studies as many authors have seen that VPA-induced thrombocytopenia is dose related and usage of high doses can be considered a potential risk factor. For example **Mehmood et al.** [8] study, 88 patients, which found that the platelet count has been shown to be inversely correlated to VPA dose and plasma VPA concentration, they found that the platelet count should be monitored for children receiving valproic acid especially on higher doses as children using higher doses of valproate are at higher risk of developing thrombocytopenia. In addition, **Nasereddine and Beydoun** [12] found that there is significant negative correlation between VPA levels and platelet counts, which were in accordance with our study.

Our study also agree with **Koenig et al.** [9] study where they were able to show a clear negative correlation between platelet count and serum valproate level. All cases of thrombocytopenia in their patients were caused by serum valproate levels above 100 mg/l. Another study by **Goyal et al.** [20] found that low platelet levels were typically noted in patients with serum valproate levels of over 140 µg/ mL. On the other hand **Sahu and Dubey** [11], 72 patients, did not find any correlation between thrombocytopenia and VPA dose.

We didn`t find significant association between age, gender and thrombocytopenia**,** which agree with **Mehmood et al.** [8] finding as they found that age and gender were not significantly associated with thrombocytopenia, also this in line with **Sahu and Dubey** [11] as they didn't find any gender difference in their study. In the other hand **Buoli et al.** [4] found that the risk factors of VPA-associated thrombocytopenia appear to be advanced age, female gender, and high doses. In addition, another study by **Goyal and Badyal** [20] disagree with our study as they found that the risk of thrombocytopenia was reported to increase with the age of the patient. The age-dependent thrombocytopenia under valproate therapy on their studies could be explained with the matured immune system and therefore

extended platelet destruction in older children.

In our study there is no statistical significant difference between studied groups as regard to duration of VA treatment and the thrombocytopenic effects this agree with **Co et al.** [21] demonstrated that the duration of VPA treatment is not a confounding factor in this decrease in platelet count. And disagree with **Sahu and Dubey** [11] as they stated that the decrease in mean platelet count was significantly correlated with duration of therapy. Also in contrast with **Kim et al.** [22] study, 281 patients, as they found that long duration of VPA therapy was associated with the development of thrombocytopenia..

In our study we found high statistical significant between increase the platelets count in patients with thrombocytopenia after modulation of VA dose, this agree with **Delgado et al.** [17] who found that the thrombocytopenia usually resolves only a few days after the dose is reduced. Because thrombocytopenia is a level-related side effect of valproate treatment, discontinuation of the drug is rarely necessary. Also agree with **Goyal and Badyal** [20] that found reduction of the medication dose usually resulted in a prompt increase in the number of platelets.

In our study the total sample of studied groups was which have no anemia was 62(85 %), 11(15%) of sample which have anemia, 6(54.5 %) cases with anemia had high serum VA level and VA dose, 5 (45.5%) cases with anemia had normal VA level and normal VA dose. bleeding cause normocytic normochromic anemia, associated diseases cause always microcytic hypochromic anemia due to iron deficiency anemia due to poor oral intake due to difficult swallowing , high serum VA dose cause 6 normocytic normochromic anemia and 1 macrocytic anemia. This is agree with **Shubha et al.** [16] who found that 8% of their patients have anemia related to VPA treatment. Also **Vasudev et al.** [18] found that pure red cell aplasia (PRCA), macrocytosis, neutropenia and bleeding disorders are some of the hematological adverse reactions to VPA therapy.

In our study the total sample of studied group was which have leucopenia was 4.1% have no leucopenia was 95.9% of samples, which were agree with **Rehman et al.** [13] as they found the prevalence of leucopenia with Valproic acid in their cases was 26%, also agree with **Shubha et al.** [16] as they found the prevalence of leucopenia with Valproic acid in their cases was only 4%, this disagree with **Fidanci et al.** [10] that found Leucopenia was not observed in any of thier patient that may be due to different type of study which was retrospectively .

CONCLUSION

VPA is currently considered a first-line treatment option for the management of both BD and different forms of epilepsy in the light of its efficacy and relative safety, Our findings underline the importance of monitoring platelet counts on patients treated with VPA, as advised in the product label, before the onset and during the therapy. This monitoring should be continued regularly. However, the discontinuation of the drug is not necessary in majority of cases. Most of the time thrombocytopenia is mild and transient which resolves after 2 weeks of modulation of VA dose.

REFERENCES

1. **Fountoulakis KN, Grunze H, Vieta E, Young A, Yatham L, Blier P et al. (2016):** The International College of Neuro Psychopharmacology (CINP)

treatment guidelines for Bipolar disorder in adults (CINP-BD-2017): part 3: the clinical guidelines. Int J Neuropsychopharmacol., 20:180–95.

