General Hospital Psychiatry 59 (2019) 67–72

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: www.elsevier.com/locate/genhospsych

Risk factors for valproic acid induced hyperammonemia and its association with cognitive functions

Berker Duman[a], Kazım Cihan Can[b,*], Ece Ağtaş-Ertan[b], Seyda Erdoğan[c], Rıfat Serav İlhan[b], Özlem Doğan[d], Hakan Kumbasar[a], Ulaş Mehmet Çamsarı[e]

[a] Division of Consultation-Liaison Psychiatry, Department of Psychiatry, Ankara University School of Medicine, Ankara, Turkey
[b] Department of Psychiatry, Ankara University School of Medicine, Ankara, Turkey
[c] Department of Neurology, Ankara University School of Medicine, Ankara, Turkey
[d] Department of Biochemistry, Ankara University School of Medicine, Ankara, Turkey
[e] Department of Psychiatry and Psychology, Mayo Clinic School of Medicine and Science, Rochester, MN, USA

ARTICLE INFO

Keywords:
Hyperammonemia
Valproic acid
Bipolar disorder
Epilepsy
Attention
Memory

ABSTRACT

Objective: Valproic acid (VPA)-induced hyperammonemia (VIH), is an increase in blood ammonia levels without any alteration of hepatic enzymes, which can occur during VPA treatment. We aimed to determine the prevalence rate and the risk factors for VIH and its association with cognitive functions.
Method: A prospective, cross-sectional study was conducted. Patients aged between 18 and 64 who were on VPA treatment and who diagnosed with mood disorders or epilepsy were enrolled in this study (n = 107). For cognitive assessment, Serial 7's and Subjective Memory Complaints Questionnaire (SMCQ) were used. Blood samples were collected for blood VPA and ammonia levels along with other laboratory tests.
Results: 55,3% of the sample were considered as VIH. Blood ammonia level significantly correlates with VPA blood levels, total daily dose of VPA and total number of medications concurrently used, but no significant correlation was found between blood ammonia level and cognitive test scores. Gender, body weight, blood VPA levels and the total number of medications concurrently used significantly predicted blood ammonia levels ($F(4,81) = 2670$, $p = 0{,}038$, $R^2 = 0{,}116$).
Conclusion: VIH is relatively high in our sample. There is a dose-dependent association between VPA and blood ammonia level. No association was found between cognitive functions and hyperammonemia however with some limitations. Future, prospective cohort studies are needed.

1. Introduction

Divalproex sodium/valproic acid (VPA) is a branched short-chained fatty acid that has been widely used in the treatment of various neuropsychiatric conditions such as bipolar disorder, epilepsy, migraine and behavioral disorders. Common side effects of VPA are fatigue, weight gain, nausea, hair loss and tremor [1]. VPA is also rarely associated with hepatotoxicity, thrombocytopenia, encephalopathy, and hyperammonemia [1,2].

Valproic acid-induced hyperammonemia (VIH), is an increase in blood ammonia levels without any alteration of hepatic enzymes, which can occur during VPA treatment and can be reversed by discontinuation of the medication. Ammonium which is known to have toxic effects on the central nervous system is a product of the protein catabolism [3]. Ammonium is converted into urea through the liver and excreted from the kidneys [4]. Previous studies have demonstrated a number of hereditary or acquired factors may affect blood ammonia levels [4,5]. Although some mechanisms including direct or indirect inhibition of urea cycle by VPA itself or its metabolites are suggested, still very little is known about how VPA causes hyperammonemia [4,6,7].

Symptoms of VIH can vary from asymptomatic hyperammonemia (probably associated with subtle cognitive impairment) to valproate-induced hyperammonemic encephalopathy associated with potentially life-threatening adverse effects such as lethargy, agitation, confusion, or even coma [2,8]. Most cases have a clinically asymptomatic course and progression to encephalopathy is rare, some have debated the clinical significance of VIH [5,9]. Previous studies have reported highly variable prevalence rates of VIH, ranging from 16% to 80% [9]. For

* Corresponding author at: Department of Psychiatry, Ankara University School of Medicine, 06950 Ankara, Turkey.
E-mail addresses: dumanb@ankara.edu.tr (B. Duman), kcan@ankara.edu.tr (K.C. Can), ozlemdogan@ankara.edu.tr (Ö. Doğan), kumbasar@medicine.ankara.edu.tr (H. Kumbasar).

https://doi.org/10.1016/j.genhosppsych.2019.05.005
Received 14 April 2019; Received in revised form 16 May 2019; Accepted 21 May 2019

instance, Raja and Azzoni reported the prevalence rate of VIH as 51% among patients with one or more psychiatric disorders [10]. A recent study with retrospective design reported prevalence rates of VIH as 36% [11]. Some studies investigated the risk factors for VIH; total daily VPA dose, concomitant use of antiepileptic and antipsychotic medications, female gender have been reported as among risk factors [5,8].

