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CASE REPORT PEER REVIEWED | OPEN ACCESS

Valproate-induced hyperammonemic encephalopathy in mania: Biochemical diagnosis may lag behind the clinical diagnosis

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ABSTRACT

Introduction: Cases of hyperammonemic encephalopathy with the use of valproate have been reported in literature and it is a rare but life-threatening adverse effect. Valproate induced encephalopathy presents usually with lethargy, confusion, tremors and gait disturbances in the presence of hyperammonemia. Case Report: We describe a case of bipolar disorder who when treated with valproate became abruptly comatose while ammonia level was normal at the onset of toxic manifestations. Our patient recovered on valproate discontinuation. Conclusion: The case report suggests that biochemical evidence may lag behind the clinical features of hyperammonemic encephalopathy and treatment decisions based on the clinical picture rather than on the biochemical parameters is vital in such situations.

Keywords: Bipolar disorder Encephalopathy, Hyperammonemia, Valproate

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INTRODUCTION

Valproate is used effectively in the treatment of seizure disorder, mania, bipolar disorder and migraine. Life-threatening complications like fulminant hepatitis, pancreatitis and hyperammonemic encephalopathy have been reported in literature with the use of valproate [1]. Hyperammonemic encephalopathy due to valproate presents usually with tremors, confusion and gait disturbances in the presence of hyperammonemia [2].

We describe a case of bipolar disorder, when treated with valproate, olanzapine and clonazepam became abruptly comatose while ammonia level was normal at the onset and was elevated later. Patient recovered on valproate discontinuation.

CASE REPORT

A 37-year-old female was brought to psychiatry emergency department by her husband with a three-day history of decreased need for sleep, talking more than usual and irritability. She had got angry with her colleagues with minimal or no provocation, verbally

abused her employer and quit her job. Family members and neighbors found it very difficult to manage her and had to tie her up physically to bring her to hospital. During nights she was more energetic and would do agricultural work like plucking weeds. She had similar episodes sixteen years, three years and six months ago. Last episode was treated with valproate 1000 mg and olanzapine 10 mg/day and patient's manic symptoms settled. Two months ago patient had discontinued treatment due to lack of insight. On mental status examination patient had elated mood and grandiose delusion. No abnormality was detected on physical examination. Patient was diagnosed to have bipolar affective disorder, current episode mania with psychotic symptoms. Investigations including complete blood count, liver function tests, renal function tests and thyroid functions tests were within normal limits. The patient was admitted and started on valproate 1000 mg, olanzapine 10 mg and clonazepam 0.5 mg per day.

The patient was severely agitated on third day of admission and hence the dose of valproate was increased to 1500 mg, olanzapine to 15 mg and clonazepam to 1.5 mg per day. By the very next day patient's irritability, sleep and over talkativeness improved. Patient's caregiver demanded for discharge and treating team planned to discharge her after a day. That day patient was active till 09:00 am and husband reported that since 09:00 am patients is too drowsy most of the time and would get up now and then would abuse him and would sleep off again. When duty psychiatrist attended the call by 11:00 am patient could open her eyes on painful stimuli only, speech could not be understood and had withdrawal response to pain (Glasgow coma scale score of 8). No history of tremors, seizure, headache or vomiting could be elicited. Her pupils were equal and reacting to light and fundi were normal. Respiration was regular, there was no neck stiffness and plantar reflexes had withdrawal response. Patient was shifted to intensive care unit.

The patient's liver enzymes and renal function tests were normal (Fasting blood sugar 98 mg/dl, serum sodium 140 mEq/L, potassium 3.8 mEq/L, SGOT 26 U/L, SGPT 18 U/L, ALP-60 IU/L, blood urea 16 mg/dL, serum creatinine 0.7 mg/dL). Valproate was stopped empirically while waited for serum ammonia result. But serum ammonia level was 44 µmol/L (N =15 to 47 µmol/L) which confused the treating team. We stopped all the drugs and to find out the cause for sudden development of coma, brain magnetic resonance imaging and EEG were done which were normal. When re-evaluated on the second day of coma, serum ammonia level was 97 µmol/L which confirmed the diagnosis of hyperammonemic encephalopathy. The patient remained unresponsive for two more days, started responding gradually since then, started talking relevantly and became alert by fifth day (serum ammonia reduced to 32 µmol/L on day-5). We decided not to challenge her with valproate again and started on lithium after a week of recovery from encephalopathy.

DISCUSSION

Various hepatic and renal mechanisms are implicated in valproate induced hyperammonemic encephalopathy [3]. Valproate inhibits carnitine synthesis and thus inhibits carbamoyl phosphate synthetase and interferes with the transformation of carbamoyl phosphate and ornithine into citrulline [3]. Neuronal injury and cerebral edema due to inhibition of glutamate uptake by astrocyte is also hypothesized. Valproate increases glutaminase activity in renal mitochondria and hence glutamine uptake and plasma ammonia level also increases [3].

Cases of valproate induced hyperammonemic encephalopathy have been reported with ammonia levels ranging 54–377 µmol/L [2, 4]. Hyperammonemia due to valproate is an idiosyncratic reaction and is not dependent on dose of valproate [2, 5]. Though a few cases of asymptomatic hyperammonemia is reported with valproate [6, 7] only a single report of symptomatic but normoammonemic encephalopathy is published yet [2, 8]. The patient was also getting olanzapine and clonazepam, but these drugs are not reported to cause hyperammonemia in literature. In our case, though there was high clinical suspicion of hyperammonemic coma on first day of coma itself, ammonia level was normal and hence we had to go ahead with investigations like MRI scan, EEG to find out the cause. Fortunately, subsequent ammonia level was elevated and we could make diagnosis of hyperammonemic encephalopathy. It suggests that clinical features of hyperammonemic encephalopathy may precede the biochemical hyperammonemia in valproate induced hyperammonemic encephalopathy.

Valproate induced hyperammonemic encephalopathy usually presents initially with features like drowsiness, lethargy, disorientation, tremors and later with asterixis, seizure and coma [2]. The time to become comatose since the development of initial toxic features like lethargy and ataxia varies from 8 hours to a week and the clinician may not get time to observe the patient more closely. Our patient became comatose abruptly over a period of two hours and there was marked absence of classical clinical features or biochemical evidence of elevated ammonia level initially. Various treatment strategies have been suggested in the treatment of valproate induced hyperammonemic encephalopathy of which the first and the most important step is to stop or reduce the dose of valproate [2]. Other treatments include L-carnitine, lactulose, charcoal and dietary protein restriction. Most patients recover over a period of 1–5 days [2]. Our patient needed only valproate withdrawal and recovered completely within 4 days of toxicity. We did not estimate serum valproate levels because we did not have laboratory facility for valproic acid estimation. Moreover, it has been reported that hyperammonemia is unrelated to valproate level in valproate induced hyperammonemic encephalopathy [2].

CONCLUSION

Summarizing, physician should be cautious of serious and abruptly deteriorating hyperammonemic encephalopathy with valproate. As described in the above case, sometimes biochemical diagnosis may lag behind the clinical diagnosis in case of hyperammonemia. Ammonia level estimation may have to be repeated if clinical suspicion is high. Early valproate discontinuation itself can ameliorate the encephalopathy induced by valproate.

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Author Contributions

Firoz Kazhungil – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Mithun C. Mohan – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Nidheesh Sankar – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Ram Narayan – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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