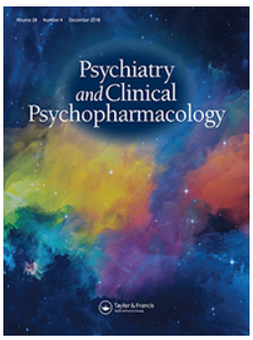

Psychiatry and Clinical Psychopharmacology

ISSN: 2475-0573 (Print) 2475-0581 (Online) Journal homepage: https://www.tandfonline.com/loi/tbcp21

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To cite this article: Mustafa Dinçer, Abdullah Akgün, Şahin Bodur, Hesna Gül, Yasemin Taş Torun, Abdullah Bolu, Cemil Çelik, Miray Çetinkaya, Halil Kara & M. Ayhan Cöngöloğlu (2018) Hyperammonemic encephalopathy without hepatic dysfunction due to treatment with valproate: four cases and a mini review, Psychiatry and Clinical Psychopharmacology, 28:4, 448-460, DOI: 10.1080/24750573.2018.1448133

To link to this article: https://doi.org/10.1080/24750573.2018.1448133

Published online: 28 Mar 2018.

PSYCHIATRY AND CLINICAL PSYCHOPHARMACOLOGY
2018, VOL. 28, NO. 4, 448–460
https://doi.org/10.1080/24750573.2018.1448133

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CASE REPORT

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Hyperammonemic encephalopathy without hepatic dysfunction due to treatment with valproate: four cases and a mini review

Mustafa Dinçer[a], Abdullah Akgün [b], Şahin Bodur[a], Hesna Gül[a], Yasemin Taş Torun[a], Abdullah Bolu[b], Cemil Çelik[b], Miray Çetinkaya[c], Halil Kara[d] and M. Ayhan Cöngöloğlu[a]

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ABSTRACT

Divalproex sodium/valproic acid (VPA) is an antiepileptic drug which is frequently prescribed in neurology and psychiatric clinics. Common side effects of VPA are side effects of the digestive system, weight gain, tremor, sedation, hematologic side effects and hair loss. Valproate-induced hyperammonemia is almost seen in 50% of patients treated with VPA, some of which may develop encephalopathy. Valproate-induced hyperammonemic encephalopathy (NE) is a well-known subject and there are numerous publications in the current literature. Although there is substantial evidence for this side effect in patients with neurological disorders, the data in the psychiatric area are limited. When we look at publications, it seems that VHE is seen more often because it starts earlier in psychiatric patients, but we think that it is often missed. Here, we presented five cases in which we followed up and treated with VHE diagnosis in our clinic within one year and other reports published previously in a table.

ARTICLE HISTORY
Received 29 September 2017
Accepted 1 March 2018

KEYWORDS
Valproic acid; encephalopathy; hyperammonemia; bipolar disorder; lactulose; side effects

Introduction

Divalproex sodium/valproic acid (VPA) is an antiepileptic drug and a mood stabilizer used in the treatment of migraines, seizures and a variety of psychiatric symptoms, including bipolar disorder (BD), borderline personality disorder (BPD), schizoaffective disorder, for agitation in setting of autism, and off-label use for impulsive control problems. Common side effects of VPA are digestive system side effects, weight gain, tremor, sedation, hematologic side effects, and hair loss. Besides these, encephalopathy is a rare side effect of VPA which may cause unwanted consequences. Valproate-induced hyperammonemia is seen in 51% of patients treated with VPA, some of which may develop encephalopathy [1]. Since the clinical condition is nonspecific and the relationship between dose, blood levels, duration of valproate treatment and the diagnosis of valproate-induced hyperammonemic encephalopathy is uncertain, this diagnosis should be primarily suspected and is rarely considered by clinicians [2]. Although the literature on hyperammonemic encephalopathy induced by valproate is mostly based on the epilepsy treatment, there are fewer reports of this condition in psychiatry. Clinical findings of valproate-associated hyperammonemic encephalopathy are nonspecific and typically present as acute or subacute ataxia, vomiting, focal neurological findings, low grade fever, drowsiness, lethargy, agitation, confusion, unconsciousness or rarely seizures, stupor, coma, permanent morbidity and may cause reversible cortical damage [3]. Below we present five cases that three of them diagnosed with BD and two of them diagnosed before schizophrenia who had manic symptoms and who received multiple drug treatment and developed hyperammonemic encephalopathy without hepatic dysfunction due to treatment with valproate [4]. These case reports emphasize that a rare but a complication to be considered may occur with valproate, an increasingly used drug in both neurology and neuropsychiatric clinics. Also we aimed to review previous cases of VHE (n = 58) in psychiatric patients to attract attention on pathophysiological mechanisms, diagnostic studies and laboratory findings, risk factors, clinical features, clinical management, and treatment of VHE.

Case presentation

Case 1: A 38-year-old woman who is under treatment for BD 1 for 20 years was admitted to our clinic with a libidinal increase, excessive talking, decreased sleep, increased motor activity, and self harm starting a week ago. Her last treatment was oxcarbazepine 800 mg/day, biperidine 4 mg/day, quetiapine 900 mg/day, and olanzapine 40 mg/day. This was the first hospitalization of the patient. She had 18 years of lithium treatment and underwent a drug change due to