In this study, our first aim was to investigate the prevalence rate and risk factors for hyperammonemia in patients receiving VPA treatment. Our second aim was to investigate the association between VIH and its adverse effects on cognitive functions.

2. Material and method

This prospective, single-center, cross-sectional and observational study was conducted at a tertiary level university hospital. The study protocol was approved by the Institutional Review Board (Approval No.: 10-679-18). The study was performed in accordance with the ethical standards of the Declaration of Helsinki and written informed consent was obtained from all participants prior to the study.

Patients who were seen at Psychiatry or Neurology Outpatient Clinics at our university hospital from June 2018 to February 2019 were enrolled in the study. Individuals of both genders between 18 and 65 of age who were on single or combination VPA regimen were included.

We excluded patients who were diagnosed with co-morbid alcohol and illicit substance use disorders, severe neurological disorders (e.g. history of CVA etc.), epileptic patients who were not on remission (interictal state), with education < 5 years, who have missing information for VPA or ammonia blood levels or had any other potential cause for hyperammonemia such as hepatic failure, urea cycle defects. Also, we excluded patients with blood VPA levels lower than 20 μg/ml who were considered as non-compliant and excluded from further analysis.

Sociodemographic and clinical characteristics of the patients were obtained through an itemized form developed by authors of this study which included age, gender, education level, body weight, body mass index (BMI), neuropsychiatric diagnoses and other medical comorbidities, presence of delusions and/or hallucinations, mood status, medication regimen, total daily dose (mg) and total duration (months) of VPA therapy, concurrent use of antipsychotics and antiepileptics, adverse effects (emesis/vomiting, somnolence, hair loss, weight gain, edema, tremor, jaundice, confusion), blood level of VPA, blood ammonia level, liver function test (ALT, AST, GGT, Albumin, Total Bilirubin, INR) results and cognitive functions (attention and subjective memory complaints).

Other relevant data were gathered from laboratory records and clinical examinations. Clinical interviews were conducted by experienced clinicians who were also among the authors of this study.

2.1. Assessment of subjective memory complaints

Memory complaints were assessed by the Turkish version of Subjective Memory Complaints Questionnaire (SMCQ) [12,13]. The SMCQ is a short, valid and reliable questionnaire in the evaluation of subjective memory complaints developed by Youn et al. [12]. The SMCQ consists of 14 questions with Yes/No responses. The total score of the questionnaire is calculated from the total number of 'Yes' responses and ranges between 0 and 14; higher scores indicating greater memory complaints.

2.2. Assessment of attention

Attention was evaluated by using five items Serial 7's, which is the attention domain of the Turkish version of Mini Mental State Examination (MMSE) [14,15]. The score ranges from 0 to 5; higher scores indicating better performance.

2.3. Assessment of blood ammonia levels

Blood samples were drawn into EDTA tubes which was immediately placed in ice water. Samples were centrifuged at 3000 rpm for 10 min to obtain plasma separated from blood. The level of ammonia was measured by using Beckmann Coulter AU 680 analyzer, which is a direct enzymatic procedure kit reagent based on the following reaction sequence.

$$NH4 + \alpha\text{ketoglutarate} + NADH \xrightarrow{\text{Glutamate dehidrogenase (GLDH)}} \text{Glutamate} + NAD + H2O$$

Blood ammonia level above 52 μmol/l was considered as hyperammonemia (standardized cut-off value for our laboratory).

2.4. Assessment of blood VPA level

Plasma concentration of VPA was measured approximately 12 h after last VPA oral administration. Chemiluminescent microparticle immunoassay (CMIA) was used for the quantitative measurement of VPA in patients' serum on the Abbot Architect *i* System with STAT protocol capability.

