Annals of Medical Case Reports

ISSN: 2689-5927

Case Report

A Rare Cause of Hemorrhage from Valproic Acid-Induced Hypofibrinogenemia and Review of Literature

Ceren Hasanoğlu, Zeynep Selen Karalök, Muhammed Doğukan Kalenderoğlu and Şenay Haspolat*

Department of Pediatric Neurology, Medicine Faculty, Akdeniz University, Antalya, Turkey

Abstract

Background: Valproic Acid (VPA) is a wide-spectrum antiepileptic drug, commonly used in the management of childhood epilepsy. One of the known hematological side effects of the drug is hypofibrinogenemia. We aimed to present a pediatric case with perioperative bleeding because of VPA-related hypofibrinogenemia.

Case presentation: A 5-year old boy with Canavan syndrome, using VPA for 2 years, was admitted to the hospital for fundoplication and circumcision. Although preoperative coagulation parameters (including fibrinogen) were in the normal range, bleeding was detected from the gastrostomy tract and at the post-circumcision area on the third day of surgery. Coagulation function test revealed decreased fibrinogen (112 mg/dL, reference value: 180-350 mg/dL) and prolonged Prothrombin time levels (19 sec, reference value: 10 sec to 14 sec). Despite an adequate volume of fresh frozen plasma transfusion, his bleeding continued, and fibrinogen levels still tended to decrease (0 mg/dL) on the fifth day. After cessation of the valproate therapy, bleeding was controlled and fibrinogen values increased to normal levels within days.

Conclusion: VPA use can cause hypofibrinogenemia and other coagulation abnormalities. Hence, physicians should be aware of the potential risk of bleeding in patients receiving VPA.

Keywords: Pediatrics; Epilepsy; Hypofibrinogenemia; Valproic acid

Introduction

Valproic Acid (VPA) is a broad-spectrum antiepileptic molecule that was first produced in 1882, with its potential anticonvulsant activity discovered in 1963. Since then, it has been used successfully for most types of seizures [1,2]. Notably, children treated with VPA have been noted to have coagulation disorders. Thrombocytopenia, platelet dysfunction, Von Wilebrand disease, factor XIII deficiency, vitamin K-dependent factor deficiency, and hypofibrinogenemia might occur during VPA therapy [3-7].

VPA-induced hypofibrinogenemia might be associated with an unknown defect in hepatic synthesis [1]. Fibrinogen deficiency can occur independent of the serum VPA level, and therefore, exerts minimal effect on bleeding risk [2,3]. Herein, we report a case of a 5-year old patient who presented with hypofibrinogenemia during VPA therapy. This case is the third case in the literature regarding hemorrhage associated with hypofibrinogenemia during VPA use.

Case Presentation

A 5-year old boy with Canavan syndrome and drug-resistant epilepsy was admitted to the hospital for fundoplication (for reflux) and circumcision. He was on VPA (for 2 years, 20 mg/kg/day, 2 doses; serum level: 53 mcg/mL), levetiracetam, and phenobarbital treatment and his seizures were under control with this politherapy. Preoperative fibrinogen (Fbg) level (184 mg/dL, reference value: 180 mg/dL to 350 mg/dL) was low but in the normal range. Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) levels were mildly prolonged (PT 16.6 sec, reference value: 10-14 sec ; APTT: 37.6 sec, reference value: 21 sec to 36 sec). He was not on salicylates or anticoagulants and had no history of bleeding and thrombosis. His renal and hepatic functions were normal. Nonetheless, bleeding was detected from the gastrostomy tract and at the post-circumcision area on the third day of surgery. Coagulation function test revealed decreased fibrinogen (112 mg/dL) and prolonged PT levels (19 sec). However, APTT levels, platelet count, and liver function tests remained normal. He received a transfusion of Fresh Frozen Plasma (FFP). Despite an adequate volume of FFP transfusion, his bleeding continued, and fibrinogen levels tended to decrease (0mg/dL) on the fifth day. The patient was reevaluated for liver and hematological dysfunctions. Disseminated intravascular coagulation and liver disease were excluded. On the same day, valproate treatment was discontinued and switched to topiramate treatment. Subsequently, fibrinogen values increased to normal levels. Thirteen days after VPA discontinuation, fibrinogen and PT values were within the normal range (Figure 1). Other laboratory findings indicated low factor 7 (49%) and factor 9 (47%) levels and normal levels of factors 5 and 8.

