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Case Report

Topiramate-induced hyperammonemic encephalopathy in a patient with mental retardation: A case report and review of the literature

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ABSTRACT

Hyperammonemia is an uncommon side effect of topiramate (TPM) that has only been reported when it is used as an adjunct to valproate. We report a patient with mental retardation who developed reversible encephalopathy from TPM. Ammonia level was monitored during the course of TPM treatment. This patient had recurring, reversible elevations in serum ammonia levels that coincided with the administration of TPM. To our knowledge, symptomatic hyperammonemia has not been reported to occur with TPM monotherapy.

1. Introduction

Metabolic encephalopathy poses a challenging diagnosis to neurologists because of the condition's varied and potentially reversible etiologies. Drug-induced metabolic encephalopathies are common but often go unrecognized. This is unfortunate as the correct identification of the cause and discontinuation of the offending agent usually result in quick and complete resolution of the symptoms. As a group, antiepileptic drugs are a relatively common cause of encephalopathy, either by direct CNS effect, or, in some cases, by inducing hyperammonemia. This is a well-established complication of valproic acid and has now been reported to occur in patients previously treated with valproic acid to which TPM was added [1–8]. Topiramate is a broad-spectrum anticonvulsant that is also extensively used for migraine prophylaxis, as a mood stabilizer, and for alcohol dependency. When given as monotherapy, the use of TPM can be associated with cognitive impairment, glaucoma, and kidney stones. Hyperammonemia has not been reported with the use of TPM monotherapy.

2. Case

A 44-year-old Hispanic male with past medical history of mental retardation, hypothyroidism, and depressive psychosis was admitted to the hospital with a two-week history of altered mental status. The etiology of developmental delay was related to birth-related problems. There was no clinical or laboratory evidence of inborn errors of metabolism. At baseline, the patient had moderate developmental delay and was able to feed himself, use the restroom on his own, communicate using a few words, and ambulate without assistance. Topiramate 100 mg bid had been started to treat mood disorder. Over a two-week period preceding admission, he stopped talking and was noted to have increasing gait instability and generalized weakness. He became unable to feed himself and became incontinent of urine. Examination on admission showed the patient to be lethargic but aroused. His language output was limited to him repeating the words “fine–fine” whenever he was asked a question. Cranial nerve exam was notable for gaze-evoked nystagmus on lateral gaze bilaterally. The patient was hyperreflexic with 3^{+} reflexes of all four extremities. He was ataxic and had gait instability. No asymmetry of the motor exam and no asterixis were observed.

The patient arterial ammonia was elevated at 77 μmol/l (upper limit of normal = 60 μmol/l) on admission. The rest of the laboratory test results were normal including other liver function tests and hepatitis panel. Electroencephalogram on admission showed generalized background slowing without triphasic waves or epileptiform discharge. Brain MRI showed generalized brain atrophy without abnormalities in the white matter or cortex. The initial diagnostic impression was hyperammonemia-induced encephalopathy. He was treated with lactulose, and TPM was discontinued on the first day of admission. No other medication changes were carried out. Within two days, mental state changes resolved, and staff who were familiar with the patient felt that he was back to his baseline. Repeat ammonia level the following day was 27 μmol/l. On the third day of admission, the patient had a

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partial seizure presenting as a behavior arrest and clonic movements of the right side of the face and the right arm. Topiramate was restarted at the same dosage as before. The seizures did not reoccur, but repeat ammonia levels over the ensuing two days showed a trend upwards, 47 μmol/l and 57 μmol/l, respectively. Given the fact that ammonia levels were again elevated with TPM, it was switched to lamotrigine (LTG). Twenty-four hours after the discontinuation of TPM, serum ammonia again decreased to 33 μmol/l.

3. Discussion

Topiramate was originally synthesized as a potential hypoglycemic agent [9]. Although the drug did not show hypoglycemic activity, it showed a wide range of CNS effects, acting as an antagonist of voltage-activated Na^+ channels, L-type voltage-activated Ca^{2+} channels, carbonic anhydrase (CA) isozymes, and AMPA/kainate receptors. Subsequently, it was also shown to be a $GABA_A$ agonist, and that paved the way to its use as an anticonvulsant. Although the use of TPM can be associated with cognitive symptoms, this side effect appears to be due to a direct effect of the drug in the CNS and is not secondary to any metabolic abnormality. Hyperammonemia secondary to the combined use of TPM and other antiepileptic drugs, particularly VPA, has been reported but is probably not common, with only a few cases reported in the literature [1–8].

3.1. Mechanism of topiramate-related hyperammonemia

To our knowledge, this is the first case of a TPM-induced hyperammonemia, without the use of any concurrent AEDs, to be reported. Whereas the hyperammonemia seen in cases of the combination of VPA and TPM appears to be related to interference with glycine metabolism and metabolic acidosis, the mechanism by which TPM itself would cause hyperammonemia is unknown. There are two major mechanisms that might contribute to this effect: 1) TPM is a carbonic anhydrase inhibitor and can decrease the production of bicarbonate (HCO_3^-), which is required in the synthesis of carbamoyl phosphate, an intermediate substrate in the urea cycle, and 2) the other direct effect of TPM is the reduction of the activity of glutamine synthetase, the main enzyme for the detoxification of ammonia [10].

3.2. Hyperammonemic encephalopathy

Hyperammonemic encephalopathy has been thoroughly described in the literature. Clinical symptoms are varied and include nausea, vomiting, seizures, ataxia, abnormal behavior, or coma, depending on the ammonia level and age of the patient [11,12]. Venous ammonia level may correlate less with clinical symptoms compared with arterial ammonia level [13–15]. This patient presented with a two-week history of mental status changes and psychomotor decline. He also exhibited ataxia, nystagmus, and gait instability and one episode of complex partial seizures during admission. The short duration of his recent symptoms and the fact that all symptoms fully reversed indicated that none of his recent symptoms were caused by progression of an underlying CNS pathology. Other common etiologies of mental status changes in patients with developmental delay such as toxic, metabolic, infectious, and subacute structural CNS lesions were also ruled out. Computerized tomography scan and MRI of the brain, EEG, renal function, electrolytes, complete blood count, thyroid function, urine analysis, and sepsis workup were all negative. The patient's EEG showed mild slowing of the background but no epileptiform abnormalities or triphasic waves. After discontinuation of TPM, the patient returned to his baseline with resolution of the ataxia and nystagmus.

Although hyperammonemia may reflect an underlying abnormal urea cycle defect (UCD), this did not appear to be the cause in this patient. No abnormalities suggestive of UCD had been detected in previous evaluations looking for the etiology of his developmental delay. Although some UCD may become manifested later in life, these cases typically do not have developmental delay. For these reasons, we do not believe that the development of TPM-induced hyperammonemia was due to an “unmasking” of an underlying UCD.

Conflict of interest

The authors declare no conflict of interest.

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