2.5. Statistical analysis

Descriptive metrics are provided by mean ± SD, n (%) or median (range) depending on the variable. Normal ammonia level group and hyperammonemia group were compared with. Mann-Whitney *U* test or Student's *t*-test was used for comparing continuous variables such as age, age at onset, duration of VPA therapy, body weight, BMI, VPA dose, plasma VPA level. Pearson or Spearman correlation was performed to investigate the association between blood ammonia levels. Multiple linear regression analyses were done by using "Enter method". All the predictors in a block were entered in a single step. Multiple linear regression analyses were performed to explore independent associations between each risk variable as a predictor of hyperammonemia. Gender, age, body weight, the dose of daily VPA were included as variables in the regression model. All statistical analyses were performed using the Statistical Package for Social Science (SPSS, version 23.0 for Windows; Chicago, IL). A p-value of < 0.05 was considered to be statistically significant.

3. Results

107 patients were enrolled in our study. Of these, 94 patients were included into further analysis. Exclusion reasons were as follows: missing values for blood ammonia level (3 patients) and VPA blood level (7 patients), blood VPA levels lower than 20 μg/ml (3 patients were considered as non-compliant with VPA therapy). Sociodemographic, laboratory and clinical variables of the sample are given in Table 1. The mean age was 41,76 ± 12,32 (18–64). 39,4% of patients (n = 37) were male. Mean body weight and BMI were 83,05 ± 18,2 (46–150), 30,19 ± 6,06 (16,3-46,3) respectively. Distribution of education level among patients is as follows: 5 years of education 22,3% (n = 21), 6–8 years 21,3% (n = 20), 9–11 years 33% (n = 31), 12 or more years 22,3% (n = 21). The majority of the diagnoses was bipolar and depressive disorders 68,1% (n = 64); other diagnoses were psychotic disorders 9,6% (n = 9), epilepsy 11,7% (n = 11), epilepsy and comorbid psychiatric disorders 8,5% (n = 8) and other disorders 2,1% (n = 2). Of these patients 7,5% (n = 7) were reported that 'rarely drinking alcohol', the others reported 'never drinking alcohol'; 59,1% (n = 55) were currently smoking, 67% of the patients (n = 63) were euthymic, 5,3% (n = 5) reported delusions and 9,6% (n = 9) hallucinations. Medical comorbidity prevalence rates for hypertension, diabetes mellitus, thyroid disorders and other medical disorders were 11,7% (n = 11), 12,8% (n = 12), 16% (n = 15), 14,9%

Table 1
Demographic variables of the sample and comparison of the groups.

	Whole sample (n = 94)	Normal blood ammonia level group (n = 42)	Hyperammonemia level group (n = 52)	p-Value
Age	41,76 ± 12,32 (18–64)	40,05 ± 13,41	43,13 ± 11,3	t = −1211 p = 0,229
Gender				χ^2 = 2249 p = 0,134
Male/female n(%)	39,4%/60,6%	31%/69%	46,2%/53,8%	df = 1
Body weight (kg)	83,05 ± 18,2 (46–150)	78,71 ± 15,57	86,52 ± 19,33	t = −2024 **p = 0,046**
BMI	30,19 ± 6,06 (16,3-46,3)	29,38 ± 5,61	30,82 ± 6,38	t = −1079 p = 0,284
Dose of VPA use (mg/day)	1223 ± 406	1125 ± 395	1303 ± 400	t = −2154, **p = 0,034**
Blood VPA level	70,07 ± 22,84	66,93 ± 21,40	72,62 23,83	t = −1203, p = 0,232
Duration of VPA therapy	84,11 ± 88,87	76,59 ± 84,23	90,74 ± 93,27	t = −0,704, p = 0,484
Plasma level of ammonia	55,82 ± 14,41	43,10 ± 6,69	66,10 ± 10,08	
Hyperamonnemia (n)	55,3%			
VPA monotherapy	9,6%	9,5%	9,6%	
VPA combined with antipsychotics	70,2%	26,1%	32,6%	χ^2 = 0,470 p = 0,493 df = 1
VPA combined with antiepileptics	14,9%	11,9%	17,3%	χ^2 = 0,535 p = 0,464 df = 1
Total number of medications used	3(1–7)	3(1–7)	3(1–7)	Z = -2125, **p = 0,034**
Serial 7's	3(0–5)	3(0–5)	3(0–5)	Z = -0,847, p = 0,397
Subjective memory complaints questionnaire	4(0–13)	3,5(0–13)	4(0–13)	Z = -0,358, p = 0,721