2. **Shadnia S, Amiri H, Hassanian-Moghaddam H. (2015)**: Favorable results after conservative management of 316 valproate intoxicated patients. J ResMed Sci., 20(7):656–661.
3. **Chateauvieux S, Morceau F, Dicato M, Diederich M. (2010):** Molecular and Therapeutic Potential and Toxicity of Valproic Acid. Journal of Biomedicine and Biotechnology, 10: 479364. doi:10.1155/2010/479364
4. **Buoli M, Serati M, Botturi A, Altamura AC. (2018)**: The Risk of Thrombocytopenia During Valproic Acid Therapy: A Critical Summary of Available Clinical Data. Drugs R D., 18(1): 1-5
5. **Iorio ML, Moretti U, Colcera S, Magro L, Meneghelli I, Motola D et al. (2007):** Use and safety profile of antiepileptic drugs in Italy. Eur J Clin Pharmacol., 63:409–15.
6. **Psaras T, Will BE, Schoeber W, Rona S, Mittelbronn M et al. (2008):** Quantitative assessment of postoperative blood collection in brain tumorsurgery under valproate medication. Zentralbl Neurochir., 69: 165–169.
7. **Loiseau P. (2003):** Sodium valproate, platelet dysfunction and bleeding. Epilepsia, 22:141–6.
8. **Mehmood T, Saleem M, Shah SSH. (2014):** Frequency of valproate induced thrombocytopenia in epileptic children. Journal of University Medical & Dental College, 5(2): 52-56.
9. **Koenig S, Gerstner T, Keller A, Teich M, Longin E, Dempfle CE. (2008):** High incidence of vaproate-induced coagulation disorders in children receiving valproic acid: a prospective study. Blood Coagulation & Fibrinolysis, 19(5): 375–382.
10. **Fidancil I, Guzel A. (2017):** Evaluation of Cases Followed and Treated Due to Valproic Acid Intoxication In Child Emergency Outpatient Clinic. Konuralp Tıp Dergisi., 9(1):7-13.
11. **Sahu MK, Dubey S. (2016):** Valproic acid-induced thrombocytopenia: A longitudinal study. J Evid Based Med Healthc., 3(65): 3552-3554.
12. **Nasereddine W, Beydoun A. (2008):** Valproate-induced thrombocytopenia: A prospective monotherapy study. Epilepsia, 49:438-45.
13. **Rehman T, Sachan D, Chitkara A. (2017):** Serum insulin and leptin levels in children with epilepsy on valproate-associated obesity. Journal of Pediatric Neurosciences, 12(2): 135-142.
14. **Kanwal A, Hassan S, Anjum ZM, Siddique MA, Idrees F, Ayesha H. (2020):** Frequency of valproic acid induced thrombocytopenia in epileptic patients in Tertiary Care Hospital, Faisalabad. The Professional Medical Journal, 27(06): 1108-1112.
15. **Gerstner T, Bell N, König S. (2008):** Oral valproic acid for epilepsy - long-term experience in therapy and side effects. Expert Opinion on Pharmacotherapy, 9(2): 285–292.
16. **Shubha HV, Vivek TG, Girish Kumar DP, Shanthala BN**. **(2019):** Hematological changes in adult patients on valproic acid therapy. International Journal of Clinical and Diagnostic Pathology, 2(2): 66-70.
17. **Delgado MR, Riela AR, Mills J, Browne R, Roach ES**. **(2016):** Thrombocytopenia secondary to high valproate levels in children with

epilepsy. Pennsylvania State Univ., 9:311–314.

18. **Vasudev K, Keown P, Gibb I, McAllister-Williams RH. (2010):** Hematological effects of valproate in psychiatric patients: what are the risk factors? J Clin Psychopharmacol., 30(3):282-5.
19. **Zighetti ML, Fontana G, Lussana F, Chiesa V, Vignoli A, Canevini MP et al. (2015):** Effects of chronic administration of valproic acid to epileptic patients on coagulation tests and primary hemostasis. Epilepsia., 56(5): 49–52.
20. **Goyal SK, Badyal DK. (2018):** Significant thrombocytopenia with sodium valproate in an adult patient with alcohol dependence. Indian Journal of Psychiatry, 60(2): 252-253.
21. **Ko CH, Kong CK, Tse PWT (2001):** Valproic acid and thrombocytopenia**.** Hong Kong Medical Journal, 7:15-21.
22. **Kim DW, Kim W, Lee CH, Chun YI. (2020):** Thrombocytopenia during intravenous valproic acid therapy in the neurological intensive care unit. Journal of Clinical Pharmacy and Therapeutics, 45:1014–1020.