Informed consent was received from both of family.

Discussion

VPA has been widely used in the treatment of epilepsy for several years. Despite its effectiveness in almost all seizure variants, adverse effects limit its use [8].

Despite several case reports and studies indicating coagulation abnormalities associated with VPA use, the incidence of significant clinical bleeding complications are rare [3]. Even though few VPA

Citation: Hasanoğlu C, Karalök ZS, Kalenderoğlu MD, Haspolat S. A Rare Cause of Hemorrhage from Valproic Acid-Induced Hypofibrinogenemia and Review of Literature. Ann Med Case Rep. 2021;3(1):1021.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Feb 05th, 2020

***Corresponding author:** Ceren Hasanoğlu, Department of Pediatric Neurology, Medicine Faculty, Akdeniz University, Antalya, Turkey, Tel: +905439171978; E-mail: cerenoktay07@gmail.com

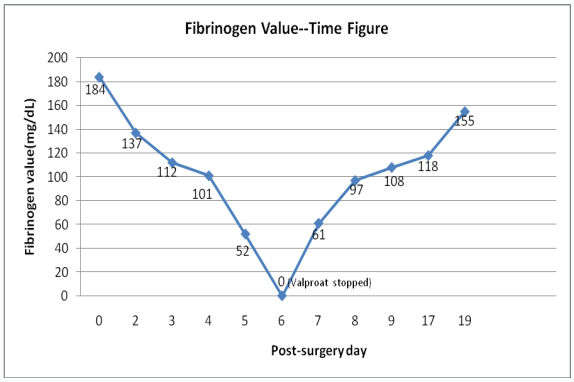

Figure 1: Fibrinogen Daily Levels.

associated hemorrhagic complications have reported, it has always been a major concern during perioperative period in patients with normal coagulation parameters [9]. It is implied that the coagulation cascade might be impaired after surgery because of an inadequate inflammatory response [10]. Although some authors recommend decreasing or changing VPA medication before surgery [5,11,12], several others oppose treatment changes in patients with normal coagulation parameters [9,13,14]. The literature, evidences only two hemorrhage cases related to VPA-induced hypofibrinogenemia. One case was postoperative cerebral hemorrhage, and the other was spontaneous intra-articular hemorrhage [2,15]. Our patient presented as the third case of hemorrhage because of VPA-induced hypofibrinogenemia.

In the literature, there are several case reports, retrospective studies, and prospective studies on VPA-related hypofibrinogenemia. We evaluated 16 publications in the literature (Table 1). Most studies reported that valproate significantly reduced fibrinogen levels, during either a short or long usage period [4,6,7,16-19]. Banerjea et al. [7] reported that 15% (12/80) of children on valproate therapy had a plasma fibrinogen concentration of less than 150 mg/dL. Another study by Koenig et al. [6] pointed out that this proportion was almost 60% of VPA-treated patients (12/23). Reduced fibrinogen concentration could be explained based on the defect in the liver synthesis or increased consumption of hemostatic proteins [7]. Moreover, in our case, prolonged APTT and PT, and decreased factors 7 and 9 levels were detected. Furthermore, Koenig et al. [6] revealed that 74% of patients with hypofibrinogenemia had other coagulation abnormalities related to valproate. They observed a statistically significant increase in APTT and PT with valporate therapy. The prospective study of Köse et al. [4] observed a significant decrease in factor 7 levels in 54.1% of patients. Factor 7 is a vitamin K-dependent protein that partakes in the extrinsic coagulation cascade (measured using PT). Nonetheless, there are limited data regarding the decrease in vitamin K-dependent coagulation factors owing to valproate usage. The underlying pathophysiological mechanism has not been elucidated, but coagulation factor abnormalities could be due to the hepatotoxic effect of valproate [4]. Notably, VPA and vitamin K primarily bind with plasma proteins. Therefore, a competition between VPA and vitamin K might shorten its half-life. Moreover, both using the same mitochondrial pathway could be responsible for this mechanism [3].

Table 1: Literature of VPA-associated hypofibrinogenemia.