(n = 14), respectively. Mean ALT, AST,GGT, albumin, INR, total and direct bilirubin levels were 25,13 ± 22,61; 22,73 ± 11,35; 34,49 ± 33,07; 41,89 ± 3,44; 0,99 ± 0,08; 0,47 ± 0,2; 0,11 ± 0,09 respectively. According to these results, none of the subjects had an evidence of liver disease.

The median value of the number of medications used was 3 (1–7). 9.6% of patients (n = 9) were on VPA monotherapy; 70,2% (n = 66) on VPA combined with antipsychotics therapy, 14,9% (n = 14) on VPA combined with antiepileptics therapy. The mean dose of VPA was 1223 ± 406 mg/day. Mean blood VPA level was 70,07 ± 22,84 μg/ml. Mean duration of VPA therapy was 84,11 ± 88,8 months. Mean plasma level of ammonia was 55,82 ± 14,41 μmol/l and 55,3% (n = 52) of the sample was considered as hyperammonemic (with a cut-off 52,5 μmol/l). The median attention score (serial 7's) was 3 (0–5), and the median subjective memory complaints questionnaire total scores was 4 (0 − 13).

3.1. Comparison of hyperammonemia group and normal ammonia level group

No statistically significant difference was found between groups with respect to age, gender, BMI, presence of antipsychotic and/or antiepileptic use (Table 1), education level, neuropsychiatric diagnoses, mood, delusions, hallucinations, adverse medication effects, smoking status, medical comorbidities, and blood levels of ALT, AST, GGT, albumin, INR, total bilirubin and direct bilirubin levels (data not shown).

The comparison of groups according to daily dose of VPA (mg/day) used, body weight (kg), total count of medications used revealed statistically significant difference (t = −2154, p = 0,034; t = −2011, p = 0,048; Z = -2125,p = 0,034). On the other hand, no statistically significant difference was found between the groups for blood VPA level (μg/ml) or VPA treatment duration (months) (t = −1203, p = 0,232; t = −0,704,p = 0,484; respectively).

No statistically significant difference was found between groups in cognitive performance (for serial 7's, Z = -0,847, p = 0,397; for SMCQ, Z = -0,358, p = 0,721).

3.2. Correlation and regression analyses

According to the correlation analyses (Figs. 1 and 2), blood ammonia level significantly correlates with VPA blood levels, total daily dose of VPA administered, and total number of medications concurrently used (r = 0,207, p = 0,045; r = 0,216, p = 0,036; r = 0,213, p = 0,039 respectively). No significant correlation was found with serial 7's or SMCQ scores (r = −0,103, p = 0,345; r = −0,066, p = 0,543 respectively).

Multiple regression analyses were performed to predict blood ammonia levels using gender, body weight, blood VPA levels and the total number of medications concurrently used (Table 2). These variables significantly predicted blood ammonia level, F(4,81) = 2670, p = 0,038, R^2 = 0,116, Adj.R^2 = 0,073. Only blood VPA levels added significantly to the prediction (p = 0,026).

3.3. Hyperammonemia and encephalopathy

Only one case (n = 1, 1%) seemed to have developed hyperammonemia and associated encephalopathy while on VPA treatment during our study. Forty-five year old male with a history of bipolar disorder and epilepsy in remission, smoker, was on VPA treatment for 96 months. In addition to VPA, his medication regimen included lithium, amisulpride, biperiden and escitalopram. During one of the routine outpatient visits, he reported nausea. Upon further investigation, sensorium was found to be clouded, his serial 7's and SMCQ scores were 0 and 13 respectively. The total daily dose of VPA was 1500 mg/day, VPA blood level was 92 μg/ml, blood ammonia level was 93 μmol/l, Liver function tests were within the normal range except for ALT level which was mildly elevated (71 units/l). Following discontinuation of VPA, confusional state was assessed to be resolved. Blood ammonia level was obtained and found to be decreased to 60 μg/ml. He was diagnosed with VPA-induced hyperammonemic encephalopathy.

