1-2018

Hypoxic respiratory failure due to hyperammonemic encephalopathy induced by concurrent use of valproic acid and topiramate, a case report and review of the literature

Yonas Raru

Fuad Zeid

Respiratory Medicine Case Reports 25 (2018) 1–3

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

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

Case report

Hypoxic respiratory failure due to hyperammonemic encephalopathy induced by concurrent use of valproic acid and topiramate, a case report and review of the literature

Yonas Raru[a,*], Fuad Zeid[b]

[a] Department of Internal Medicine, Marshall University Joan C. Edwards School of Medicine, Huntington, WV, USA
[b] Pulmonary and Critical Care Medicine, Department of Internal Medicine Marshall University Joan C. Edwards School of Medicine, Huntington, WV, USA

ABSTRACT

Valproic acid (VPA) is widely used for the treatment of epilepsy, migraine, and a variety of psychiatric symptoms, including bipolar disorder, borderline personality disorder, and alcohol withdrawal. Valproate is associated with severe idiosyncratic adverse effects, the most notable being valproate-induced hyperammonemic encephalopathy (VHE). Topiramate is also a broad-spectrum anticonvulsant that is also extensively used for migraine prophylaxis, as a mood stabilizer, and for alcohol dependency. There is increased occurrence of VHE when valproate is used with other medications like phenytoin, phenobarbital, and topiramate. Our case report is on a young patient who was on valproic acid and topiramate and developed metabolic encephalopathy with hypoxic respiratory failure. We reviewed the causes and management of the hyperammonemic encephalopathy. We believe that clinicians should be aware of possible hyperammonemic encephalopathy in any patient who is taking valproic acid and presenting with impaired consciousness and cognitive decline. We also underline the importance of early recognition and high index of suspicion of encephalopathy related to hyperammonemia.

1. Introduction

Valproic acid is a broad-spectrum antiepileptic drug that inhibits degradation, and promotes postsynaptic transmission of gamma-aminobutyric acid (GABA) [1]. Valproic acid (VPA) is widely used for the treatment of epilepsy, migraine, and a variety of psychiatric symptoms, including bipolar disorder, borderline personality disorder, and alcohol withdrawal. VPA has been used effectively to reduce agitation and aggression in both acute and post-acute traumatic brain injury patients, as well as a variety of other neuropsychiatric syndromes, including dementia and mental retardation [2–4]. Valproate is associated with severe idiosyncratic adverse effects, the most notable being valproate-induced hyperammonemic encephalopathy (VHE), which is seen in up to 0.9% of patients taking valproate [5]. Topiramate is also a broad-spectrum anticonvulsant that is also extensively used for migraine prophylaxis, as a mood stabilizer, and for alcohol dependency. There are studies in the literature which has shown an increased occurrence of VHE when valproate is used with other medications like phenytoin, phenobarbital, and topiramate [6].

The combined antiepileptic valproate and topiramate therapy causes reduction of topiramate metabolism through cytochrome P 450 pathway and topiramate decreases levels of valproate by increasing its metabolism [7].

VHE causes metabolic encephalopathy which is defined as a diffuse cerebral dysfunction, typically manifesting as changes in cortical functions and as disorders of consciousness, ranging from confusion to coma [8].

Recognition of VHE requires a high level of clinical suspicion, as clinical presentation is nonspecific and correlates poorly with dosage, blood levels, or duration of treatment [9].

The development of hyperammonemia, the consequences of which are difficult to differentiate from the pathology itself and that can be misdiagnosed as therapeutic failure instead of an adverse drug reaction related to the use of VPA [10].

This case report illustrates the importance high clinical suspicion and early recognition of VHE and its management.