Study/year	Study Design	Hypofibrin-ogenemia patients, n/N	Minimum level of fibrinogen (mg/dL)	Mean level of fibrinogen (mg/dL)	Discontinuation of therapy/ dosage revision	Effect on the bleeding	Correlation with serum level/dosage	Accompany-ing coagulopathy
Dale/1978 [20]	Case report	44197	125	NA	Yes	No	NA	No
Sussman/1979 [21]	Case series	44448	90	120	Yes	No	Yes	Low platelet(4/9), Prololonged APTT(3/9)
Hauser/1996 [16]	Prospective cohort	NA/50	76	192	NA	NA	No	NA
Anderson Gail/1997 [14]	Prospective cohort	8/111	132	223	NA	No	No	NA
Echaniz/1999 [22]	Case report	44197	170	190	Yes	No	No	Prolonged APTT
Gruppo/2000 [23]	Cross secional	43862	125	NA	NA	No	No	NA
Banerjea/2002 [7]	Prospective cohort	29556	64	203	NA	No	No	NA
Serdaroglu/2002 [5]	Cross sectional	47331	139	240	No	No	No	NA
Gerstner/2006 [3]	Retrospective	5/385	78	NA	Yes	No	Yes	vW Disase, F 13 deficiency
Koenig/2008 [6]	Prospectve cohort	45261	97	151	No	No	No	26% isolated
Köse/2009 [4]	Prospective cohort	45323	88	199	NA	No	No	NA
Ünal/ 2009 [17]	Prospective cohort	44197	<150	235	NA	NA	No	NA
Eberl/2009 [18]	Prospective cohort	14855	<150	222	NA	NA	Yes	NA
Topf/201119	Comparison study	NA/40	126	230	NA	NA	No	NA
Chen/2013 [2]	Case report	44197	53	NA	Yes	Yes	No	No
Karakayalı/2016 [15]	Casereport	44197	0	NA	Yes	Yes	No	Prolonged PT, Prolonged APTT

APTT: Activated Partial Thromboplastin Time; NA: Not Available; PT: Prothrombin Time

Some studies have invastigated the effect of VPA monotherapy and polytherapy on the coagulation panel. Banerjea et al. [7] demonstrated that fibrinogen concentration was lower in the polytherapy group, with patients on valproate and phenobarbital therapy showing the lowest levels. Like in our case, a combination of valproate and phenobarbital could be responsible for reduced fibrinogen concentration because of possible increased liver toxicity. In our case, the VPA level was in the therapeutic range when hypofibrinogenemia- induced hemorrhage was detected. Similar to our study, in most studies, no differences were noted between the fibrinogen concentration and serum VPA level [2-4,7,14-16,19]. A study by Köse et al. [4] observed no differences in any coagulation parameters related to serum VPA level (<100 mcg/mL and >100 mcg/mL). On the contrary, some studies demonstrated a negative correlation between serum fibrinogen and valproate levels [3,6,18]. Contrary to the study of Köse et al. [4], Koeing et al. [6] claimed that high-dose valproate therapy with a serum level greater than 100 mcg/mL had exerted negative effects on fibrinogen levels. It was emphasized that most adverse effects on the coagulation system were dose-dependent, and VPA concentration >100 mcg/mL should be avoided unless necessary for seizure control [3].

Several studies and case reports have revealed increase in fibrinogen levels after dose reduction or discontinuation of VPA [2,3,20-23]. In most cases, fibrinogen levels returned to normal values within 3 days to 14 days [2,20,21]. In our case, the fibrinogen level increased rapidly after cessation of the drug and reached 155 mg/dL on day 14.

This case report reveals that VPA-induced hypofibrinogenemia is crucial factor in VPA-related bleeding disorder. Therefore, it should be borne in mind that VPA can cause postoperative bleeding owing to VPA-induced hypofibrinogenemia. Contrary to suggestions in the literature [3,9,13,21], in cases with a high risk of bleeding, VPA treatment changes can be considered before surgery.