4. Discussion

Association between hyperammonemia and VPA therapy has been previously investigated in the literature [8,10,16]. In this prospective cross-sectional study, we found a prevalence rate of 55,3% for hyperammonemia. Previous data mostly focused on epilepsy patients and pediatric population [8,17]. Few studies reported VPA associated hyperammonemia in psychiatric adult patients [2,7]. In this study, the majority of our sample carried a diagnosis of a mood disorder. We also included patients diagnosed with epilepsy to increase statistical power and to be able to compare diagnostic categories. Indeed, we found no

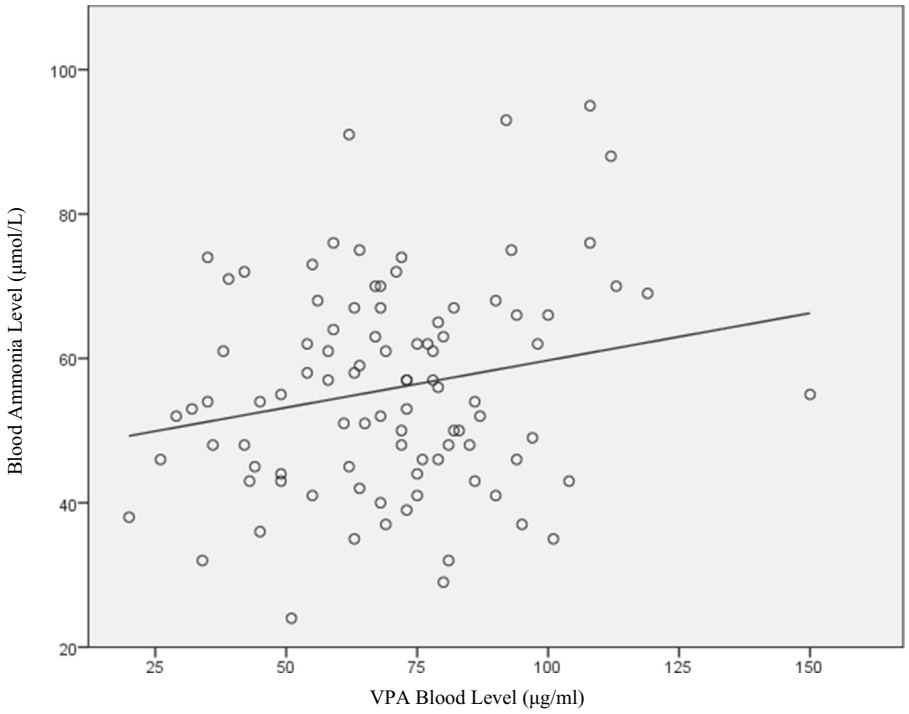

Fig. 1. Relationship between the blood ammonia level and the blood concentration of valproic acid.

statistically significant difference between epileptic and psychiatric patients regarding blood ammonia levels. We observed no statistically significant difference between groups for age, gender, BMI, neuropsychiatric diagnoses, mood symptoms or psychotic symptoms. It is known that pediatric and geriatric populations may be at higher risk of VPA induced hyperammonemia [18]. Given the fact that the age range of our study population was from18 and 64, our results should be interpreted with caution.

We found no statistically significant difference between hyperammonemia group and normal blood ammonia level group for blood VPA levels, total duration of VPA therapy, adverse effects of VPA, VPA monotherapy or combination with antipsychotics and other antiepileptics. Comparison of blood VPA level of these two groups did not reach a statistical threshold. One possible explanation could be the diagnostic distribution of our sample which included a higher percentage of mood disorders as opposed to epileptic disorders. We believe that this is of particular importance as mental health providers traditionally target blood VPA levels in between 50 and 100 µg/ml when