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subclinical hypothyroidism about 2 years ago and switched to oxcarbazepine treatment and other drugs were added over time. There was no accompanying medical condition. Through her psychiatric examination at the time of admittance, sociability was unrestricted, mood was cheerful, grimace like mimics and gestures, speech speed was increased, thought flow was accelerated, thought content was focused on new plans and libidinal investments, mood was euphoric and occasionally dysphoric, movements were restless and fast, and overall functionality was reduced. The condition of the patient was evaluated in accordance with the manic episode. Young mania rating scale score was 38. Blood test results of the patient were normal except for TSH: 5.1 μU/ml (0.27–4.2). Sodium valproate 1000 mg/day was added to the treatment of the patient. During the first week, lorazepam, haloperidol and zuklopenthixol depot were occasionally used for the behavioral pathologies and clinical discrepancy of the patient. At the end of the first week, the treatment was gradually reduced to oxcarbazepine 600 mg/day, quetiapine 300 mg/day, olanzapine 30 mg/day, valproate 1000 mg/day. After 1 week, the patient's valproate level was 64.10. On the 10th day of hospitalization, there were findings such as lethargy, sedation, blurring of consciousness, loss of eye contact, noncompliance with commands, but pathological reflexes and meningial irritation signs were absent. No other pathological conditions were found in vital signs and physical examination. The blood ammonia level of the patient was 379 mg/dL (27–90) and the other blood values (ALT, AST, LDH, GGT, Na, Cl, CK, PTZ, INR, TK, …) were within normal limits.Considering hyperammonemic encephalopathy induced by valproate in the patient, VPA treatment was discontinued and the patient was given 3000 cc 0.9% NaCl solution. The patient's condition stabilized after 36 hours of stopping VPA and 24 hours after the administration of NaCl solution. After 24 hours, the level of ammonia detected was 106 mg/dL. No morbidity was observed in the subsequent follow-up of the patient.

Case 2: A 21-year-old woman who has been treated with schizophrenia for approximately 6 years has recently been admitted to our clinic with symptoms such as irritability, restlessness, insomnia, increased speech and psychomotor activity, reference, and persecution delusions. Previously treated with olanzapine, risperidone, and aripiprazole, the treatment of the patient was changed due to side effects. The most recent treatment was paliperidone 9 mg/day, lorazepam 1.5 mg/day, and quetiapine 25 mg/day. The findings of the psychiatric examination at the time of admission were as follows: attention to the environment increased, mood was euphoric and sometimes disphoric and affect was consistent with the mood, the tone of voice was high, thought stream was accelerated, thoughts were falling short of the goal, there were persecution and referential delusions in thought content, and social functioning was inadequate.

The current status of the patient was assessed as schizophrenia. No abnormality could be detected in the blood values and physical examination. The current treatment of the patient (paliperidone 9 mg/day, lorazepam 1.5 mg/day, quetiapine 25 mg/day) was resumed. On the fifth day of admission, the patient's treatment was changed to olanzapine 10 mg/day and clonazepam 4 mg/day. Paliperidone, lorazepam, and quetiapine treatments were reduced and discontinued. On the 18th day of admission, VPA was added to the treatment of the patient who did not recover from psychiatric examination findings. Because the body weight of the patient was 92 kg, VPA was increased up to 1500 mg/day. On the 8th day of VPA treatment, patient's vital findings were evaluated, physical examination was performed, and blood tests were planned due to the onset of symptoms such as confusion and speech difficulty. No pathological reflexes or signs of meningeal irritation were found on physical examination and vital signs were normal. Blood VPA level was 130.32 μg/mL and blood ammonia level was 130.6 mg/dL. The results of other laboratory and imaging studies were evaluated as normal. As the patient's condition was evaluated as VPA-induced hyperammonemic encephalopathy, VPA was discontinued and IV hydration started. Approximately 36 hours after discontiuation of VPA treatment, the patient's medical condition improved. Blood ammonia level decreased to 88.8 mg/dL. No morbidity was observed in the patient's follow-up.

Case 3: A 41-year-old man who has been treated with schizophrenia for approximately 9 years has recently been admitted to our clinic with symptoms such as impaired drug compliance, refusal to eat, auditory and visual hallucinations, persecution delusions, and hostile behaviors. Previously, he used treatments such as haloperidol, olanzapine, and quetiapine. The most recent treatment was quetiapine 200 mg/day. He has been using this treatment for about 3 years. He was also diagnosed with epilepsy 1 year ago and has been using VPA 2000 mg/day as antiepileptic treatment since that day. The findings of the psychiatric examination at the time of admission were as follows: consciousness and orientation were complete, attention to the environment was diminished, self-care was bad, relationship form was cold/distant, speech was diminished and voice tone was monotonous, mimic and gestures were silent, auditory and visual hallucinations were present, thought stream was slowed down and his thoughts were falling short of the goal, there were persecution delusions in thought content, psychomotor activity decreased, and social functioning was inadequate.

The current status of the patient was assessed as schizophrenia. No abnormality could be detected in

the blood values and physical examination. The patient started treatment with quetiapine 400 mg/day. VPA, which he was using as antiepileptic, was also added to the treatment at a dose of 2000 mg/day. On the 6th day of the hospitalization, the patient was found to be deeply asleep, unable to wake up. He was observed to be lethargic when examined. Bilateral light reflexes were taken. Brain stem reflexes were present. Flexor response towards painful stimuli was present. Deep tendon reflexes were normal. The patient's VPA treatment was discontinued and he was started on IV hydration. EEG, brain imaging studies and blood tests were planned. The patient's EEG and brain imaging studies were reported as normal. VPA blood level was 109 μg/mL and ammonia blood level was 139 mg/dL. The clinical condition of the patient was evaluated as valproic acid-induced hyperammonemic encephalopathy and IV hydration was continued. Approximately 18 hours after the start of hydration and discontinuation of VPA treatment, the patient's condition improved. Repeated blood tests showed blood ammonia levels of 92 mg/dL. Three days after the condition improved, the patient was restarted with VPA treatment; the dose was gradually increased to 1500 mg/day. The EEG applied for control was reported as normal. No epileptic seizure was observed in the clinical follow-up of the patient. VPA blood levels were 77.47 μg/mL 8 days after the dose was raised to 1500 mg/day. There was no findings of encephalopathy or another morbidity in clinical follow-up and examination of the patient.