2. Case report

Our patient is a 21-year-old female patient with past medical history of medically refractory epilepsy, hypothyroidism and mood disorder came with altered mental status. She started to have seizure disorder

* Corresponding author.
E-mail addresses: raru@marshall.edu (Y. Raru), zeid@marshall.edu (F. Zeid).

https://doi.org/10.1016/j.rmcr.2018.05.026
Received 16 May 2018; Received in revised form 26 May 2018; Accepted 26 May 2018

from childhood and she was not eating and drinking because of her clinical condition. She was also not taking her medications for the last 3 days. She underwent vagal nerve stimulation procedure for her epilepsy and she was on Levetiracetam, Valproic acid and topiramate. She still had seizures even if she is on these treatments but her mood disorder was well controlled. Last seizure episode happened a month ago. She was also having cough and mild shortness of breath but no fever or chills. She is not a smoker and lives with her mother who takes care of her. In the emergency room, she was found to be tachycardic and hypoxic with a PH of 7.37, PCO2 of 39 and PO2 of 56 on arterial blood gas. CT chest performed there showed bilateral lung infiltrates suggestive of pneumonia. On physical examination, blood pressure was 124/86, heart rate was 107 beats per minute, respiratory rate was 19 breaths per minute and temperature was 99.2-degree fahrenheit. Well developed, well-nourished but limited spontaneous speech, mild confusion. Scattered soft crepitations in the lower posterior chest bilaterally and has regular rate and rhythm of the pulse with no murmur and no gallop. She didn't have any edema. On neurologic examination, she was alert, follows some specific commands and names simple objects. She had no gaze preference and facial strength and sensation were intact and symmetric. Neck was supple with no neck stiffness. Hearing was grossly intact and symmetric. Strength was 5/5 in all 4 extremities without evidence of pronator drift. She had intact sensation to light touch and pin prick sensation in all her extremity without evidence of asymmetry. She had no evidence of dysmetria with finger to nose bilaterally. She was admitted to a step-down unit and she was started on broad spectrum antibiotics and maintenance intravenous fluids. Her antiepileptic medications were also restarted at the same dose that she was getting at home. Her procalcitonin and lactic acid levels were found to be with in normal range. Atypicals and viral panel were found to be negative and blood and sputum culture were negative. Antibiotics were deescalated accordingly. On the next day of admission, patient was still having mild confusion and ammonia level was ordered and it was found to be elevated at 102 μg/deciliter (mcg/dl). Her valproic acid level in the same day was 77 mcg/dl (normal 50–125 mcg/dl). Her TSH level was within the normal limit. At this point, metabolic encephalopathy due to hyperammonemia was considered and she was started on L-carnitine and Lactulose. Patient's clinical condition stayed the same with this treatment.

Her ammonia level increased to 126 mcg/dl. EEG was performed and reported to show intermittent generalized slowing consistent with a mild encephalopathy but there were no electroencephalographic seizures or any interictal epileptiform activity. The cause of the hyperammonemia was thought to be related to valproic acid. Her epilepsy was relatively well controlled by her seizure medications and there was a reluctance to stop any of her medications from the primary team.

Neurology evaluation suggested decreasing the dose of topiramate as it was a relatively new medication. Her topiramate dose was halved and was continued with L- Carnitine and lactulose but her confusion stayed the same and her ammonia level on the next day increased to 162. Her repeat valproic acid level was 77 mcg/dl. Since there was no clinical improvement with the treatment, valproic acid was stopped. The clinical condition of the patient improved day by day after that and her ammonia level was trended daily and it came down from 161 to 115 mcg/dl at first and within 3 days it went down to 52 mcg/dl. Five days after valproic acid was stopped, patient's clinical condition stabilized and her seizure medications were changed to Levetiracetam and lacosamide. She was not having any seizure activity and her mood disorder stayed stable and her general condition got back to her baseline.

3. Discussion

In one report, it is estimated that up to 50% of patients taking valproate develop hyperammonemia. Most of these patients have elevations of ammonia with normal liver function and are asymptomatic [11,12]. There is also no clear correlation between blood ammonia levels and the severity of encephalopathy, suggesting that mechanisms other than those involving ammonia contribute to the neurological dysfunction [1]. Approximately 0.9% of patients using valproate develop hyperammonemic encephalopathy. This number could be higher if patients are taking sedatives and other antiepileptic medications like lamotrigine, topiramate and risperidone [13]. Carnitine deficiency and urea cycle enzyme abnormalities also expose patients for valproate and topiramate induced hyperammonemic encephalopathy [2–4]. Our patient was on topiramate in addition to the valproic acid but she was not checked for carnitine deficiency or urea cycle enzyme defect. Topiramate was originally synthesized as a potential hypoglycemic agent even if it was found not to have that effect and it was later found out that it is an important medication for seizure, migraine prophylaxis and mood disorder due to its effect in the CNS and sodium and calcium channels [5,6]. The presence of pneumonia in our patient might be responsible for her deterioration and presentation to us but her clinical response with the decrease in the level of the ammonia supports the fact that the hyperammonemia is responsible for her deterioration.

