



Hypothyroidism exacerbating valproate induced hyperammonemic delirium, an unknown clinical concern: Short communication

Chung-Chieh Hung^{†,1}

ABSTRACT

From the literature reviews, valproic acid (VPA) induced hyperammonemia is a commonly adverse event and usually asymptomatic. VPA is a well-tolerated and an effective agent for the treatment of epilepsy, bipolar disorder, schizoaffective disorder, off-label use for the impulsive control problems and etc. However, several case reports have indicated that VPA may induce serious symptomatic hyperammonemia and even lethal. Based on the analysis of susceptible patients, several possible mechanisms and risk factors have been proposed to identify the patients at risk.

Nevertheless, the co-morbid hypothyroidism patients suffer from the more tentative risk in the vulnerability of VPA induced hyperammonemia. Few researches focused on this clinical phenomenon and underlying mechanism of action.

In this short communication, we aimed to review the articles about the VPA induced hyperammonemia. We also summarized the risk factors of hypothyroidism related to such clinical condition. We especially focused on the neuropsychological side effects such as consciousness disturbance or delirium.

We found out these patients mainly female. Most of them didn't suffer from the underlying psychiatric disorder. In addition, only one case report reveals that the merely subclinical hypothyroidism without any treatment would have the risk of VPA induced hyperammonemia and the consequent delirium.

Keywords

Delirium, Hypothyroidism, Hyperammonemia, Valproate

Introduction

The hypothyroidism is differentiated preliminarily as primary, secondary and tertiary etiologies according to the causative reasons [1]. Each of the above condition may contribute to neurological and psychiatric manifestations [2]. When the patients suffer from the hypothyroidism, they are easier to be found with anxiety, depression, cognitive and executive

dysfunction. These neurological and psychiatric symptoms are more likely to occur in the elderly group [3].

Although it is well known that valproic acid (VPA) can induce hyperammonemia [4], scanty reports concerned of its association or relationship with the hypothyroidism. In the previous case report [5], we presented a bipolar affective patient with hypothyroidism (in

¹Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan

[†]Author for correspondence: Chung-Chieh Hung, MSc, Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan; Tel: +886-921-067260, Fax: +886-4-22361042, email: alouette_rouge@yahoo.com.tw, D16893@mail.cmuh.org.tw

fact, merely subclinical hypothyroidism) who experienced from the delayed hyperammonemic delirium during VPA treatment.

In this following reviewed article, we searched for the literature for the VPA-induced consciousness disturbance. In addition, we also updated the delirium cases resulted from hypothyroidism. The aim of this short communication is to address the important issues for the VPA treated patient in the neurological and psychological setting. We should be highly alert when they had the underlying hypothyroidism even merely subclinical.

When the patients have the concomitant clinical pictures, they are prone to suffer from lethal side effect of consciousness disturbance.

Discussion

VPA induced hyperammonemia can be either asymptomatic or symptomatic. The prevalence of such adverse event remains mysterious but rare in the adulthood population [6]. In addition, it may occur with both therapeutic and supra-therapeutic concentrations of the serum VPA drug level, indicating other influence of potential risk factors. The patients who have been on VPA for several years without developing any complications can suddenly develop symptoms of encephalopathy. The acute (outlined in **Table 1**) [7-14] and the delayed [5] effects of VPA induced hyperammonemia are all documented. Nevertheless, nearly all reports reveal and discuss about the acute onset adverse events. This communication summarized the acute effect cases of VPA induced hyperammonemia in the **Table 1**. These cases are revealed the onset from 2 days to 10 days. We only found one case report [5] about the delayed onset VPA induced hyperammonemia with the occurrence 4 years later. Though these adverse events are well reviewed, only one retrospective study [15] examines the causative relationship. In the above study, adult patients in the psychiatric setting are treated with a mood stabilizer and checked for hyperammonemia. The 51.2% of the patients receiving VPA (N=123) had asymptomatic hyperammonemia (level >97 µg/dl) [15].