Case 4: A 23-year-old male patient with no prior history of psychiatric diagnosis was admitted to our clinic for 10 days of ongoing symptoms such as increased energy and psychomotor activity, reduced need for sleep, increased spending, increased self-esteem, visual hallucinations, strange speech, and behavior. The findings of the psychiatric examination at the time of admission were as follows: consciousness and orientation were complete, his interest in the surroundings increased, he was cheerful and behaving inopprapriate towards the examiner, speed rate increased, gestures were exeggarated, affect was euphoric, visual hallucinations were present, thought stream was accelerated, there were grandiose delusions in thought content, psychomotor activity increased, and social functioning was inadequate. The patient's condition was assessed as a manic episode. No abnormality was detected in blood tests. No pathological findings were found on physical examination. It was learned that the patient had no history of any other medical conditions. The patient's treatment started with olanzapine 20 mg/day and VPA 1000 mg/day. On the 9th day of admission, the blood levels of VPA were 59.3 μg/mL. A week later, it was learned that the patient lost his consciousness, fell, and started having epileptic-like contractions while spending time in the clinic's yard. Blood tests, EEG and brain imaging studies were planned for the patient who had no history of epileptic or conversive seizures. Blood tests resulted in as AST 94 U/L, ALT 186 U/L and ammonia 106 mg/dL. IV hydration was started immediately. VPA dose was reduced to 750 mg/day. The next day's blood ammonia level was found to be 84 mg/dL. One day later, the patient had epileptic seizure-like movements again, contracted, lost consciousness, and bitten his tongue. Blood levels of ammonia was 135 mg/dL, AST was 91 U/L, and ALT was 200 U/L. IV hydration was started on the patient again. No pathology was found in brain imaging studies. EEG results showed marked spike-wave paroxysmal epileptiform anomalies in bihemispheric frontal areas. Treatment with carbamazepine 200 mg/day was begun in the patient who underwent neurological examination. After 5 days, carbamazepine was increased to 400 mg/day. Ammonia level was found to be 85 mg/dL in the blood test performed 24 hours after stopping the VPA treatment. After 48 hours, the blood ammonia level was 54 mg/dL. However, blood AST/ALT values were still high (AST 71 U/L, ALT 166 U/L). The patient's olanzapine 20 mg/day treatment was discontinued switched with risperidone with daily dose of 4 mg. It was observed that AST/ALT values in blood tests performed 1 week later were within normal limits (AST 23 U/L, ALT 45 U/L). The carbamazepine blood level measured on the same day was 8.64 μg/mL. The patient's medical condition was stabilized with carbamazepine 400 mg/day and risperidone 4 mg/day. During the follow-up period, the patient did not have epileptic seizure again and no other morbidity was found (Table 1).

Discussion

1. Pathophysiological Mechanisms: Valproate-induced hyperammonemic encephalopathy usually occurs during the therapeutic titration of valproate at the beginning (50%) and may occur especially in those who are susceptible to hyperammonemia due to urease cycle enzyme deficiency or carnitine deficits [47]. This risk increases even further due to drug interactions when polypharmacy is present. VPA-induced encephalopathy is a rare and life-threatening clinical syndrome; although pathogenesis is still not fully understood, various mechanisms have been proposed and are often associated with hyperammonemia and normal liver functions. One reason for the occurrence of symptoms is probably the degradation of the aminogenesis and urea cycle by VPA, and therefore ammonia cannot be removed. The most likely mechanism of action of valproate is to enhance the inhibitor effect of GABA by affecting gamma-amino butyric acid (GABA) synthesis or metabolism in the brain. It weakens neuronal excitation induced by *N*-methyl-D-aspartate (NMDA) and also

Table 1. Characteristics of previous psychiatric VHE patients.

Author	Age, gender	Diagnosis	Co-morbid psychiatric diagnosis	Medical comorbidities	Additional medication	Daily VPA dosage mg	Serum VPA levels (µg/mL)	Serum ammonia levels (µmol/L)	VPA duration (day)	VIHE symptoms	Time to recovery day	VHE treatment a b c d e f g h	Time to onset of indication	Image study (EEG, CT, etc.) Genetic, enzyme defect	Risk factors, explanation
Settle (1995) [5]	57, F	BD II	–	Millard– Gubler Syndrome	Clonazepam	US	67	134	7	Slurred speech, mild ataxia, obtundation, coma	5		NEW	EEG: Generalized slowing tniphasic wave activity CT: Cerebellar atrophy, cerebral edema	Clonazepam added and 1 day after symptoms starting, comorbidity
Raby (1997) [6]	24, F	BPD	MD (atypical)	–	Tranylcypromine, liothyronine, thioridazine, clonazepam	1000	89.9	101.5	10	Fatigue, lethargy, persistent nausea	10		BPD	–	Strict vegeterian regimen, TRP
Raby (1997) [6]	38, F	BD I	–	–	Venlafaxine, L-thyroxine, lithium	1000	73	101	180	Cognitive changes, lethargy	14		22 YEARS	–	Vegeterian regimen, TRP
Eze et al. (1998) [7]	69, F	BD II	AD, BZD dependence, grief	–	Sertraline, alprozolam, trimipramine, meclizine, nabumetone, trazodone, clonidine	750	107.2	143	4	Disorientation to time, feeling slowed, coma	5		MOST OF HER LİFE	CT: NORMAL	Multiple drugs, BZD dependence
Pannikar Gilman (1999) [8]	53, F	BD I	Alcohol dependence	–	Haloperidol, benztropine	1750	107	79	17	Wandering, illogical speech, confusion, lethargy	3	*	MOST OF HER LİFE	–	Alcohol dependence
Pannikar Gilman (1999) [8]	23, M	SCAD	Alcohol dependence, crack cocaine abuse	–	Olanzapine	1500	75	193	14	Bizarre speech, confusion, lethargy	2		US	–	Alcohol dependence, crack cocaine abuse
Rottach et al. (2000) [9]	28, M	BD I	–	–	Doxepine, lorazepam, risperidone, biperiden	600	72	Normal	14	Tiredness, drowsiness tremor, generalized epileptic seizure	4		5 YEARS	EEG: Moderate general change MR: NORMAL	Multiple drugs
Barrueto and Hack (2001) [10]	41, M	BD I	–	Psoriasis, gout, and hypertension	Acebutolol, hydrochlorothiazide, ibuprofen, haloperidol, benztropine, gemfibrozil, lorazepam, multivitamin	US	73.5	377	1095	İnappropriate behavior, increasing lethargy	1		US	CT: NORMAL, any urea cycle deficiencies	Multiple drugs
Nicolai et al. (2001) [11]	33, M	SCZ	–	Clozapine-induced diabetic ketoasidosis	Clozapin	1000	30	582	1460	Unconscious	26		4 YEARS	Any urea cycle deficiencies but he had carnitine deficiencies	Comorbidity
Feil et al. (2002) [12]	88, M	Unclear, possible dementia	–	Generalized tonic clonic seizures	Phenytoin	1000	48	First: 836 Second: 130	First:60 Second: 7	Lethargic and confused, MMSE:16	3_60		2 YEARS	EEG: Bilateral 5–7-Hz slowing, suggestive of diffuse encephalopathy, and abnormal, irregular 2 Hz–3 Hz activity on the right,	Multiple drugs, second session tried

