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Case Report

NON-HEPATIC HYPERAMMONEMIC COMA: A CASE REPORT

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ABSTRACT

While the most common cause of hyperammonemic (HA) coma is hepatic disorder, other rare etiologies to be considered include congenital causes, drug induced states, portosystemic shunts, and urinary tract infections with urea-splitting organisms. HA usually results from one of the following three mechanisms: A relative excessive nitrogen load on a normal functioning liver via the portal circulation (e.g., parenteral nutrition in a patient with urea cycle defect); ammonia bypassing liver (e.g., congenital vascular malformations, portal hypertension in cirrhotic patients); or from impaired ammonia metabolism. Herein, we describe a case of HA coma secondary to an interplay of multiple psychiatric drugs mainly sodium valproate and probably an added effect by the lithium-induced hypothyroidism/myxedema.

Keywords: Drug-induced, Hyperammonemia, Lithium, Myxedema, Valproic acid.

INTRODUCTION

Hyperammonemic (HA) coma in the absence of hepatic failure is an unusual phenomenon. The most common causes are drug induced or congenital enzyme deficiencies. The most common causes are drug induced, congenital enzyme deficiencies, portosystemic shunts, and urinary tract infections with urea-splitting organisms. Herein, we describe a case of drug-induced HA coma who recovered with supportive measures. The drugs contributing to his HA were valproic acid (VPA) and/or lithium. VPA inhibits carbamoyl phosphate synthetase 1 (CPS1) enzyme which leads to HA and is not related to serum levels of VPA. Lithium-induced hypothyroidism resulting in myxedema coma is rare at therapeutic levels of lithium. We present a patient who, based on his clinical diagnostic scoring for myxedema, had a high probability of myxedema.

CASE REPORT

A 26-year-old male, a known case of attention deficit hyperactive disorder and bipolar affective disorder, was referred from a nearby psychiatric rehabilitation facility and brought by family members to the emergency department with a history of excessive drowsiness since 1 week which has increased over the last 2 days. The patient was found to be drowsy and of altered sensorium. He denied a history of fever, vomiting, loose motions, seizures and drug or substance abuse. He was on lithium 1300 mg day, sodium valproate 1500 mg/day and carbamazepine 1200 mg/day. On admission, his vitals were a pulse rate 55/minutes, blood pressure 110/70 mmHg, temperature 97°F and SpO_2 99% on room air.

The patient was admitted to ICU with suspicion of drug toxicity. The initial workup (Table 1) revealed elevated serum ammonia levels, with very high thyroid stimulating hormone (TSH) and parathyroid hormone levels. He had low vitamin D levels and hypocalcemia. The routine testing including complete blood counts, renal and liver function tests, clotting profile, serum electrolytes, serum cortisol, and urinalysis were normal. Drug screen for 9 drugs was negative. Serum lithium was within therapeutic range (0.5-1.1 meq/l), while carbamazepine (4-12 mg/dl) and VPA (50-100 mg/dl) serum levels were well below therapeutic range; 0.22 mcg/mol and 28.9 mcg/mol, respectively. Ultrasound abdomen showed fatty hepatomegaly.

Valproate-induced HA and/or lithium-induced myxedema coma leading to high serum ammonia was suspected. His serum T3 and T4 indicated a lithium-induced hypothyroidism. Sodium valproate was stopped and lithium continued with anti-encephalopathic measures and thyroxine (25 mcg/day) and vitamin D supplementation. He also received L-carnitine (500 mg TID) and Vitamin B12 supplements. His encephalopathy resolved and the patient improved symptomatically over the next 48-72 hrs, which was accompanied by a decreasing trend in serum ammonia on day 5 of admission. The patient was discharged back to his previous psychiatric rehabilitation center.

DISCUSSION

HA coma often is associated with hepatic dysfunction; however, lesser known etiologies include congenital defects, drug induced states, portosystemic shunts and urinary tract infections with urea-splitting organisms. Drug-induced HA can occur with or without hepatic involvement (Table 2) [1].

Among the drugs causing HA without hepatic involvement, Sodium valproate or VPA is the most widely used. VPA is an analog of valeric acid, mainly used as a solvent in the early days, later proved to be a versatile antiepileptic drug. It is the first line drug for partial seizures but is used in the management of all types of seizures, as a mood stabilizing agent, for neuropathic pains, migraine, idiopathic olfactory hallucinations, Alzheimer's disease, dyskinesias, and to treat toxoplasmosis. Apart from the regular gastrointestinal and neurological side effects of antiepileptics, it causes metabolic disturbances which include HA, hyperglycemia, and hyperglycinuria [2]. Risk factors for the development of valproate-induced HA encephalopathy (VHE) are polypharmacy (multiple antiepileptics), urea cycle disorders, carnitine deficiency and mental retardation. It has no sexual predilection and is not related to dosage of VPA or duration of therapy. In children below 2 years of age, there is an observed association between dose and serum levels of VPA [3].

VHE may occur in people with normal liver function, with normal doses and serum levels of VPA. The pathophysiological mechanism of VPA-induced HA involves inhibition of the CPS1activity, the first and rate-limiting enzyme of the urea cycle. CPS-1 action is dependent on N-acetyl glutamate (NAG) derived from acetyl-coA and glutamate, which acts as an allosteric activator for CPS1. A recent study has proposed that NAG synthetase the enzyme responsible for NAG production gets inhibited by propionate and 4-en-VPA, the metabolic end products of VPA metabolism [4,5].

