CASE REPORT

# Encephalopathy Induced by Combination Therapy with Valproic Acid and Topiramate: Challenging the Utility of Serum Ammonia Measurement

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## INTRODUCTION

The combination of valproic acid and topiramate has been shown to increase the risk of encephalopathy.[1-5] Certain authors have proposed that this combination evokes a synergistic mechanism that produces hyperammonemia, which in turn results in encephalopathy.[2,6] Described here is a case of encephalopathy potentially induced by the combination of valproic acid and topiramate, in which serial serum ammonia measurements suggested that encephalopathy may occur before hyperammonemia. This case challenges the proposed mechanism in this clinical situation and the utility of measuring serum ammonia concentration

## CASE REPORT

A 45-year-old HIV-positive patient with known seizure disorder involving general tonic–clonic and possibly absence seizures was admitted to hospital with status epilepticus of tonic–clonic seizures.* The home anticonvulsant regimen, with which the patient was adherent, consisted of topiramate 200 mg twice daily and levetiracetam 1500 mg twice daily. At the time of admission, computed tomography of the head showed no acute intracranial abnormalities. Lumbar puncture revealed that the cerebrospinal fluid had a normal cell count, with no bacterial organisms (no growth after 7 days' culture) or viral organisms (negative results on testing by polymerase chain reaction for herpes simplex and varicella viruses). The result of a screening test for syphilis using serum rapid plasma reagent was also negative.

The patient received an IV loading dose of phenytoin in the emergency department and was simultaneously started on clonazepam 1 mg twice daily. The patient was transferred to the intensive care unit for monitoring. The patient's home anticonvulsant regimen was continued in hospital. The seizure activity lasted about 24 h, the patient's level of consciousness improved within the first day, and the post-ictal period ended on the second day of admission.

On day 3 of the admission, following termination of the seizures, valproic acid was added to the regimen of topiramate, levetiracetam, and clonazepam and was then titrated up to 750 mg orally tid by day 7 of the admission. On day 8, the patient became febrile, tachypneic, and acutely agitated and confused. Aspiration pneumonia was suspected, and the patient was started on piperacillin–tazobactam, which was continued for a total of 7 days. On day 9, clonazepam was discontinued to eliminate any contribution of benzodiazepine-induced delirium. On day 10, the patient remained delirious and increasingly drowsy, despite improvement in the respiratory symptoms with the IV antibiotics. Electroencephalography (EEG) performed on day 10 showed severe generalized slowing of background activity and the presence of bilateral, frontally predominant triphasic waves, which together indicated profound encephalopathy, but no epileptiform activity. The patient was not known to have liver disease, and serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), alkaline phosphatase, and total bilirubin were all within normal ranges on the day of admission. Blood work on day 10 showed serum ammonia concentration of 31 µmol/L (normal range 9 to 33 µmol/L) and normal levels of AST, ALT, alkaline phosphatase, and total bilirubin, but isolated elevation of GGT (142 U/L; normal range < 50 U/L). The serum valproic acid concentration was 395 µmol/L (target range 350–835 µmol/L). On day 11, the patient's confusion continued, the serum ammonia concentration rose to 72 µmol/L, and there was no change in liver enzymes.

*Informed consent was not obtained from the patient described in this case. Potential identifiers not pertinent to description of the case have been omitted.

Valproic acid–induced encephalopathy was suspected, so the dose of valproic acid was reduced. Clonazepam was restarted for prophylaxis of seizures, at 1 mg twice daily. On day 12, serum ammonia concentration rose to 140 µmol/L, and the valproic acid was discontinued. On day 13, serum ammonia concentration returned to near normal, at 34 µmol/L, but the patient remained confused. EEG performed the same day showed continuing encephalopathy, though less severe than what previous EEG had shown, but no seizure activity. On day 14, the patient's orientation improved but some confusion remained (serum ammonia concentration 16 µmol/L), and by day 15 the confusion had resolved. The patient continued taking topiramate and levetiracetam throughout the course of treatment.

## DISCUSSION

The patient described here experienced encephalopathy after the addition of valproic acid and clonazepam to the existing antiepileptic regimen of topiramate and levetiracetam. We believe that the encephalopathy was most likely caused by the antiepileptic drug therapy, more specifically, addition of valproic acid to topiramate. The patient's hospital-acquired pneumonia could have contributed to the encephalopathy, but we feel that this was unlikely, as the patient's neurologic status did not improve after treatment with antibiotics, despite improvement in respiratory symptoms. Other causes of encephalopathy, such as viral infection and impairment of hepatic function, were excluded. The patient's symptoms improved without adjustment in the levetiracetam dosage, and the patient tolerated the reintroduction of clonazepam without worsening encephalopathy. Monotherapy with either valproic acid or topiramate or combination therapy with the 2 drugs has frequently been reported to cause encephalopathy.[2-5,7-9] In a recent retrospective chart analysis, the odds ratio for development of encephalopathy was 10 for patients receiving valproic acid – topiramate combination therapy relative to patients receiving valproic acid alone.[1] In the case reported here, the patient's improved neurologic status after withdrawal of valproic acid suggested that this drug had a role in the development of encephalopathy. The Naranjo score was 7, which suggested that the encephalopathy was probably a drug-induced adverse event.[10]