(*Continued*)

Table 1. Continued.

Author	Age, gender	Diagnosis	Co-morbid psychiatric diagnosis	Medical comorbidities	Additional medication	Daily VPA dosage mg	Serum VPA levels (µg/mL)	Serum ammonia levels (µmol/L)	VPA duration (day)	VIHE symptoms	Time to recovery day	VHE treatment a b c d e f g h	Time to onset of indication	Image study (EEG, CT, etc.) Genetic, enzyme defect	Risk factors, explanation
														suggestive of structural changes	
McCall and Bourgeois (2004) [13]	62, F	BD	AD	Hypothyroidism, hypertension, fibromyalgia, chronic pain, brain injury, seizure disorder, dementia	Estradiol, levothyroxine, diazepam, cyclobenzaprine, trazodone, acetaminophen with codeine, sulindac	1000	75	99	US	Somnolance, confusion, unresponsive, MMSE: 16	5		US	CT: Increased size of ventricle EEG: Slow waves and epileptiform activity because of injury	Multiple drugs, medical history (right encephalomalacia associated with past craniotomy), TRP
Elgudin et al. (2003) [14]	35, M	BD I	AD, Alcohol Dependence	–	Temazepam, lorazepam	1500	100	83	1796	Unresponsive	>3		5 YEARS	Estimated inborn or acquired deficiency CT:N EEG:N MRI: Mild generalized atrophy	alcohol dependence
Reif et al. (2003) [15]	42, M	MDD with Psychotic sympthoms	–	Obesity and mild diabetes mellitus treated with acarbose	Lithium, risperidone, flupentixol, clomipramine	1500	102	96	7	Sedation, tremor, myoclonus	2		2 YEARS	No Carnitine deficiency EEG: A prominent, generalized slowing with theta-/delta-rhythm (basal frequency, 2.5 Hz) during the whole recording of 13 min	Multiple drugs, history of harmful alcohol abuse
Yehya et al. (2004) [16]	9, M	İntermitten t Explosive Disorder	MR, Oppositional Defiant Disorder	–	Quetiapine, lithium	1000	113	127	210	Aggressive behaviour, confussion	4		NEW	EEG: Symmetrical 5- to 6-Hz waves, no slowing	MR, multiple drugs
Ricard et al (2005) [17]	58, M	BD I	–	–	Amisulpride, liothyronine, ciprofibrate, benfluorex, trihexyphenidyl	1000	79	124	210	Cognitive changes, disorientation, MMSE:16, extrapyramidal hypertonia	30		10 YEARS	EEG: Generalized slowing waves CT: Cerebral and cerebellar atrophy with enlarged ventricles.	Multiple drugs, TRP
Stewart (2005) [18]	79, M	SCZ	–	Seizure disorder, coronary artery disease, and benign prostatic hypertrophy	Olanzapine, phenytoin, amlodipine, finasteride, risedronate, aspirin	2250	48.5	89	2	Lethargy, confusion, disoriented	2		MOST OF HİS LİFE	No Carnitine deficiency	Multiple drugs
Kimmel et al. (2005) [19]	50, F	SCAD	–	Hypothyroid	Lamotrigine, quetiapine, lorazepam, levothyroxine	1250	101	242	1460	Loss of consciousness, bladder incontinence,a fine resting tremor in her head and bilateral upper extremities, cognitive changes	2		4 YEARS	–	Multiple drugs, TRP
Carlson et al. (2007) [20]	11,M	Asperger's syndrome, ADHD	A history of psychosis and manic symptoms	–	Lithium, risperidone, aripiprazole, dextroamphetamine	500	90	213	7	Agitation, disinhibition and manic behavior, vomiting	3		ND	EEG : NORMAL MRI: NORMAL	Multiple drugs
Carlson et al. (2007) [20]	11,M	ADHD	Borderline intelligence, new- psychotic symptoms	Absence seizures	Risperidone, ethosuximide	US	71	113	7	Agitation, disinhibition and manic behavior	14		US	EEG:3-Hz spike	Multiple drugs
Wadzinski et al. (2007) [21]	51,F	PTSD	MD	–	Topiramate, quetiapine	1000	145	232	7	Nonresponsive	4		US	–	Multiple drugs