To the best of our knowledge, one of the reviewed articles reveals and summarizes the neuropsychiatric symptoms as well as the tentative risk factors led to the mechanism of VPA induced hyperammonemia [6]. Regarding the proposed mechanism of action, the animal studies convince in both the role of kidney

and liver for the underlying cause [16,17]. The animal model of kidney and the renal uptake of glutamine which increases the serum ammonia would be dangerous to be hyperammonemic [16]. The other potential mechanisms within the liver lead to hyperammonemia. The description of the underlying biochemical pathway shows that the VPA is believed to increase the ammonia by reducing the free carnitine and co-enzyme A. Nevertheless, loss of carnitine prevents importation of long-chain fatty acids into the mitochondrial matrix for metabolism. Loss of co-enzyme A prevents the beta-oxidation of fatty acids into acetyl-co-enzyme A, which is a substrate of N-acetylglutamate, the required activator of the initial enzyme in the urea cycle.

Therefore, the increased ammonia level affects the urea cycle inside the hepatocytes. There is an association between VPA induced hyperammonemia, consciousness disturbance and genetic impairment in the urea cycle [18]. The risk factors exist that urea cycle disorders, infancy (immature hepatic function), carnitine deficiency due to either genetic abnormalities or dietary restrictions [18] effects of nutritional intake such as higher nitrogen load [19], or possibly increased carbohydrate intake [20], polypharmacy, and complicating medical conditions.

We could take a look at the **Table 1** [7-14] and summarized the demographic data of the currently acute VPA induced hyperammonemia. We deduced that the other factors that few study notified about the brain image studies. From our review, some cases with VPA induced hyperammonemia are revealed generalized slowing and intermittent slowing electroencephalogram (EEG). As the authors of the reviewed literatures suggest that the patients with pre-existing epilepsy would have their EEG pronounced general slowing, an increase in epileptiform discharges [17]. The unknown pathology inside the brain via EEG testing could be one of mechanism or even consequences of VPA induced hyperammonemia. However, the systematic study of the EEG of the patients without epilepsy but suffering from VPA induced hyperammonemia is lacking.

From the **Table 2** [5,21,22], we searched for the three case reports excluding the Hashimoto thyroiditis. We compared the difference among the hypothyroidism cases with consequent consciousness disturbance. As the case [22] demonstrates the relationship between the

Table 1: Acute effect cases of VPA induced hyperammonemia.

Authors	Sex	Age	Diagnosis	Substance	Exposure	Symptoms	Recovery	Valproate acid		Elevated ammonia		Co-medications	Image study
								Dose	level	Level	ratio		
Settle EC [7]	♀	57	BD	BZD	7 days	Coma	<5 days	N/A	67	134	1.9	Clonazepam	Generalized slowing EEG
Raby WN [8]	♀	24	BPD, MDD	BZD	10 days	Fatigue, lethargy, nausea	10 days	750	89.9	173	2.9	Clonazepam, Liothyronine, Thioridazine, Tranylcypromine	None
Eze et al. [9]	♀	69	BD	BZD	4 days	Coma	5 days	750	107.2	244	3.1	Alprazolam, Clonidine, Hydrochloride, Meclizine, Nabumentone, Sertraline, Trazodone, Trimipramine	Normal brain CT
Pannikar and Gilman [10]	♀	53	BD	Alcohol	10 days	Lethargy, confusion	3 days	1750	107	135	2.2	Benzotropine, Haloperidol	None
Pannikar and Gilman (1999) [10]	♀	23	SCZA	Alcohol, cocaine	14 days	Confusion	2 days	1500	70	329	5.5	Olanzapine	None
Stewart JC [11]	♂	79	SCZ, epilepsy	None	2 days	Lethargy, confusion	4 days	2250	48500	152	2.2	Amlodipine, Aspirin, Finasteride, Olanzapine, Phenytoin, Risedronate	None
Eubanks et al. [12]	♀	33	BD, BPD, PTSD	BZD	3 days	Confusion	3 days	1500	120	482	9.5	Bupropion, Clonazepam, Hydroxyzine, Mirtazapine, Venlafaxine,	Normal brain CT
Hung. et al. [13]	♀	21	SCZA	None	4 days	Vomiting, confusion, ataxia	2 days	750	107.7	228	3.3	None	Intermittent slowing EEG
Anupama [14]	♂	46	BD	None	18 days	Confusion, lack of orientation	6 days	1000	N/A	92	2.5	Lorazepam	None
	♂	53	BD	None	2 days	Confusion, lack of orientation, impaired memory	3 days	1000	N/A	147	4.1	Olanzapine, Lorazepam	None
	♀	36	BD	None	2 days	Drowsy, loss of consciousness	3 days	600	N/A	77	2	Lithium, Lorazepam	None