The mechanism by which valproate causes hyperammonemia is not clear but hepatic and renal metabolic pathways have been proposed. Propionate, a metabolite of valproate reduces hepatic N-acetylglutamate concentration, which is an obligatory activator of carbamoyl phosphate synthetase 1 (CPS-1), the first enzyme of the urea cycle. Decline in CPS-1 activity results in defective ammonia utilization and accumulation of ammonia. Another mechanism thought to play a role is reduction of hepatic carnitine levels by valproate. This results in decreased beta-oxidation of fatty acids, which in turn results in reduced levels of Acetyl Co-A. This decrease in Acetyl Co-A ultimately disrupts the urea cycle resulting in ammonia accumulation [2]. The less common mechanism is that valproic acid stimulates kidney tubule glutaminase that subsequently enhances glutamine uptake into renal cortical cell mitochondria. The conversion of glutamine ultimately leads to increased ammonia production [4]. The cytosolic ammonia accumulated within astrocytes and neuronal cells which is conjugated with glutamine by glutamine synthetase is responsible for the oxidative stress and subsequently leads to mitochondrial swelling and cytosolic edema [2,14]. Availability of electroencephalogram recordings may help improve diagnostic validity, but it is unlikely to facilitate differentiation of VPA from other causes of encephalopathy [13].

We have EEG recordings done in our patient which showed intermittent generalized slowing consistent with a mild encephalopathy but there were no electroencephalographic seizures or any interictal epileptiform activity. Our patient could possibly have a non-convulsive seizure due to drug withdrawal with subsequent deterioration since she was not taking her medications for 3 days before presentation. This is very difficult to prove as we only have EEG 2 days after her presentation.

The mainstay of VHE treatment is discontinuation of VPA, which leads to complete recovery in most patients [1–4]. We decreased the dose of both valproate and topiramate in our patient but patient's clinical condition didn't improve. So, both medications were stopped and she was started on L-carnitine. Persistence of VHE despite reduction or discontinuation of VPA is an indication for additional ammonia-depleting agents such as lactulose, charcoal, neomycin, rifaximin, or L-carnitine [2,3]. We have used L-carnitine and lactulose in our patient since discontinuation of the medications didn't completely improve her clinical condition. L-carnitine is an amino acid derivative and important nutrient involved in fat metabolism. Up to 75% of L-carnitine is provided by diet, particularly red meat and dairy products. It is also biosynthesized endogenously from dietary amino acids (methionine, lysine), especially in the liver and in the kidneys. Carnitine is responsible for 2 metabolic functions. It eases the fatty acyl-group transport into mitochondria and it also preserves the ratio of acyl-CoA to free CoA in the mitochondria.

As VPA-induced hyperammonemia and VHE could be mediated at least in part by carnitine deficiency, it has been hypothesized that L-

carnitine supplementation may prevent, correct, or attenuate these adverse effects [5–9]. L-carnitine should be given intravenously because of the low bioavailability of enteral L-carnitine [7]. There is also a literature on the use of arginine supplementation for treatment of hyperammonemic encephalopathy even if we haven't used it in our patient. Arginine supplementation tends to normalize elevated plasma ammonia concentrations. Arginine plays a critical role in ammonia detoxification, as ammonia is detoxified via its metabolism into urea. On the one hand, it has been accepted that arginine is an activator of N-acetyl glutamate synthetase (NAGS) via agmatine; on the other hand, arginine entering the liver via the portal vein is metabolized to provide ornithine for citrulline and aspartate synthesis and for the priming of the urea cycle [6,10]. The clinical response of our patient was correlated with the decrease in the serum ammonia level but literature has shown that serum levels of ammonium do not correlate with the severity of valproate-induced encephalopathy and there is no conclusive evidence of a major causative role of hyperammonemia on encephalopathy in human clinical studies [1–3]. Because of that it is suggested to follow patients clinically rather than monitor the level of serum ammonia once the diagnosis of hyperammonemic encephalopathy was made and the right treatment started. The valproic acid level of our patient stayed in the normal range the whole time in our patient but still there is no concordance with respect to a direct relationship between the development of VHE and serum valproic acid levels [2–5].