Wadzinski et al. (2007) [21]	29,F	BD	OCD	–	Fluvoxamine, clonazepam	1500	113	182	17	Confussion, slurred speech, disorientation, hypersomnia and memory loss, blurred vision	2			US	–	–
Stewart (2008) [22]	76,M	BD	–	Familial essential tremor, recurrent supraventricular tachycardia, hypertension, hyperlipidemia, ocular melanoma postenucleation	Quetiapine, primidone, metoprolol, atorvastatin, lisinopril, levothyroxine, aspirin	3000	73	214	4015	Confussion, lethargy, near mute	3			US	–	Multiple drugs, Comorbidity, TRP
Fan et al. (2008) [23]	72, F	BD I	–	–	Clozapine, lamotrigine	900	85.9	101	42	Weakness, hand tremor, lethargy, asterixis	7			15 YEARS	EEG: Triphasic waves	There was no symptoms in the second use
Dealberto and Sarazin (2008) [24]	41,F	BD I	–	A cold thyroid nodule	Olanzapine	1000	131	61	1	Disorientation , drowsiness, agitation,ataxia with adiadochokinesia along with asterixis	2			US	EEG: Symmetric slowing with mild diffuse disturbances	Morbidity after VHE, TRP
Eubanks et al. (2008) [25]	33,F	BD	PTSD, Substance abuse, BPD	–	Clonazepam, venlafaksine, bupropion, hydroxyzine, mirtazapine	1500	120	283	3	Altered mental status, minimally responsive	1			US	CT:NORMAL	Multiple drugs
Abreu et al. (2009) [26]	47,F	BD I	–	–	–	2500	83.5	48	210	Apathy, confusion, memory loss, parkinsonism, catatonia	7			10 YEARS	CT: Pseudo Sulci atrophy and ventricular enlargement	
Deutsch et al. (2009) [27]	31,F	BD I	BPD	–	Citalopram, quetiapine, topiramate	1000	104	41.52	14	Somnolance, ataxia, dysarthria, memory problems	1			NEW	–	Multiple drugs
Young and Coffey (2010) [28]	15, M	BD I	–	MODY	Haloperidol, clonazepam	1750	100	96	–	Excessive daytime sleepiness, drowsiness	–			NEW	–	Comorbidity
Sunkavalli et al. (2013) [29]	52,F	SCAD	–	Remote seizures	Risperidone, phenytoin, haloperidol, lorazepam, ciprofloxacin	–	81	218	2	Altered mental status, suicidal ideation, low grade temperature, worsening seizures	2			US	EEG: During drowsy diffused background slowing intermixed with 2–2.5 Hz of high- amplitude any epileptiform activity	Multiple drugs
Chopra et al. (2012) [2]	19, F	BD I	–	–	clonazepam	1500	87	124	7	Cognitive slowing, ataxia, lethargy, drowsiness, nausea, vomiting	1			NEW	–	–
Chopra et al. (2012) [2]	36, M	SCAD	Alcohol and canabis dependence	Hepatitis C	risperidone, clozapine, clonazepam, disulfiram, topiramate, lithium	1000	114	111	7	Slurred speech, drowsiness, slowed cognition	3				EEG: generalized dysrhythmia	Substance use disorder, Multiple drugs
Chopra et al. (2012) [2]	53, F	BD II	Alcohol dependence	–	quetiapine	750	52	97	US		3			US	–	Substance use disorder

(*Continued*)

Table 1. Continued.

Author	Age, gender	Diagnosis	Co-morbid psychiatric diagnosis	Medical comorbidities	Additional medication	Daily VPA dosage mg	Serum VPA levels (µg/mL)	Serum ammonia levels (µmol/L)	VPA duration (day)	VIHE symptoms	Time to recovery day	VHE treatment a b c d e f g h	Time to onset of indication	Image study (EEG, CT, etc.) Genetic, enzyme defect	Risk factors, explanation
										Nausea, vomiting, clumsiness, incoordination					
Chopra et al. (2012) [2]	41, F	BD	Mild MR	–	Olanzapine	1250	96	133	1	Bizarre behaviour	1		5 MONTHS	–	Mild MR, Symptoms appeared in 1 day when the dose was increased
Chopra et al. (2012) [2]	71, F	SCAD	Mild MR	–	Lithium	1500	26	133	21	Declinining alertness	2		US	EEG: Generalized slowing and triphasic waves	Mild MR
Sarlon et al. (2013) [30]	57, US	SCAD	–	–	Lorazepam	US	NORMAL	583	8	Somnolance, psychomotor agitation	a few days		US	Lack of carnitin, EEG: Slow scattered theta and delta-waves	
Mangewal a et al. (2013) [31]	17, M	Autistic disorder	–	Epilepsy	–	1500	81	High	150	Drowsy, asterixis, fluctuated councousness	7		ND	–	
Silva et al. (2013) [32]	41, F	BD	–	–	risperidone	1000	94.5	213.4	10	Psychomotor retardation, slurred speech, ataxia	2		US	–	Regimen
Cheng et al. (2013) [3]	15,F	BD I	–	–	Sertraline, alprozolam,	1000	106.8	138.7	9	Psychomotor agitation, alertness, drowsiness, headache, confused, lethargy	14	c*	NEW	EEG: Generalized theta and delta activity	–
Halaby et al. (2013) [33]	31,M	BD I	–	–	Lithium, quetiapine	1500	65	137	21	Violent, confusion, disoriented	1		NEW	MR:NORMAL	–
Halaby et al. (2013) [33]	21,M	BD II	Opioid Dependence and Cannabis Abuse	–	Paracetamol, ketoprofen diazepam quetiapine	1000	55	480	730	Lethargy, confusion, disoriented	2		2 YEARS	–	Opioid Dependence and Cannabis Abuse, Multiple drugs
Twilla and Pierce (2014) [34]	52, F	SCAD	–	Essential tremor, migraines, seizure disorder, cerebrovasculer accident,COPD	Primidone, topiramate, paroxetine, gabapentine, quetiapine, clonazepam	1000	120	132	4	Altered mental status, somnolance	6		US	CT:NORMAL EEG: Severe slowing activity	Comorbidity, Multiple drugs
Selvi et al. (2014) [35]	20, F	BD I	–	–	–	1000	116	237	9	Nausea, vomiting, lethargy, disorientation, confusion, agitation	1	e**	3 YEARS	–	–
Muraleed haran et al. (2015) [36]	46, M	BD	–	–	Lorazepam	1000	US	81	18	Confusion, disoriented	3		20 YEARS	–	–
Muraleed haran et al. (2015) [36]	53, M	BD	–	–	Olanzapine, lorazepam	1000	US	130	4	Confusion, disoriented	3		12 years	–	–
Muraleed haran et al. (2015) [36]	36, F	BD	–	–	Lorazepam, Lithium	600	US	68	2	Drowsy, unconscious	3		19 YEARS	–	–
Dawson et al. (2016) [37]	57, M	BD	–	DM II, Chronic renal failure, hypertension, obesity, uriner tract infection	Quetiapine, lithium	3000	102.6	126	1095	Ataxia, confusion,	5		30 years	–	comorbidity, started twice and syptoms have been repeated