The other contributing factor for his HA was hypothyroidism/myxedema secondary to lithium. Lithium, a time-tested drug, has been the drug of choice for bipolar disorder since 1949. Studies show that

Table 1: Initial investigations

Serial number	Investigations	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
1	Hemoglobin g/dl	12.1					
2	PCV	38					
3	TLC	8410					
4	Platelet count	118,000					
5	ESR	28					
6	Serum creatinine	1.2	1.3	1.3	0.9	1.0	
7	BUN	7.6		13.8	12.3	11.8	
8	Uric acid	9.2					
9	Sodium	138.9	137.9	134	137.9	137	137.3
10	Potassium	3.9	4.2	4.0	3.9	3.9	3.5
11	Chloride	103.3	104	102	105	104.6	105
12	CPK						
13	Total bilirubin	0.32					
14	Direct	0.09					
15	Total protein	6.7					
16	Albumin	3.2					
17	AST	59.8					
18	ALT	54					
19	Alk phosphatase	71.3					
20	GGT	31.1					
21	PT/INR/PTT	12.4/0.95/28.9					
22	Urine analysis	1-2 WBC					
23	Serum calcium		8.1		9	8.8	
24	Serum phosphorous		5.7				
25	Serum lithium (0.5-1.1 meq/l)	0.62					
26	Serum valproic acid (50-100 mg/dl)			28.9			
27	Serum carbamazepine (4-12 mg/dl)			0.22			
28	Serum TSH		>150				
29	T3		4.09				
30	T4		0.7				
31	Free T3		0.4				
32	Free T4		1.14		0.54		
33	HbA1c	4.7					
34	PTH		398				
35	Vitamin D3		<4.2				
36	Ammonia	86.9			47.5		

PCV: Packed cell volume, TLC: Total Leukocyte count, ESR: Erythrocyte sedimentation rate, BUN: Blood urea nitrogen, CPK: Creatine phosphokinase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, PT: Prothrombin time, INR: International normalized ratio, PTT: Partial thromboplastin time, WBC: White blood cell, TSH: Thyroid stimulating hormone, HbA1c: Hemoglobin A1c, PTH: Parathyroid hormone

Table 2: Drugs associated with hyperammonemia

Drugs associated with fulminant hepatic failure	Drugs associated without hepatic failure
Acetaminophen	With UCDs
Lipid-lowering agents: Atorvastatin	Glycine
Anti-inflammatories: Ibuprofen, celecoxib, diclofenac	Salicylates
Anesthetics: Halothane	Valproate
Antibiotics: Amoxicillin, amoxicillin clavulanate, flucloxacillin, telithromycin, moxifloxacin, levofloxacin, trovafloxacin, minocycline, sulfamethoxazole, trimethoprim	Carbamazepine
HIV medications: Indinavir, nevirapine	Sulfadiazine
Antifungals: Fluconazole, terbinafine	Pyrimethamine
Anti-tuberculous medications: Isoniazid, rifampin, rifabutin, pyrazinamide	Topiramate
Antiparasitic: Dapsone	Primidone
Anti-epileptics: Carbamazepine, valproate, phenytoin, phenobarbital	TPN
Anti-depressants: Nefazodone, sertraline, duloxetine, bupropion	
Other psychoactive: Lamotrigine, donepezil, disulfiram	
Illegal drugs: MDMA (ecstasy) *MDMA 3,4 methylenedioxymethamphetamine	

UCDs: Urea cycle disorder, TPN: Total parenteral nutrition

lithium-induced hypothyroidism and subclinical hypothyroidism with/without concomitant goiter is very common, with incidences range from 0% to 52% [6-8]. A diagnostic scoring system for myxedema score was 6, raising the possibility of myxedema [9]. A review of literature showed very few reported cases of lithium-induced myxedema coma, and those encountered occurred in the setting of supranormal lithium levels. Lithium has effects at multiple levels ranging from the hypothalamic-pituitary axis to thyroid autoimmunity and thyroid hormone synthesis. Notably, at the level of the thyroid organ itself, it inhibits colloid formation in the apical pole of the thyrocyte, inhibits release of thyroid hormone, and inhibits thyroglobulin-iodination. The culminated result of all the above effects is a drug induced hypothyroid state. Lithium-induced hypothyroidism is marked by low serum T3 levels, in contrast to a low serum T4 found in lithium-free hypothyroidism. Lithium-induced hypothyroidism is to be treated with thyroxine supplementation; however. Withdrawal of lithium is not indicated unless the patient manifests overt signs of hypothyroidism or there is a change in the underlying disease for which the lithium was started. Lithium-induced hypothyroidism can mimic liver disease, known as pseudo-liver disease; however as the patient's hepatic derangements were insignificant, it is unlikely the cause HA. The lithium levels were within therapeutic range, which indicated VPA as the probable cause of HA.

In our patient, the propensity to develop VPA-induced HA was further compounded by the presence of lithium-induced hypothyroidism. He was found to have vitamin D deficiency, leading to hypocalcemia and resultant elevated serum parathyroid level hormones. As the patient is mentally challenged, vitamin D deficiency may be due to insufficient

sunlight exposure. In view of the elevated serum TSH, the possibility of a clinically significant hypothyroidism was addressed on day one with thyroid supplements.

The treatment for VHE was withdrawal of VPA. Routine hepatic anti encephalopathy measures including lactulose, protein restriction and local gut antibiotics, help in symptomatic recovery. Carnitine supplementation aids in binding and excretion of VPA hence hastening recovery. Carnitine is relatively safe at a dose of 50-100 mg/kg/day and the main side effects were nausea, diarrhea, and a fishy body odor [6].

In conclusion, in unexplained coma/semi-comatose state in a patient on multiple drugs, one should consider HA. A high index of suspicion and prompt initiation of anti-encephalopathic measures positively affects patients' prognoses and outcomes.

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