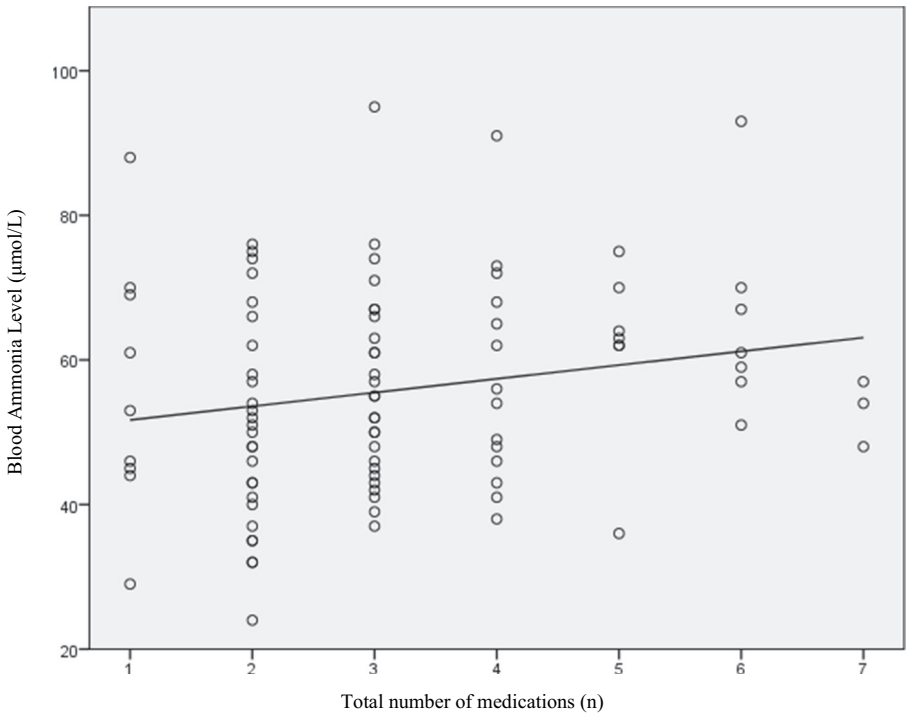

Fig. 2. Relationship between the blood ammonia level and number of medications used.

Table 2
Multiple regression analyses for blood ammonia levels.

	B	Std. error	Beta	p-Value
Constant	28,111	9330		p = 0,003
VPA level	0,154	0,068	0,238	**p = 0,026**
Total medications used	1673	1030	0,174	p = 0,108
Body weight	0,078	0,090	0,096	p = 0,389
Gender	3562	3323	0,119	p = 0,287

*R = 0,341, R^2 = 0,116, Adj.R^2 = 0,073; F(4,81) = 2670, p = 0,038.

monitoring VPA for mood stabilization whereas neurologists rarely rely on VPA blood levels in the management of epileptic disorders. This could be the reason for the limited range of VPA blood level distribution in our study, which, as a result, could be interpreted as type 2 statistical error. The current study found that the duration of VPA therapy had no effect on blood ammonia levels which is confirmed by previous studies [19,20].

Epileptic patients included in this study were on several other antiepileptic medications along with VPA which could have caused an inducing effect on CYP450 system, that might have required higher total daily VPA dosing in order to obtain a target blood VPA level in blood which is known to increase the risk of hyperammonemia as previously reported [19,21].

It is well known that impaired attention is one of the earliest signs of encephalopathy. Indeed, West Haven Criteria lists shortened attention span and impaired addition or subtraction ability as Grade 1 hepatic encephalopathy [22]. In our study, we used serial 7's for rapid evaluation of attention. It is also suggested that short term memory deficit is a feature of mild hepatic encephalopathy which was explained by impaired encoding due to attentional impairment [23]. We used SMCQ in an attempt to assess short term memory deficits. We found no statistical difference between groups in cognitive test scores; between blood ammonia level and serial 7 performance or SMCQ total scores. We failed to demonstrate an association between VIH and cognitive impairment. However, this result should be interpreted with some considerations. Our study was cross-sectional therefore we did not know the entire duration and severity of CNS ammonia exposure which limits our ability to interpret dose-dependent toxicity. Prospective cohort design with frequent evaluations would be ultimately needed. Additionally, it is quite possible that our screening methods did not have enough sensitivity to capture cognitive deficits.

Statistically significant difference was found between groups regarding body weight, the total number of medications concurrently used or total daily VPA dose. Previous studies reported that hyperammonemia is more prevalent in patients on polypharmacy [19,21]. Consistent with the literature, our findings also suggest that polypharmacy was associated with an increased risk of hyperammonemia. One possible explanation could be impaired detoxification of ammonia by the increased pharmacological burden on the liver.