Surendran et al. (2016) [38]	57, M	BD	Alcohol Dependence Syndrome, Tobacco Dependence Syndrome	DM II, chronic kidney disease and benign prostatic hyperplasia	Quetiapine, lorazepam, risperidone, bupropion	2000	US	159	10	Constipation, tremor/ asterixis and cog-wheel rigidity in the limbs, disoriented, sleep-wake cycle, confused, MMSE:16	10		17 YEARS	EEG: Diffuse slowing suggestive of encephalopathy MR: NORMAL	alcohol dependence syndrome, After 2555 days of use stopped for surgery then started again
Ciftci et al. (2016) [39]	19, F	ADHD	–	–	–	1000	44	588	1	Confused, uncooperative	13		12 YEARS	CPS 1 DEFİCİENCY MR: bilateral cortical and subcortical diffusion restriction with corresponding ADC hypointensity and Flair hyperintensity on the same localizations EEG: diffuse slowing with delta activity	CPS 1 DEFİCİENCY
Prarthana et al. (2017) [40]	58, M	BD	–	–	–	1000	US	190	4	Altered mental status, irrelevant and slurred speech, drowsiness, disorientation, difficulty in walking, altered sleep pattern, abdominal discomfort	2		US	EEG:NORMAL	After 3 months the dose was increased
Elwadhi et al. (2017) [41]	52, M	BD	–	–	–	1500	56.2	148	2	Constipation, altered sensorium	2		20 YEARS	–	–
Elwadhi et al. (2017) [41]	26, F	SCAD	–	Hypothyroidism	Levothyroxine, risperidone, benzodiazepines	800	120	291	2	Drowsy, vomiting	3		NEW	–	TRP
Elwadhi et al. (2017) [41]	18,M	BD	Rheumatic Heart Disease, Cannabis Dependence	–	–	1500	100	204	7	Sedation, vomiting, disoriented	2		US	–	cannabis dependence
Elwadhi et al. (2017) [41]	20, M	BD	Cannabis Dependence	–	–	1000	56	122	3	Constipation, slurring speech, vomiting	US		US	–	cannabis Dependence, Alcohol intake in harmful pattern
Nguyen et al. (2017) [42]	16, F	BD	OCD	–	Fluvoxamine , clonazepam	1500	120	186	30	Confusion, disorientation, hypersomnia and blurred vision	3		US	–	using 1000 mg for 8 months, dose increased 1 month ago
Farooq et al. (2017) [43]	44, M	SCAD	–	–	Risperidone	750	110	383	1	Abnormal twitching movements of his head and appeared drowsy, unresponsive	2		7 YEARS	CT:NORMAL	Multiple drugs, using 500 mg for 6 weeks
Gandolfo et al. (2017) [44]	62, F	SCAD	–	DM II, chronic diarrhoea, recent coronary stenting	Acetylsalicylic acid, clopidogrel,	500	48.7	114	US	Lethargy	7		Since adolescence	CT:NORMAL EEG: NORMAL	Multiple drugs, hypoalbuminaemia

(*Continued*)

Table 1. Continued.

Author	Age, gender	Diagnosis	Co-morbid psychiatric diagnosis	Medical comorbidities	Additional medication	Daily VPA dosage mg	Serum VPA levels (µg/mL)	Serum ammonia levels (µmol/L)	VPA duration (day)	VIHE symptoms	Time to recovery day	VHE treatment a b c d e f g h	Time to onset of indication	Image study (EEG, CT, etc.) Genetic, enzyme defect	Risk factors, explanation
Patel et al. (2017) [45]	48, F	BD	–	for myocardial infarction Congestive heart failure, hypertension, degenerative joint disease	lansoprazole, atorvastatin Olanzapine, atenolol, pregabalin, oxycontin, roxicodone	1000	First:US-Second:112	First:188–Second:88	First:6–Second:4	Sedation, dizziness, fatigue,vomiting	First:2–Second:3		US	–	Multiple drugs, Started twice and syptoms have been repeated
Cattaneo et al. (2017) [46]	29, M	BD	Substance use disorder	Childhood epilepsy	haloperidol decanoate, lorazepam, chlorpromazine, haloperdol	1800	124	594	13	Counsciousness, lethargy	1		US	EEG:Slow-wave theta activity across the temporal cortex	Substance use disorder, Multiple drugs, 1500 mg for 1 week

