Neurology Asia 2006; 11 : 135 – 137

CASE REPORTS

A case of non-hyperammonemic valproate-induced encephalopathy

Deb Sankar GUIN, Samar BISWAS, Kartik SAHA, Amar MISHRA, Shyamal Kumar DAS

Bangur Institute of Neurology, Kolkata, India.

Abstract

A 24-year-old lady receiving sodium valproate for control of myoclonic seizure*s*, developed acute onset deterioration of level of consciousness from 4th the day of starting valproate, without any other focal neurodeficit. All (the) biochemical parameters including liver function test*s* and arterial ammonia levels were normal. EEG showed diffuse slow wave suggesting diffuse encephalopathy. Her sensorium improved rapidly after stoppage of valproate with normalization of EEG. This case highlights the existence of non-hyperammonemic valproate induced encephalopathy, suggesting mechanisms other than hyperammonemia responsible for this encephalopathy.

INTRODUCTION

Valproic acid is a versatile drug that has demonstrated efficacy against primary generalized tonic-clonic, absence, and myoclonic seizures as well as in different non-epileptic conditions such as migraine and bipolar disorders. Other than commoner side effects like tremor, weight gain, abnormalities of hair, valproic acid is also known to cause rare side effects such as encephalopathy. In most of the cases it is associated with hyperammonemia. The reported incidence of asymptomatic hyperammonemia in children was 20% and symptomatic in 5% of cases.[1] Rarely this valproate induced encephalopathy may not be associated with hyperammonemia and other mechanism might be responsible for this side effect. Recently we have encountered a case of valproate-induced encephalopathy where we did not find hyperammonemia further strengthening this fact. To the best of our knowledge, very few cases have been reported on this non-hyperammonemic encephalopathy in the English literature.[11,12,14]

CASE REPORT

A 24-year-old lady, non-hypertensive, non-diabetic, right handed, who is a known case of generalized seizure disorder associated with tonic-clonic and myoclonic type, was treated with carbamazepine (CBZ) with apparent response. About 20 days before admission she took one extra dose of CBZ and subsequently developed toxicity in the form of diplopia, slurring of speech, ataxia and drowsiness, which improved within 24 hours of stopping of CBZ. Then she was put on clobazam; subsequently valproate (600 mg daily in divided doses) was added to clobazam for control of seizures. After 4 days of starting valproate she became gradually drowsy for which she was admitted to our institute on the 8th day. There was no history of yellowish discoloration of urine or eyes. She did not complain of fever, headache, vomiting, and stiffness in the neck or any exacerbation of seizure. She was experiencing long standing dyspepsia, anorexia and sleep disturbances. On examination after admission, her blood pressure was 96/70 mmHg, heart rate and respiratory rate was normal. Nervous system examination showed that she was drowsy and disoriented with inappropriate answers to questions. Over next 2 days she remained stuporous. Meningeal signs were absent. Examination of cranial nerves and motor system was normal. Deep tendon jerks were elicited in all 4 limbs. Plant*a*r reflex was bilaterally flexor. Abdominal reflexes were present in all quadrants. Examination of sensory system and cerebellar functions were normal. Other systemic examination was unremarkable.

Address for correspondence: Prof. Shyamal Kumar Das, Professor of Neurology, Bangur Institute of Neurology, 52/1A, Sambhunath Pandit Street, Kolkata – 700025, INDIA.

With this examination we started investigating the cause of her altered sensorium.

Her hemoglobin, full blood count, ESR, blood glucose, renal and liver function tests, serum electrolytes, prothrombin time and serum arterial ammonia levels were all normal. The serum ammonia level was 0.52 μgm/ml. In view of outbreak of dengue during that time, serology for dengue (IgM) was carried out which was negative. MRI of brain was normal. EEG done after admission during drowsy state showed a marked diffuse background slowing intermixed with 2-2.5 Hz of high-amplitude slow waves, occurring synchronously over both hemispheres, which did not change after injection of IV diazepam. ECG, ultrasonography of abdomen and echocardiography were normal.

Keeping in mind the possibility of valproate induced encephalopathy, we stopped valproate. The patient's condition slowly improved over next three days and became fully oriented again. During that time repeat EEG was performed, which showed normalcy. Patient was subsequently put on lamotrigine for alternative antiepileptic therapy. She was discharged in satisfactory condition, and remained stable on follow-up visits to date without any recurrence of seizures or altered sensorium.

DISCUSSION

Encephalopathy is an uncommon adverse effect of sodium valproate. The clinical presentation of valproate-induced encephalopathy can be varied and includes irritability, agitation, drowsiness, and coma and occasionally these patients may have paradoxical seizures.[2,3] The other symptoms include loss of appetite, nausea and vomiting.[4]

Our patient presented with increasing drowsiness and disorientation without any localizing signs or focal neurodeficit or convulsive seizure. EEG during drowsy state showed a marked diffuse background slowing inter mixed with 2-2.5 Hz of high-amplitude slow waves, which occurred synchronously over both hemispheres without any epileptiform activity and also no response to IV diazepam, suggesting generalized encephalopathy and excluding non-convulsive status epilepticus. Relevant laboratory investigations excluded any metabolic cause of encephalopathy. Cerebrospinal fluid study was not carried out because we considered central nervous system infection as the least likely possibility since there was no clinical, hematological or MRI evidence indicative of central nervous system infection. After exclusion of all these common causes we thought it to be a case of valproate induced encephalopathy as there was a temporal relation with valproate therapy, and this was confirmed when the clinical condition improved after stoppage of valproate with normalization of EEG.

