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A RARE CASE OF VALPROIC ACID INDUCED HYPERAMMONEMIA IN ELDERLY

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ABSTRACT
Hyperammonemia is commonly seen in patients with liver failure, porto-systemic shunts, urinary tract infection and parenteral nutrition. Drugs causing hyperammonemia is extremely rare. A 65 year-old male, known case of diabetes, hypertension and old case of intra cerebral (IC) bleed one year back, was taking tablet Divalproex sodium 125mg twice daily since 1 year for seizures after IC bleed. He was brought to our hospital with history of drowsiness and generalized weakness since 2 days. Hyperammonemia secondary to tablet Divalproex sodium was diagnosed. Patient was successfully treated with Inj phenytoin, lactulose syrup, tablet carnitine, adequate hydration and stopping of Divalproex sodium tablet. Serum ammonia levels were normalized on day 5. Patient was discharged home on day 7. This case report mainly highlights the rare cause of hyperammonemia in adult patients on long term treatment with Divalproex sodium with normal liver function. Early diagnosis and treatment can reduce morbidity and mortality.

INTRODUCTION

Divalproex sodium is a broad spectrum anticonvulsant drug. It acts by increasing the inhibitory neurotransmitter- GABA in the brain. It is also used in the treatment of bipolar disorder, agitation, refractory anxiety disorder and migraine [1]. Complications include nausea, diarrhoea, tremors, convulsion, nystagmus, hyponatremia and rarely hyperammonemia due to prolonged usage.

CASE REPORT

A 65 year-old male, known case of diabetes, hypertension and old case of intra cerebral (IC) bleed a year ago, presented to our tertiary hospital emergency department (ED) with history of drowsiness and generalized weakness since 2 days. In the ED he was drowsy and arousable, his pupils were bilaterally equal and reactive, no neck stiffness and moving all four limbs. Funduscopic examination was normal. He was afebrile with a pulse rate of 84 beats/min, blood pressure was 150/90 mmHg. On auscultation, bilateral normal vesicular breath sounds were heard. The patient was transferred to ICU for further management.

Table – 1shows laboratory values at the time of admission. Hemoglobin 10.7 gm/dl, WBC 6700 cells/mm^3, platelets 3.4 lakhs/cumm. Arterial blood gas analysis showed pH-7.34, PO_2-165, PCO_2-34, and HCO_3-21. Blood sugar was 154 mg/dl. Serum electrolytes, liver function test, kidney function test and routine urine analysis were normal. Serum ammonia was 69 m mol/L (Normal 3-30 m mol/L). Procalcitonin was normal. EEG showed slow background waves. CSF study, blood culture, urine culture, chest x-ray, ECG and 2D-echocardiogram were normal. CT brain showed diffuse cerebral atrophy. Patient was taking tablet Divalproex sodium 125mg twice daily since 1 year for seizures. Hyperammonemia secondary to this tablet was suspected and hence it was stopped, however started with Inj phenytoin, syrup lactulose, tablet carnitine (500mg twice daily) and adequate hydration. His level of consciousness improved over 5 days along with

normalization of serum ammonia shown in table - 2. Patient was discharged home on day 7.

Table 1. Showing lab results of the patient at the time of admission

Hemoglobin	10.7 gm/dl.
WBC	6,700 cells/mm^3
Platelets	3.4 lakhs/cumm.
S. Sodium	137 meq/l.
S. Potassium	4.2 meq/l.
S. Chloride	104 meq/l.
Arterial blood gas	
pH-	7.34
PCO_2-	34
PO_2-	165
HCO_3-	21
GRBS	154 mg/dl.
S. Ammonia.	69 m mol/L.
Bl. Urea.	22 mg/dl.
S. Creatinine.	0.8 mg/dl.
T. Bilirubin.	1.1 mg/dl.
SGOT	35 IU/L.
SGPT	40 IU/L.
ALP	61 IU/L.
PT	13.2 s
INR	1.02
APTT	27 s

Table 2. Showing serum ammonia values over a period of 5 days

Days of Admission	S. Ammonia Value
Day - 1	69 m mol/L (Normal 3-30 m mol/L).
Day - 2	65 m mol/L.
Day - 3	44 m mol/L.
Day - 4	38 m mol/L.
Day - 5	27 m mol/L.

DISCUSSION

Divalproex sodium also known as valproate semisodium, consists of compound sodium valproate and valproic acid in 1:1 ratio. Valproic acid and its derivatives are known to cause encephalopathy due to hyperammonemia. Most of the data comes from children and younger adults [2]. Only few case reports has been published regarding hyperammonemia due to Divalproex sodium [3, 4] in adults. Feil et al first reported hyperammonemia (836 mmols/L) in 88-year-old man with normal liver function test, he taking valproate for seizures and presented with confusion. The confusion resolved after discontinuation of valproate and reappeared once that the valproate was reinitiated [5].

Mechanisms of Hyperammonemia is unclear, proposed mechanisms are increased production of ammonia in kidney [6], inhibition of Carbomylphosphatase synthetase I (CPS I) enzyme [7] which is involved in conversion of ammonia to urea. Inhibition of N-acetyl glutamate an activator of CPS-I enzyme and carnitine deficiency due to long term treatment with Valproate (carnitine is required for metabolism of Valproic acid).

Clinical features of hyperammonemia include confusion, personality changes, irritability, ataxia, visual disturbance, lethargy, somnolence, hyperventilation, nausea, vomiting, coma and death [8]. Risk factors for development of hyperammonemia include higher dose of Divalproex sodium, concomitant use of antiepileptic-Topiramate, carnitine deficiency and inborn errors of metabolism. Common causes of hyperammonemia are liver disease, porto-systemic shunts, hyperinsulinemic hypoglycemia, carnitine deficiency, leukemia, myeloma, urinary tract infection, surgery and parenteral nutrition [9]. Our patient didn't have these risk factors except with history of Divalproex sodium intake since one year for seizures.

Diagnosis is based on clinical features, high degree of suspicion, elevated ammonia levels in blood, normal liver function, history of treatment with Divalproex sodium and EEG showing slow background waves. All these factors were present in our patient. Treatment is mainly stopping the causative drug, adequate hydration, L-carnitine supplementation, and protein restriction to 60grams per day. Complete recovery occurs within few days. The key points of this case report is to have suspicion

for a rare cause of drug induced hyperammonemia in patients taking Divalproex sodium and with normal liver function test. Early diagnosis with supportive treatment can reduce morbidity and mortality.

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DECLARATION OF INTEREST

None declared.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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