a: VPA discontinuation, b: Discontinuaton of other drugs , c: Hidration, d: Lactulose, neomycin, protein restriction, e: L-carnitine, f: Hemodialysis, g: Other drugs for CNS or comorbidities(Naloksan, insulin, etc.) h: charcoal.
*: Reduction of vpa, **: L-Ornithine-L-aspartate, E**: Furosemide, Mannitol, Acetaglutamide, Ornithine
US: Unspecified, N: Normal, BZD: Benzodiazepine, MMSE: Mini–Mental State Examination, BD: Bipolar Disorder, BPD: Borderline Personality Disorder, MD: Major Depressive Disorder, MR: Mental Retardation, AD: Anxiety Disorder, ADHD: Attention Deficit Hyperactivity Disorder, PTSD: Posttraumatic Stress Disorder, OCD: Obsessive Compulsive Disorder, SCZ: Schizophrenia, ND:Neurodevelopmental Disorder, SCAD: Schizoaffective Disorder, DM: Diabetes Mellitus, MODY: Maturity Onset Diabetes of the Young, COPD: Chronic Obstructive Pulmonary Disease, TRP: Thyroid-Related Patients.

modulates dopaminergic and serotonergic neurotransmission. It is accepted that the mechanism of action of valproate depends on the presynaptic action to GABA metabolism and/or the strengthening of GABA-mediated inhibition by direct postsynaptic action on the ion channels in the neuronal membrane. In addition, it is known that VPA binds to plasma proteins, particularly albumin, by a saturable metabolism. It is also important to note that it has also been extensively metabolized by microsomal glucuronide conjugation (50%), mitochondrial β-oxidation (40%), and omega-2-oxidation by cytochrome P450 (10%) [48].

VPA reduces mitochondrial carbamoyl phosphate synthetase-1 (CPS1), which is the first enzyme in the urea cycle, with direct inhibition and reduces hepatic citrulogenesin through indirect inhibition; therefore it acts as a urea cyclus inhibitor and indirectly leads to the reduction of carnitine [49]. Carnitine is essential for the oxidation of fatty acids and protects the ratio of acyl-CoA to free CoA in mitochondria. VPA inhibits carnitine transport and causes an increase in renal carnitine excretion. VPA also increases ammonia production in the kidney by stimulating renal glutaminase. Normally, 25% of ammonia is produced in the kidney, while the rest is produced in the liver. VPA first combines with carnitine to form valproylcarnitine, which is soluble in water and excreted in the urine. VPA also inhibits renal tubular reabsorption of carnitine and acylcarnitine and causes more carnitine loss [50]. It has also been reported that VPA reduces the synthesis of carnitine production by inhibiting butyrobetaine hydroxylase and blocking the membrane carnitine transporter. VPA also inhibits the b-oxidation, ATP production and intracellular CoA-SH pool, leading to restoration of the acylcarnitine for free carnitine. Hyperammonemia can be seen as a consequence of the following effects of VPA on the liver and kidney pathways: the storage of carnitine is reduced by different mechanisms; VPA acts primarily as a urea cycle inhibitor by indirectly inhibiting hepatic mitochondrial carbamoyl phosphate synthetase-1 (CPS1), the first enzyme of the urea cycle, which leads to reduction of hepatic citrullinogenesine [51].

Normally, 2-propyl-2-pentenoic acid (2-en-VPA), 3-hydroxy-2-propylpentanoic acid (3-OH-VPA) and 3-hydroxy-3-propylpentanoic acid (3-keto-VPA), which are non-toxic metabolites, are produced by β-oxidation. However, long-term or high-dose VPA use shifts metabolism from β-oxidation to omega-2 oxidation and increases the production of 2-propyl-4-pentanoic acid and propionic acid, which causes high levels of ammonia and hepatotoxicity. Propionic acid also reduces hepatic N-acetylglutamate (NAG) production, which inhibits mitochondrial CPS1 in the liver and consequently compromises the hepatic urea cycle. Increasing 4-en-VPA levels result in a similar result by reducing the availability of acetyl Co-A, an element

of NAG. Another reason for the decrease in NAG production is the lack of carnitine. Inhibition of NAG from the end result of activation of Valproyl-CoA leads to an increase in ammonia level [52].

Ammonia, a byproduct of the amino acids which are normally converted to α-keto acids, is ultimately converted into urea in the liver. During hyperammonia, ammonia is conjugated with α-ketoglutarate and causes α-ketoglutarate to be consumed as a block in the Krebs cycle and damages neurons. Ammonia easily crosses the blood–brain barrier and inhibits glutamate re-uptake into the cell. Excessive NMDA receptor activity induced by high levels of extracellular glutamate increases the risk of encephalopathy and reduces seizure threshold. Hyperammonemia may also lead to impairment in the membrane aquaporin system and brain electrolyte homeostasis, all of which may result in neuronal toxicity and cerebral edema in astrocytes [53].

If we were to look at the treatments applied to the before presented cases, we must first say that oxcarbazepine is metabolized to the 10-monohydroxy derivative (MHD), which is often the active metabolite. Approximately 40% of the MHD binds to serum proteins, mainly albumin. Approximately 93% of olanzapine is bound to plasma proteins, especially albumin and a1-acid glycoprotein. Olanzapine is metabolized in the liver by conjugative and cytochrome P450-dependent oxidative pathways, whereas quetiapine binds to approximately 83% of plasma proteins and is metabolized by oxidative pathways associated with cytochrome P450, just like oxcarbazepine and olanzapine. The interaction of VPA with these drugs partially explains why adverse events occurred in the presented cases.

