LETTER TO THE EDITOR

To The Editor

Hyperammonemic Encephalopathy Associated with Perampanel: Case Report and Discussion

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Hyperammonemic encephalopathy (HE) can manifest with variable symptoms ranging from mild to severe such as lethargy, fatigue, seizure exacerbation, altered behavior, insomnia, impaired consciousness, gait instability, and flapping tremor.[1,2,3]

Valproate-induced HE has long been described, but can be under-recognized, as mild symptoms can mimic side effects of antiepileptic drugs (AEDs). Hyperammonemia may occur even if serum valproic acid (VPA) levels are within the reference range with normal or slightly elevated liver enzymes serum levels.[2,3]

Other AEDs have rarely been associated with HE. Adding Levetiracetam (LEV), Phenobarbital (PB), or Topiramate (TPM) to a patient already taking VPA has been reported to trigger HE.[1,4,5] TPM, in particular, may increase that risk 10-fold[5] Moreover, there are case reports describing HE in patients taking Carbamazepine (CBZ) either as monotherapy or in combination with other AEDs,[6] and with TPM monotherapy.[7]

We report a case of HE associated with Perampanel (PER).

The patient is a 27-year-old male with a history of autism, microcephaly, developmental delay, and seizures associated with an 11 Mb pathogenic 8p23.3p23.1 deletion, involving *CLN8*, *ARHGEF10*, *MCPH1*, *and RP1L1* genes. There was no family history of epilepsy, autism, or developmental delay. He was the product of a normal pregnancy and uncomplicated delivery at 36 weeks. His seizures began at the age of 8 years, consisting of focal onset with impaired awareness, evolving to bilateral tonic–clonic convulsions. The focal symptoms were characterized by staring, cyanosis of the lips, frothing, and eye fluttering. He had several hospital admissions due to status epilepticus. At the age of 15 years, his seizures stopped on a combination of TPM 500 mg/day and CBZ 800 mg/day. After 12 years of seizure freedom, antiepileptic drug tapering was attempted. CBZ was successfully weaned, but after reducing TPM his seizures recurred. CBZ was reintroduced, TPM was increased and lastly, phenytoin was added after one emergency room visit. As seizures did not abate, 8 months after adding phenytoin, PER was added and titrated up to 4 mg/day. One month after adding PER, his mother reported he was drowsy, fatigued, and began to have events described as "collapsing" episodes where he would lose consciousness and fall, with few associated jerks. His mother described these events as clearly different from his previous seizures. He was admitted to the hospital where blood work showed increased levels of ammonia: 139 umol/L (11–35) and slightly elevated liver enzymes (AST: 69 U/L [7–40], ALP: 92 U/L [40–150]). He was then transferred to the Epilepsy Monitoring Unit (EMU). During video EEG monitoring, two of his typical focal onset seizures with impaired awareness were recorded, without clear localization or lateralization on EEG. He also experienced one "collapsing" episode in the EMU, witnessed by a nurse, and described to involve loss of consciousness, jerky movements in all limbs, and respiratory arrest for 1 min. Breathing returned spontaneously. Unfortunately, his EEG electrodes were removed just before this episode, therefore, the precise nature of it remains unknown. Although the collapsing episode was not recorded, his EEG around that time showed diffuse background slow in the theta and delta frequency range, compatible with a diffuse encephalopathic process. This was different from a 2-day ambulatory EEG done 18 months earlier which was normal, without slowing or interictal epileptiform activity.

A full metabolic workup for inborn errors of metabolism including plasma amino acid profile, urinary organic acid profile, plasma acylcarnitine profile, and urinary orotic acid level was negative. Abdominal imaging and hepatitis screening were negative. Brain MRI scan, cardiac Holter monitoring, and echocardiogram were unremarkable. After a thorough investigation that did not disclose a cause for the "collapsing events" or the presumptive HE, PER was weaned and TPM was titrated down from 500 to 300 mg/day. Within 2 weeks of these changes, he became more alert and had no further "collapsing" episodes. At discharge, serum ammonia and liver enzyme levels had normalized.

Hyperammonemia associated with AEDs is most often attributed to drug-induced liver injury. However, it has also been reported in patients without evidence of liver dysfunction. Other causes of hyperammonemia such as inborn errors of metabolism, cancer, urinary tract infections, and portosystemic shunting should be considered.[1] Our patient underwent extensive investigations to rule out these other causes, but all results were negative. When PER was discontinued, his serum ammonia levels normalized, and he improved clinically. At the time of this paper, the patient has been followed for over 10 months, his ammonia levels continue to be normal and symptoms of HE have not returned.

Ammonia is produced by the catabolism of amino acids released during hydrolysis of dietary and tissue protein; small proportions are reutilized for protein biosynthesis. The rest is neurotoxic.[1] Ammonia crosses the blood–brain barrier, inhibiting intracellular glutamate uptake, leading to excessive N-methyl-D-aspartate receptor activity and reduced seizure threshold.[2] HE is a well-recognized potential side effect of VPA treatment. Proposed mechanisms include inhibition of the hepatic mitochondrial enzyme carbamoyl-phosphate synthase-I, reduction of hepatic carnitine levels, and increased ammonia production in the kidneys.[2,3]

TPM may cause increased ammonia levels by inhibition of carbonic anhydrase and cerebral glutamine synthetase.[7] Our patient was on TPM which might have influenced the increase in ammonia levels, nonetheless, he was previously on high-dose TPM for more than a decade without side effects. Moreover, improvement of his symptoms and decreased ammonia levels occurred after discontinuation of PER, in the setting of continued TPM therapy. PER is a selective inhibitor of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors and the first of this class of drugs.[8] Although its main metabolism is through liver enzymes, notably CYP3A4 and CYP3A5, the explanation for why PER might have caused HE in our patient is unknown.

Signs of HE can be easily mistaken as AED side effects. In patients with an intellectual disability, it can be more challenging

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to identify symptoms associated with HE, therefore requiring a higher degree of suspicion. In such cases, behavioral changes, sleep disruption, or increased seizure frequency may be the most evident symptoms. As far as the authors know, the "collapsing" events reported here, which appeared to involve a respiratory arrest, have not been previously associated with HE and HE has not been reported in patients taking PER. The association of PER with other AEDs, especially TPM, might have contributed to the appearance of hyperammonemia, even though the patient improved only by discontinuing PER. It is not clear if PER alone would have been sufficient to cause the described symptoms, therefore, more studies are necessary to clarify the relation between PER and hyperammonemia and understand the mechanisms underlying this condition. Serum ammonia levels should be considered when beginning the treatment with AEDs and if certain AED side effects occur.

Conflicts of Interest

None of the authors has any conflict of interest to disclose.

Statement of Authorship

Conception and design of study: PTM, RAW, DMA.
Acquisition of data: PTM, QZA, AS.
Analysis and/or interpretation of data: HF, RAW, DMA.
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