Abbreviation: BD: bipolar disorder, BPD: borderline personality disorder, BZD: benzodiazepine, CT: computed topography, EEG: electroencephalogram, MDD: major depressive disorder, PTSD: posttraumatic stress disorder, SCZA: schizoaffective disorder, SCZ: schizophrenia. Valproic acid dose is expressed as mg/d and its level µg/ml. Elevated ammonia level is expressed as µg/dL.

enzymatic activity of thyroid hormone and the urea cycle enzymes. The passage emphasizes the hyperammonemia associated with hypothyroidism. On the other sides, the case [21] argues that hyperammonemia in the hypothyroidism may be explained by the pathophysiological studies of the urea cycle, especially from the rat liver model. Hence the hyperammonemia occurs on the consequence of discontinuation of levothyroxine and improves after the supplement of the levothyroxine. The

current study [5] connects the risk factors of hyperthyroidism and VPA long time therapy in the role of hyperammonemia. We could find out that all these three cases all had the delayed onset consciousness disturbance related to hypothyroidism.

The mechanism may be competition between VPA and thyroid hormones [23]. On the other side, VPA treatment didn't always alter thyroid hormones in another study [24]. More investigation such like cohort study or

Table 2: Co-morbid hypothyroidism (exclusions of Hashimoto's thyroiditis) and consciousness disturbance reviewed case series.

Authors	Age	Sex	Aggravating factor	Onset (years)	Psychiatric Disease	Neurological outcome	Brain Image
Doron Rimar et al. [21]	82	♀	Levothyroxine discontinuation	10	None	Coma	High intense globus pallidus and hypothalamus in brain MRI-T1
Seiji Hitoshi et al. [22]	53	♀	Portal-systemic encephalopathy	2	None	Slow speech and intermittent coma	Generalized slowing and triphasic waves
Hung C.C. et al. [5]	41	♀	Valproic acid association	4	Bipolar disorder	Delirium	Normal brain CT

CT: computed topography, EEG: electroencephalogram, MRI: magnetic resonance image

clinical trials are suggested while the results are controversial.

Conclusions

The exact mechanism of hypothyroidism aggravating VPA induced hyperammonemia remains unknown but still reminds us of a clinical concern. Thyroid hormones are hypothesized to regulate hepatic mitochondrial catabolism [25]. The competition between thyroid hormone and VPA would influence the uric cycle and hence hyperammonemia occurred. From the above summary, hypothyroidism could mandate for decompensating liver diseases, hyperammonemia from the production of urea cycle (although obviously in rat but not human), or inefficient urea synthesis.

To answer such clinical concern, we presumed that VPA probably competed with thyroid hormones. Frankly speaking, VPA might be the consequence of hypothyroidism and hypothyroidism predisposed to the hyperammonemia. Besides, the summation of the two risk factors of the hyperammonemia would make this clinical situation worse.

Undoubtedly, we should be more cautious while prescribing VPA in patients with hypothyroidism, even merely subclinical hypothyroidism in our previous case report.

Acknowledgement

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019).