2. Diagnostic Studies and Laboratory Findings: The diagnosis of VHE can be established by ruling out other causes of impaired consciousness along with laboratory (VPA and ammonia level) and diagnostic studies (EEG, MRI, CT). Laboratory tests can help us while diagnosing VHE, researching etiology and following it up. Running kidney and liver function tests, checking serum glutamate and serum carnitine levels, and looking for urea cycle disorders (OTC and CPS1 deficiency) may also be useful. OTC deficiency (an X-linked disease) is the most common inherited cause of hyperammonemia [54]. Male homozygots usually die in the neonatal period. Liver function tests are expected to be within normal limits. EEG findings are mostly in the direction of severe encephalopathy and slow wave activity or triphasic waves are the most common electrophysiologic finding. MRI findings in patients with psychiatric disorders often suggest reversible atrophy, altough cases with normal EEG and MRI have also been reported.

3. Risk Factors: There is a relationship between VPA dose and hyperammonemia in children under 2 years of age because of the greater sensitivity. In adults, there seems to be no relationship between VPA daily dose and VHE severity. Also, there was no correlation between the duration of VPA use and the onset of VHE [32]. The fact that the individual has been treated without any previous complications with VPA does not indicate that VHE will not occur in the next treatment. Possible risk factors for VHE are polypharmacy (drug–drug interactions), the combination of VPA with other antiepileptic medication, carnitine or urea cycle enzyme deficiency, hypercatabolic state, poor nutrition like vegetarian diet (reducing free carnitine), and psychiatric comorbid conditions such as mental retardation and thyroid-related diseases [55].

4. Clinical Features and Clinical Management: The clinical presentation of VHE may vary and includes gastrointestinal symptoms (such as loss of appetite, nausea, vomiting, constipation, and bladder incontinence) and is characterized typically by acute onset of cognitive changes and altered mental status (such as headache, dizziness, feeling slowed, tiredness, slurred/illogical/bizarre speech, confusion, unconsciousness, fatigue, lethargy, sedation, somnolance, declinining alertness, obtundation, hypersomnia, blurred vision, wandering, memory loss, disorientation to time, inappropriate or aggressive behaviour, tremor, myoclonus, extrapyramidal hypertonia, parkinsonism, mild ataxia, adiadochokinesia along with asterixis, apathy, catatonia, psychomotor retardation or psychomotor agitation, irritability, drowsiness, coma, and paradoxical seizures). It may be useful to screen for hyperammonemia in otherwise asympthomatic patients on VPA treatment who are experiencing cognitive impairment [4]. Neuropsychological testing, such as MMSE or Glasgow Coma Scale, is more sensitive than observational methods to assess subclinical VHE. In the case of VPA treatment, if the clinical condition worsens in favour of encephalopathy, the physician must evaluate the patient in terms of VHE so that the diagnosis cannot be dismissed; thus the follow-up can be done appropriately.

5. Acute Treatment: When we evaluated the treatment of the present case and 58 previously presented cases, it was observed that the clinical status was shortly restored by cutting only VPA without needing additional treatment in 31 of the patients. Reduction of VPA dose in 1 patient, discontinuation of risperidone treatment with continuing VPA in 1, withdrawal of VPA and other drugs in 2 patients led to the same result. These results indicate that the discontinuation of VPA in the case of VHE is the first stage of treatment and that most patients respond positively to it. Hydration, lactulose, rifaximin, neomycin, and protein restriction should be considered as other treatment modalities. L-carnitine supplementation has been shown to improve the symptoms of VHE [28]. Treatment with furosemide, acetaglutamide, and mannitol

may also be used for severe VPA toxicity, as they may play a significant role in reducing cerebrocellular edema and hyperammonemia [3]. In case of severe hyperammonemia, hemodialysis may also be a therapeutic option [56]. *N*-carbamylglutamate (NCG), also known as carglumic acid, which is a synthetic analogue of *N*-acetylglutamate (NAG), is one of the cofactors essential to the proper functioning of urea cycle [57]. NCG is indicated for treatment of hyperammonemia secondary to NAG-synthetase deficiency [58].

6. Prevention: It is not possible to predict which patient will develop VHE or to prevent the development of VHE within the available information. However, carnitine supplementation may be recommended for those with carnitine deficiency. On the other hand, there is a need for research to control thyroid, kidney, and liver functions, as well as serum glutamate and serum carnitine levels in patients who are scheduled to start valproate therapy and how effective screening for urea cycle deficiency (OTC and CPS1 deficiency) may be in terms of morbidity and mortality [1].

7. Future Directions: Another question mark is the lack of encephalopathy in some patients with hyperammonemia. The prognosis of VHE is a wide spectrum, from complete healing to death. In the neurological literature, there are 6 reported cases of death, with 5 of them showing OTC deficiency [45]. In the psychiatric literature, no cases of death due to VHE have been reported so far. It is noteworthy that no morbidity or mortality was observed in controls performed after the recovery of patients except for one of the cases of hyperammonemic encephalopathy induced by valproate in the psychiatric clinic. The question should be asked whether this is because of the early diagnosis and treatment of the physicians, whether the controls were not done in a healthy way, or the neuroprotective effect of valproate [59]? More research is needed for pathophysiology, drug interactions, and risk factors in VHE. It seems that there is also a need to study the possible benefits of prophylactic treatment to prevent VHE, which is the result of valproate toxicity.

Conclusion

Adjustment of dose or discontinuation of VPA may be necessary in the symptomatic patients with altered mental status. It is also important to check the ammonia levels immediately in these patients. Supportive care and discontinuation of VPA is currently the mainstay of treatment for VHE. L-carnitine replacement, discontinuaton of other drugs, hydration, lactulose, rifaximin, neomycin, protein restriction, carglumic acid, hemodialysis, L-ornithine-L-aspartate, L-arginine, charcoal, furosemide, acetaglutamide, mannitol, and other supportive treatments for CNS or other comorbidities are sometimes useful.

Disclosure statement

No potential conflict of interest was reported by the authors.

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