The presentation of encephalopathy is similar whether induced by valproic acid – topiramate or by valproic acid monotherapy.[1,7] Encephalopathy can occur whether serum ammonia concentration is normal or elevated, its onset occurs days to months after initiation of or change in the dose of valproic acid or topiramate, and it can occur with or without elevation of valproic acid concentration.[1,7] EEG findings are typically nonspecific but may show diffuse slowing and predominance of rhythmic theta and delta activity triphasic waves.[1,2,7] This patient's presentation was consistent with previous reports: the encephalopathy developed about 5 days after valproic acid was added to topiramate, and the EEG findings shortly after achievement of therapeutic valproic acid concentrations were consistent with drug-induced encephalopathy.

Valproic acid–induced encephalopathy is hypothesized to be caused by disruption of the urea cycle in hepatic mitochondria, which causes impairment of ammonia elimination and hyperammonemia. Some patients with hyperammonemia have elevated ammonia concentration in the central nervous system (CNS), which may reduce uptake of glutamate by astrocytes. This in turn results in an increase in extracellular glutamate and overexcitation of the astrocytes. Increased ammonia concentrations in the CNS cause increased production and accumulation of glutamine within the astrocytes, which ultimately causes cerebral edema and astrocyte dysfunction.[2,6] Ammonia concentrations were not measured in the CNS of the patient described here, but ammonia is thought to rapidly cross the blood–brain barrier.[7] The mechanism for topiramate-induced encephalopathy has been suggested to involve accumulation of glutamate in the CNS due to direct inhibition of glutamine synthetase, a consequence of long-term topiramate therapy.[11]

According to previous observations, as many as 50% of patients who are receiving valproic acid therapy are asymptomatic despite hyperammonemia,[6,7,12] whereas other patients experience encephalopathy in the presence of normal serum ammonia concentrations.[7,13,14] One hypothesis proposed to reconcile the presentation of encephalopathy with various concentrations of serum ammonia is that the threshold of CNS ammonia concentration that causes encephalopathy varies from one patient to another.[7,15]

To our knowledge, this case is one of the first to follow serial serum ammonia concentrations during encephalopathy suspected to have been induced by combination therapy with valproic acid and topiramate and may shed some light on the trend in serum ammonia concentration during the onset of encephalopathy. The patient showed the first signs of encephalopathy 36 h before the first measurement of serum ammonia concentration, which was within normal limits. The concentration of ammonia rose rapidly on subsequent testing, doubling at 17 h and again at 40 h. Throughout this period, the patient remained persistently encephalopathic. The serum ammonia concentration subsequently declined to near normal about 24 h after discontinuation of the valproic acid, but the patient's confusion persisted. The confusion improved significantly about 48 h after discontinuation of valproic acid and had resolved by 72 h after discontinuation. The serial serum ammonia values indicated the lack of a strong association between serum ammonia and symptoms of encephalopathy. The patient was encephalopathic when the serum ammonia level was normal, and the symptoms remained unchanged as serum ammonia concentrations rose. Furthermore, once the serum ammonia concentration fell, the patient remained confused for another 48 h. The estimated half-life of valproic acid in adult patients is 9 to 19 h,

so it is possible that resolution of the patient's encephalopathy was more closely mirroring the falling valproic acid levels.

Lack of a strong correlation between serum ammonia concentrations and clinical encephalopathy suggests that measuring serum ammonia concentration is not clinically useful in this situation. More specifically, a normal serum ammonia concentration cannot rule out valproic acid–induced encephalopathy, particularly in the presence of topiramate. The serum ammonia concentration could be rapidly rising, or the patient could be symptomatic with normal serum ammonia concentrations. We believe that recognizing the potential for combination valproic acid – topiramate therapy to cause encephalopathy is more important than measuring serum ammonia concentrations. We encourage clinicians to avoid this combination whenever possible and, if the combination is deemed necessary, to monitor patients closely for symptoms of encephalopathy.

## CONCLUSION

The case presented here suggests that serum ammonia concentrations measured early after the onset of encephalopathy in patients being treated concurrently with valproic acid and topiramate are not clinically useful in ruling out drug-induced encephalopathy. The case also suggests that the combination of valproic acid and topiramate therapy may induce encephalopathy. If encephalopathy is suspected, the combination therapy should be stopped as early as possible. Clinicians should be aware of this interaction and should avoid combination therapy with valproic acid and topiramate whenever feasible.

**References**

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