References

1. Chateauvieux S, Morceau F, Dicato M, Diederich M. Molecular and Therapeutic Potential and Toxicity of Valproic Acid. J Biomed Biotechnol. 2010;2010:479364.
2. Chen HF, Xu LP, Luo ZY, Yu ZQ, Li ZY, Cui QY, et al. Valproic acid-associated low fibrinogen and delayed intracranial hemorrhage: case report and mini literature review. Drug Des Devel Ther. 2013;7:767-70.
3. Gerstner T, Teich M, Bell N, Longin E, Dempfle CE, Brand J, et al. Valproate-associated coagulopathies are frequent and variable in children. Epilepsia. 2006;47(7):1136-43.
4. Köse G, Arhan E, Unal B, Ozaydın E, Guven A, Sayli TR. Valproate-associated coagulopathies in children during short-term treatment. J Child Neurol. 2009;24(12):1493-8.
5. Serdaroglu G, Tütüncüoğlu S, Kavakli K, Tekgiil H. Coagulation abnormalities and acquired von Willebrand's disease type 1 in children receiving valproic acid. J Child Neurol. 2002;17(1):41-3.
6. Koenig S, Gerstner T, Keller A, Teich M , Longin E, Dempfle CE. High incidence of vaproate-induced coagulation disorders in children receiving valproic acid: a prospective study. Blood Coagul Fibrinolysis. 2008;19(5):375-82.
7. Banerjea MC, Diener W, Kutschke G, Schneble HJ, Korinthenberg R, Sutor AH. Pro-and anticoagulatory factors under sodium valproate-therapy in children. Neuropediatrics. 2002;33(04):215-20.
8. Kreuz W, Linde R, Funk M, Meyer-Schrod R, Foll E, Nowak-Gottl U, et al. Valproate therapy induces von Willebrand disease type I. Epilepsia. 1992;33(1):178-84.
9. Kurwale N , Garg K, Arora A, Chandra PS, Tripathi M. Valproic acid as an antiepileptic drug: Is there a clinical relevance for the epilepsy surgeon? Epilepsy Res. 2016;127:191-4.
10. Devine EB, Chan LN, Babigumira J, Kao H, Drysdale T, Reilly D, et al. Postoperative acquired coagulopathy: a pilot study to determine the impact on clinical and economic outcomes. Pharmacotherapy. 2010;30(10):994-1003.
11. Abdallah C. Considerations in perioperative assessment of valproic acid coagulopathy. J Anaesthesiol Clin Pharmacol. 2014;30(1):7-9.
12. Tetzlaff JE. Intraoperative defect in haemostasis in a child receiving valproic acid. Can J Anaesth. 1991;38(2):222-4.
13. Psaras T, Will BE, Schoeber W, Rona S, Mittelbronn M, Honegger JB. Quantitative assessment of postoperative blood collection in brain tumor surgery under valproate medication. Zentralbl Neurochir. 2008;69(04):165-9.
14. Anderson GD, Lin YX, Berge C, Ojemann GA. Absence of bleeding complications in patients undergoing cortical surgery while receiving valproate treatment. J Neurosurg. 1997;87(2):252-6.
15. Karakayalı B, Ozturk DO, Yazar AS, Guven S, Islek I. Hypofibrinogenemia and intra-articular hemorrhage due to valproic acid. Pediatr Int. 2016;58(12):1358-9.
16. Hauser E, Seidl R, Freilinger M, Male C, Herkner K. Hematologic manifestations and impaired liver synthetic function during valproate monotherapy. Brain Dev. 1996;18(2):105-9.
17. Ünal Ö, Deda G, Teber S, Ertem M, Akar N. Thrombophilic risk factors in epileptic children treated with valproic acid. Pediatr Neurol. 2009;40(2):102-6.
18. Eberl W, Budde U, Bentele K, Christen HJ, Knapp R, Mey A, et al. Acquired von Willebrand syndrome as side effect of valproic acid therapy in children is rare. Hämostaseologie. 2009;29(2):137-42.
19. Topf HG, Lischetzki G, Trollmann R, Rascher W, Rauh M. The effect of valproate therapy on thrombin generation determined by calibrated automated thrombography. Klin Padiatr. 2011;223(3):165-8.
20. Dale BM, Purdie GH, Rischbieth RH. Fibrinogen depletion with sodium valproate. Lancet. 1978;311(8077):1316-7.
21. Sussman NM, McLain LW. A direct hepatotoxic effect of valproic acid. JAMA. 1979;242(11):1173-4.
22. Echaniz-Laguna A, Thiriaux A, Ruolt-Olivesi I, Marescaux C, Hirsch E. Lupus anticoagulant induced by the combination of valproate and lamotrigine. Epilepsia. 1999;40(11):1661-3.
23. Gruppo R, DeGrauw A, Fogelson H, Glauser T , Balasa V, Gartside P. Protein C deficiency related to valproic acid therapy: a possible association with childhood stroke. J Pediatr. 2000;137(5):714-8.