Our results are in line with prior studies that reported total daily VPA dose as a risk factor for VIH [5,8,24]. Among the main findings of our study was that blood ammonia level was found to be significantly correlated with blood VPA level, total number of medications concurrently used and total daily dose of VPA.

Our regression model significantly predicts blood ammonia level with total body weight, gender, blood VPA levels and total number of medications concurrently used by the patient. However, this significant finding explains only a small percentage of the variance which demands further investigation.

In our study, more than half of our sample was found to have hyperammonemia. One of our patients was diagnosed with suspected VHE and his symptoms resolved after discontinuation of VPA.

It is even contraindicated to use VPA with very rare conditions such as urea cycle disorder [25] and it is generally advised to monitor liver function tests in the setting of VPA use. We did not find any liver function impairment correlated with hyperammonemia which is consistent with the literature. We would like to stress the fact that, to our knowledge, there are no established guidelines which would recommend monitoring blood ammonia level in patients on VPA. Indeed, our methodology did not allow us to draw conclusions for routine monitoring for ammonia levels on VPA therapy. Future well-designed follow-up studies are needed to support guidelines for monitoring blood ammonia levels in the setting of VPA treatment.

There are several limitations of our study. First, aside from one-time measurement of blood ammonia level, we did not have a baseline value obtained prior to VPA initiation, we also did not have any measurement available during VPA treatment, which is clearly a limitation of our cross-sectional study design. Second, hyperammonemia can be associated with other liver etiology, such as steatohepatitis, viral hepatitis, urea cycle disorders. We obtained a detailed medical history, we also completed thorough physical and mental status examinations, we did obtain most indicators of liver disease including INR, albumin, platelet count, bilirubin, transaminase levels prior to recruitment of our subjects. We did not perform any further testing such as liver ultrasound or viral screening which could be considered as a limitation. Third, cognitive screening methods we used had both limitations and strengths. We chose to perform serial 7's and SMCQ due to the fact that we needed a practical yet sensitive method in a busy clinic to detect sustained attention and memory deficits which are the main cognitive domains we specifically aimed to measure in this study. A more thorough evaluation of these cognitive domains could be assessed by other tests such as Trail Making Test or Continuous Performance Test. Although the majority of our sample was euthymic at the time of assessment, the use of subjective memory scales in mood disorders still has some limitations [26]. Important to mention that cognitive impairment is associated with many psychiatric disorders as well as epileptic disorders. Fourth, patients included in our sample were on multiple medications which is a confounding factor, in order to eliminate this as possible we attempted to classify our sample using different categories including VPA monotherapy, concurrent use of antiepileptics, concurrent use of antipsychotics.

To our knowledge, this is the first study which attempted to explore the association between cognitive functions and asymptomatic hyperammonemia. Unlike most previous studies which focused on epileptic patients and pediatric populations, our study sample mainly consists of patients with psychiatric diagnoses. Most data reported with psychiatric patients come from case reports, case series or from retrospective data analysis, our study is the first to use a prospective design.

5. Conclusion

The results of our study have shown that VIH is relatively high in adult psychiatric and epileptic patient populations. Our findings clearly indicate that there is a dose-dependent association with the administered VPA dose (and also with VPA plasma levels) and blood ammonia level. The total number of concurrently used medications and body weight are possibly associated with increased blood ammonia level. Although no deterioration in cognitive functions was found to be associated with hyperammonemia in our study, more comprehensive cognitive tests may reveal different results. Well-designed prospective cohort studies are needed to further clarify the relationship between VPA use, hyperammonemia and cognitive functions.

Declaration of Competing Interest

None.