4. Conclusion

Metabolic encephalopathy represents a serious problem that needs to be addressed in a multidisciplinary approach as there could be complications related to the respiratory and central nervous system. We need to have a high index of suspicion for diagnosing VHE in patients receiving valproate presenting with impaired consciousness and acute cognitive decline. Serum ammonia level is a useful test to guide in diagnosing VHE but it is very important to know that its level does not correlate with the severity of VHE. Increased familiarity with the diagnosis and appropriate treatment of VHE is also essential. Resolution or prevention of hyperammonemia may be enhanced with the administration of intravenous L-carnitine as the oral form has low bioavailability.

References

[1] Adeva, MM. et al. Ammonium metabolism in humans metabolism - Clin. Exp., Volume 61, Issue 11, 1495–1511.
[2] S. Tantikittichaikul, J. Johnson, et al., Topiramate-induced hyperammonemic encephalopathy in a patient with mental retardation: a case report and review of the literature, Epilepsy Behav. Case Rep. 4 (2015) 84–85.
[3] Walker, Valerie. Severe hyperammonemia in adults not explained by liver disease. Ann. Clin. Biochem.. Vol 49, Issue 3, pp. 214–228.
[4] A. Chopra, B.P. Kolla, M.P. Mansukhani, P. Netzel, M.A. Frye, Valproate-induced hyperammonemic encephalopathy: an update on risk factors, clinical correlates and management, Gen. Hosp. Psychiatr. 34 (03) (2012) 290–298.
[5] Ido Laish, et al., Noncirrhotic hyperammonaemic encephalopathy, Liver International 31 (9) (October 2011) 1259–1270.
[6] Cheng, Minfeng et al. Valproate (VPA)-associated hyperammonemic encephalopathy independent of elevated serum VPA levels: 21 cases in China from May 2000 to May 2012. Compr. Psychiatr., Volume 54, Issue 5, 562–567.
[7] Lewis, Chandani et al. Valproate-induced hyperammonemic encephalopathy in general hospital patients with one or more psychiatric disorders. Psychosomatics, Volume 58, Issue 4, 415–420.
[8] Maldonado C., Guevara N, et al. L-Carnitine supplementation to reverse hyperammonemia in a patient undergoing chronic valproic acid treatment: a case report J. Int. Med. Res.: Vol 45, Issue 3, pp. 1268–1272.
[9] M. Vázquez, P. Fagiolino, C. Maldonado, et al., Hyperammonemia associated with valproic acid concentrations, BioMed Res. Int. 2014 (2014) 2172697 pages.
[10] C.I. Cattaneo, et al., Sudden valproate-induced hyperammonemia managed with L-carnitine in a medically healthy bipolar patient: essential review of the literature and case report, Medicine 96 (39) (2017) e8117.
[11] G. Yeung, et al., K.W. Chau, et al., A fatal case of valproate-induced hyperammonemic encephalopathy: an update on proposed pathogenic mechanisms and treatment options, Int. J. Epilepsy 04 (02) (2017) 181–183.
[12] Y.L. Tseng, C.-R. Huang, C.H. Lin, Y.T. Lu, C.H. Lu, N.C. Chen, Y.C. Chuang, Risk factors of hyperammonemia in patients with epilepsy under valproic acid therapy, Medicine 93 (11) (2014) e66.
[13] Berisavac IIet al., How to recognize and treat metabolic encephalopathy in Neurology intensive care unit, Neurol. India 65 (2017) 123–128.
[14] C. Sousa, Valproic acid-induced hyperammonemic encephalopathy − a potentially fatal adverse drug reaction, SpringerPlus 2 (01) (2013) 13, http://dx.doi.org/10.1186/2193-1801-2-13.