In most of the cases valproate-induced encephalopathy, as reported in the literature, is associated with hyperammonemia. Hyperammonemia is more common in children[1] and develops within days to weeks of initiation of treatment.[2] Underlying urea cycle enzyme deficiencies may predispose to valproate-induced hyperammonemia.[5] The risk factors included high initial dose[1], long-term valproate therapy [2], and long-term valproate therapy with concomitant topiramate.[2]

The pathogenesis of valproate-induced encephalopathy is unclear. Decreased levels of consciousness may be due to hyperammonemia, but could be related to other compounds including toxic metabolites of sodium valproate or other organic acids. The presence of the latter may explain encephalopathy in cases with normal ammonia. Patients with valproate-induced encephalopathy typically have a substantial elevation in serum ammonia, at least two fold the upper normal limit.[9,10] However, a few patients, including the present one, who exhibited a typical valproate-induced encephalopathy, revealed normal or only slightly elevated ammonia levels.[11,14] In these cases, serum ammonia seemed unable to fully explain the encephalopathic effect of valproic acid. Based on this finding, valproate-induced encephalopathy has been considered as multifactorial rather than secondary to hyperammonemia only. In fact, using a model of ammonium-induced coma, Stephens *et al* showed in the presence of sodium valproate, a lower concentration of ammonia produced coma.[12] Thus, valproic acid might have a dual effect on encephalopathy - beside a hyperammonemic effect, it might also cause a direct cortical depression to enhance encephalopathy associated with specific ammonia levels.[12] However, it has recently been suggested that brain ammonia concentrations may remain high despite normal serum levels.[6] Hyperammonemia is believed to produce encephalopathy through inhibition of glutamate uptake by astrocytes. This leads to potential glutamate mediated excitotoxic neuronal injury, cerebral edema, and, possibly, seizures.[7] Our patient did not show any hyperammonemia, and hence, as discussed above, mechanisms other

than hyperammonemia may be involved in this case. Our aim of reporting this case is to highlight this fact.

In patients with non-hyperammonemic valproate induced encephalopathy, early diagnosis and prompt discontinuation of sodium valproate is always associated with subsidence of clinical manifestations.[9,10,13] Nevertheless, the following pitfalls might lead to a delayed diagnosis or misdiagnosis. First, most cases had a non-toxic serum valproate concentration.[9,10,13] Measurement of serum valproate level is not helpful in establishing the diagnosis. Second, symptoms of encephalopathy could be mistaken for a postictal confusional state. In our patient, the diagnosis was helpfully made by characteristic EEG findings, which usually encompassed a diffuse background slowing intermixed with high-amplitude slow waves or triphasic waves, especially when there were clinical symptoms and signs indicating an encephalopathy.[2, 9]

In conclusion, the diagnosis of valproate-induced encephalopathy should be suspected in any patient on valproate therapy with altered sensorium. Patients taking valproic acid may have mild to marked encephalopathic signs that can progress to lethargy and stupor. Early recognition of subtle cognitive and behavioral changes can lead to therapeutic interventions to avoid this progression. Response to therapy is rewarding. Valproate-induced encephalopathy has no correlation with the amount of the valproate dosage and its serum level. Temporal relation after the administration of valproate and reversibility of state of consciousness following its withdrawal establish the diagnosis.

ACKNOWLEDGEMENT

The authors would like to thank Dr Purnabrata Burma for editing the photograph.

REFERENCES

1. Iinuma K, Hayasaka K, Narisawa K, Tada K, Hori K. Hyperaminoacidaemia and hyperammonemia in epileptic children treated with valproic acid. *Eur J Pediatr* 1988; 148: 267-9.
2. Marescaux C, Warter JM, Micheletti G, Rumbach L, Coquillat G, Kurtz D. Stuporous episodes during treatment with sodium valproate: Report of seven cases. *Epilepsia* 1982; 23: 297-305.
3. Barrueto F Jr, Hack JB. Hyperammonemia and coma without hepatic dysfunction induced by valproate therapy. *Academic Emerg Med* 2001; 8: 999-1001.
4. Browne TR. Drug therapy: Valproic acid. *N Engl J Med* 1980; 302: 661-6.
5. Bogdanovic MD, Kidd D, Boriddon A, Duncan JS, Land JM. Late onset heterozygous ornithine transcarbamylase deficiency mimicking complex partial status epilepticus. *J Neurol Neurosug Psychiatry* 2000; 69: 813-5.
6. Hamer HM, Knake S, Rosenow F. Reply from authors. *Neurology* 2000; 55: 606.
7. Hamer HM, Knake S, Schomburg U, Rosenow F. Valproate-induced hyperammonemic encephalopathy in the presence of topiramate. *Neurology* 2000; 54: 230–2.
8. Lockwood AH. Hepatic encephalopathy. Boston: Butterworth-Heinemann, 1992.
9. Duarte J, Macias S, Coria F, Fernandez E, Claveria LE. Valproate-induced coma: case report and literature review. *Ann Pharmacother* 1993; 27: 582-3.
10. Coulter DL, Allen RJ. Secondary hyperammonemia: a possible mechanism for valproate encephalopathy. *Lancet* 1980; 14;1: 1310-1.
11. Pakalnis A, Drake ME, Denio L. Valproate-associated encephalopathy. *J Epilepsy* 1989; 2: 41-4.
12. Stephens JR, Levy RH. Effects of valproate and citrulline on ammonium-induced encephalopathy. *Epilepsia* 1994; 35: 164-71.
13. Zaret BS, Beckner RR, Marini AM, Wagle W, Passarelli C. Sodium Valproate-induced hyperammonemia without clinical hepatic dysfunction. *Neurology* 1982; 32: 206-8.
14. Reif A, Leonhard C, Mossner R, Lesch KP, Fallgatter AJ. Encephalopathy and myoclonus triggered by valproic acid. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; 28(6): 1061-3.