Acknowledgements

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Chateauvieux S, Morceau F, Dicato M, Diederich M. Molecular and therapeutic potential and toxicity of valproic acid. J Biomed Biotechnol 2010;2010.
[2] Lewis C, Tesar GE, Dale RJP. Valproate-induced hyperammonemic encephalopathy in general hospital patients with one or more psychiatric disorders. 58. 2017. p. 415–20.
[3] Oja SS, Saransaari P, Korpi ER. Neurotoxicity of ammonia. Neurochem Res 2017;42:713–20.
[4] Auron A, PDJPn Brophy. Hyperammonemia in review: pathophysiology, diagnosis, and treatment. 27. 2012. p. 207–22.
[5] Tseng Y-L, Huang C-R, Lin C-H, Lu Y-T, Lu C-H, Chen N-C, et al. Risk factors of hyperammonemia in patients with epilepsy under valproic acid therapy. 2014. p. 93.
[6] Hung C-C, Li T-M, Wei I-H, Huang C-CJGhp. The real mechanism of VPA-induced hyperammonemia remains unknown. 33. 2011. [84. e3-84. e4].
[7] Chopra A, Kolla BP, Mansukhani MP, Netzel P, MAJGhp Frye. Valproate-induced hyperammonemic encephalopathy: an update on risk factors, clinical correlates and management. 34. 2012. p. 290–8.
[8] Yamamoto Y, Takahashi Y, Suzuki E, Mishima N, Inoue K, Itoh K, et al. Risk factors for hyperammonemia associated with valproic acid therapy in adult epilepsy patients. 101. 2012. p. 202–9.
[9] Chicharro AV, de Marinis AJ, Kanner AMJE, Behavior. The measurement of ammonia blood levels in patients taking valproic acid: looking for problems where they do not exist? 11. 2007. p. 361–6.
[10] Raja M, AJJocp Azzoni. Valproate-induced hyperammonaemia. 22. 2002. p. 631–3.
[11] Baddour E, Tewksbury A, Stauner N. Valproic acid-induced hyperammonemia: incidence, clinical significance, and treatment management. Ment Health Clin 2018;8:73–7.
[12] Youn JC, Kim KW, Lee DY, Jhoo JH, Lee SB, Park JH, et al. Development of the subjective memory complaints questionnaire. Dement Geriatr Cogn Disord 2009;27:310–7.
[13] Özel-Kizil E, Duman B, Altıntaş Ö. Öznel Bellek Yakınmaları Anketi Türkçe Formunun Psikometrik Özelliklerinin Değerlendirilmesi. Turk Geriatri Derg 2013;16:150–4.
[14] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
[15] Güngen C, Ertan T, Eker E, Yaşar R, FJTpdTjop Engin. Reliability and validity of the standardized Mini Mental State Examination in the diagnosis of mild dementia in Turkish population. 13. 2002. p. 273–81.
[16] Cheng M, Tang X, Wen S, Yue J, HJCp Wang. Valproate (VPA)-associated hyperammonemic encephalopathy independent of elevated serum VPA levels: 21 cases in China from May 2000 to May 2012. 54. 2013. p. 562–7.
[17] Inoue K, Suzuki E, Takahashi T, Yamamoto Y, Yazawa R, Takahashi Y, et al. 4217C > a polymorphism in carbamoyl-phosphate synthase 1 gene may not associate with hyperammonemia development during valproic acid-based therapy. 108. 2014. p. 1046–51.
[18] Maldonado C, Guevara N, Queijo C, González R, Fagiolino P, Vázquez MJBRI. Carnitine and/or acetylcarnitine deficiency as a cause of higher levels of ammonia. 2016. 2016.
[19] Rousseau M-C, Montana M, Villano P, Catala A, Blaya J, Valkov M, et al. Valproic acid-induced encephalopathy in very long course treated patients. 23. 2009. p. 981–4.
[20] Rath A, Naryanan TJ, Chowdhary G, Murthy JJNI. Valproate-induced hyperammonemic encephalopathy with normal liver function. 53. 2005. p. 226.
[21] Zaccara G, Paganini M, Campostrini R, Moroni F, Valenza T, Messori A, et al. Effect of associated antiepileptic treatment on valproate-induced hyperammonemia. 7. 1985. p. 185–90.
[22] Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei ATJH. Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. 35. 2002. p. 716–21.
[23] Dhiman RK, YKJIJoG Chawla. Minimal hepatic encephalopathy. 28. 2009. p. 5–16.
[24] Tesen H, Katsuki A, Hori H, Atake K, Yoshimura R, Nakamura JJN. Plasma ammonia levels in patients treated with valproic acid. 7. 2017. p. 42–7.
[25] M-JCJIcp Dealberto. Valproate-induced hyperammonaemic encephalopathy: review of 14 cases in the psychiatric setting. 22. 2007. p. 330–7.
[26] Duman B, Kizil ETÖ, Baran PZ, Kirici PS, Turan EJTPD. Discrepancy between subjective memory complaints and objective memory deficits in elderly patients with depression compared to mild cognitive impairment. 2016. p. 27.