References

- Querido A, Stanbury JB. The response of the thyroid gland to thyrotropic hormone as an aid in the differential diagnosis of primary and secondary hypothyroidism. *J. Clin. Endocrinol. Metab* 10(10), 1192-1201 (1950).
- Martin JM, Stanbury JB. The response of the l131-treated thyroid gland to thyrotropic hormone. *J. Clin. Endocrinol. Metab* 15(7), 811 (1955).
- Davis JD, Tremont G. Neuropsychiatric aspects of hypothyroidism and treatment reversibility. *Minerva. Endocrinol* 32(1), 49-65 (2007).
- Lewis C, Deshpande A, Tesar GE, et al. Valproate-induced hyperammonemic encephalopathy: a brief review. *Curr. Med. Res. Opin* 28(6), 1039-1042 (2012).
- Hung CC, Lin CH, Lane HY. Hypothyroidism may exacerbate valproate-related hyperammonemic delirium. *Biomedicine (Taipei)* 6(2), 12 (2016).
- Carr RB, Shrewsbury K. Hyperammonemia due to valproic acid in the psychiatric setting. *Am. J. Psychiatry* 164(1), 1020-1027 (2007).
- Settle EC, Jr. Valproic acid-associated encephalopathy with coma. *Am. J. Psychiatry* 152(8), 1236-1237 (1995).
- Raby WN. Carnitine for valproic acid-induced hyperammonemia. *Am. J. Psychiatry* 154(8), 1168-1169 (1997).
- Eze E, Workman M, Donley B. Hyperammonemia and coma developed by a woman treated with valproic acid for affective disorder. *Psychiatr. Serv* 49(10), 1358-1359 (1998).
- Panikkar GP, Gilman SM. Valproate-induced hyperammonemia in the psychiatric setting: 2 cases. *J. Clin. Psychiatry* 60(8), 557-559 (1999).
- Stewart JT. Treatment of valproate-induced hyperammonemia. *J. Am. Geriatr. Soc* 53(6), 1080 (2005).
- Eubanks AL, Aguirre B, Bourgeois JA. Severe acute hyperammonemia after brief exposure to valproate. *Psychosomatics* 49(1), 82-83 (2008).
- Hung CC, Li TM, Wei IH, et al. The real mechanism of VPA-induced hyperammonemia remains unknown. *Gen. Hosp. Psychiatry* 33(1), 84. e3-4 (2011).
- Muraleedharan A, Palappallil DS, Gangadhar R, et al. Valproate Induced Hyperammonemic Delirium. *J. Clin. Diagn. Res* 9(12), FR01- FR03 (2015).
- Raja M, Azzoni A. Valproate-induced hyperammonemia. *J. Clin. Psychopharmacol* 22(1), 631 (2002).
- Elhamri M, Ferrier B, Martin M, et al. Effect of valproate, sodium 2-propyl-4-pentenoate and sodium 2-propyl-2-pentenoate on renal substrate uptake and ammoniogenesis in the rat. *J. Pharmacol. Exp. Ther* 266(1), 89-96 (1993).
- Verrotti A, Trotta D, Morgese G, et al. Valproate-induced hyperammonemic encephalopathy. *Metab. Brain. Dis* 17(4), 367-373 (2002).
- Raskind JY, El-Chaar GM. The role of carnitine supplementation during valproic acid therapy. *Ann. Pharmacother* 34(5), 630-638 (2000).

Hypothyroidism exacerbating valproate induced hyperammonemic delirium, an unknown clinical concern: Short communication Short Communication

19. Laub MC. Nutritional influence on serum ammonia in young patients receiving sodium valproate. *Epilepsia* 27(1), 55-59 (1986).
20. Warter JM, Marescaux C, Chabrier G, et al. Increase of valproate-induced hyperammonemia in normal subjects by carbohydrate intake. *Neurology* 34(11), 1487-1489 (1984).
21. Rimar D, Kruzel-Davila E, Dori G, et al. Hyperammonemic coma-barking up the wrong tree. *J. Gen. Intern. Med* 22(4), 549-552 (2007).
22. Hitoshi S, Terao Y, Sakuta M. Portal-systemic encephalopathy and hypothalamic hypothyroidism: effect of thyroid hormone on ammonia metabolism. *Intern. Med* 32(8), 655-658 (1993).
23. Benedetti MS, Whomsley R, Baltes E, et al. Alteration of thyroid hormone homeostasis by antiepileptic drugs in humans: involvement of glucuronosyltransferase induction. *Eur. J. Clin. Pharmacol* 61(12), 863-872 (2005).
24. Isojarvi JI, Turkka J, Pakarinen AJ, et al. Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. *Epilepsia* 42(7), 930-934 (2001).
25. Tajiri J, Shimada T, Naomi S, et al. Hepatic dysfunction in primary hypothyroidism. *Endocrinol. Jpn* 31(1), 83-91 (1984).