

LETTER TO THE EDITOR**TO THE EDITOR****An Acute Encephalopathy Accelerated by a Large Amount of Milk Consumption**

Following the report of two Canadian Aboriginal patients with severe hepatic failure by Mhanni et al. (2006),¹ suffering from hyperammonemia, hyperornithinemia, and hyperhomocitrullinuria (HHH) syndrome, to the best of our knowledge, we are presenting the third and the oldest Aboriginal patient with HHH syndrome. Our patient, a 34-year-old male of Métis descent, with chronic cognitive dysfunction, presented with acute inappropriate behavior and recurrent hostility. Previously, he was healthy with no seizure or vascular risk factor. He complained of an inability to “think right” and impaired concentration. On assessment, his vital signs were normal. He was alert, moderately cooperative, and his language was normal. Motor examination including muscle tone was normal. Deep tendon reflexes were brisk and left plantar response was extensor. Sensation, coordination, and gait were normal. There was no meningismus or asterixis. During the first week in the hospital, the patient had episodes of aggression and disorientation requiring physical restraint occurred. The episodes were refractory to quetiapine and occurred in the evenings. During the day, he was calm and oriented. On reassessment, his Montreal Cognitive Assessment score was 12/30, visuospatial skills were impaired (Figure 1A), deep tendon reflexes were brisk, plantar responses were extensor, coordination was impaired, and gait was unsteady. Subsequently, he became unconscious with intermittent colonic movements of the extremities that were treated with intravenous lorazepam and phenytoin load.

Blood work was normal on admission, which included complete blood count, electrolytes, Ca^{2+} , Mg^{2+} , Po_4^{2+} , glucose, creatine kinase, liver enzymes, and bilirubin. Further investigation showed negative vasculitis panel (antinuclear antibody, anti-neutrophil cytoplasmic antibody, extractable nuclear antigen, rheumatoid factor, and C-reactive protein) and thrombophilia workup, negative urine toxicology on several occasions, hypodensities in the right frontal lobe on cranial computed tomography scan, slow electroencephalogram background, negative cerebrospinal fluid, including polymerase chain reaction for herpes simplex virus. His brain magnetic resonance imaging (MRI) was suspicious for acute demyelinating encephalomyelitis or vasculitis (Figure 2A).

The vasculitis workup, hepatitis panel, Venereal Disease Research Laboratory, and HIV tests were all negative. Repeated brain MRI revealed infarcts in the cingulate and insular cortices bilaterally (Figure 2B). Magnetic resonance angiogram and stroke workup including 24-hour Holter monitoring were negative. Left ventricular ejection fraction was decreased (45% to 50%) on echocardiogram. A repeated electroencephalogram taken while the patient was comatose showed diffuse slowing with no epileptiform discharges or triphasic waves. Arterial blood gas showed respiratory alkalosis (pH: 7.47 [7.38-7.46]; bicarbonate: 24 mmol/L [21-28]; partial pressure of carbon dioxide: low at 33 mmHg [35-48], partial pressure of oxygen: 91 mmHg), and blood ammonia level was markedly elevated at 291 $\mu\text{mol/L}$. Homocysteine was high at 25.97 $\mu\text{mol/L}$ (3-15). The results

also showed increased serum glutamine at 1154 $\mu\text{mol/L}$ (371-788), ornithine at 463 $\mu\text{mol/L}$ (14-145), and high urine methionine and orotic acid/creatinine at 51/1.5 (0.4-1.2 $\mu\text{mol/mmol}$). Homocitrulline was not measured directly; however, there is

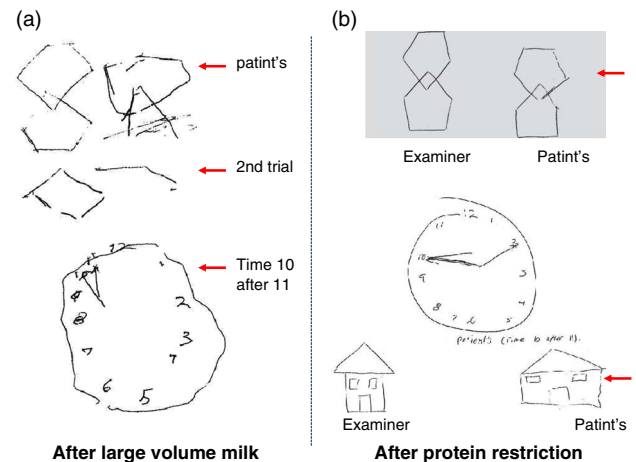


Figure 1: Patients visuospatial assessment (A) before and (B) after protein restriction. Please note severe visuospatial impairment and impaired abstract thinking (clock hands) before protein restriction (A).

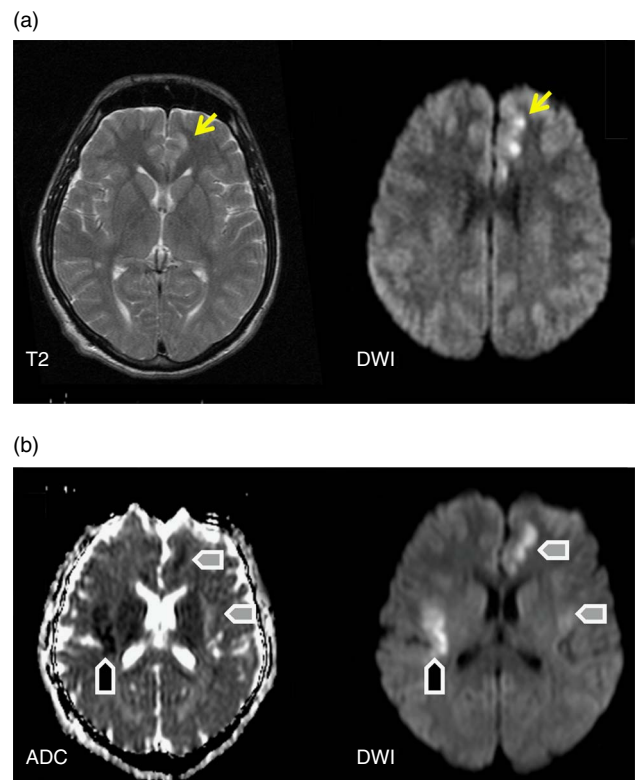


Figure 2: MRI brain with DWI (A) on presentation showing left cingulate hyperintensity with diffusion restriction (arrows); (B) one week later, there is diffusion restriction in the right insular cortex (black arrowheads) and left cingulate (gray arrowheads).

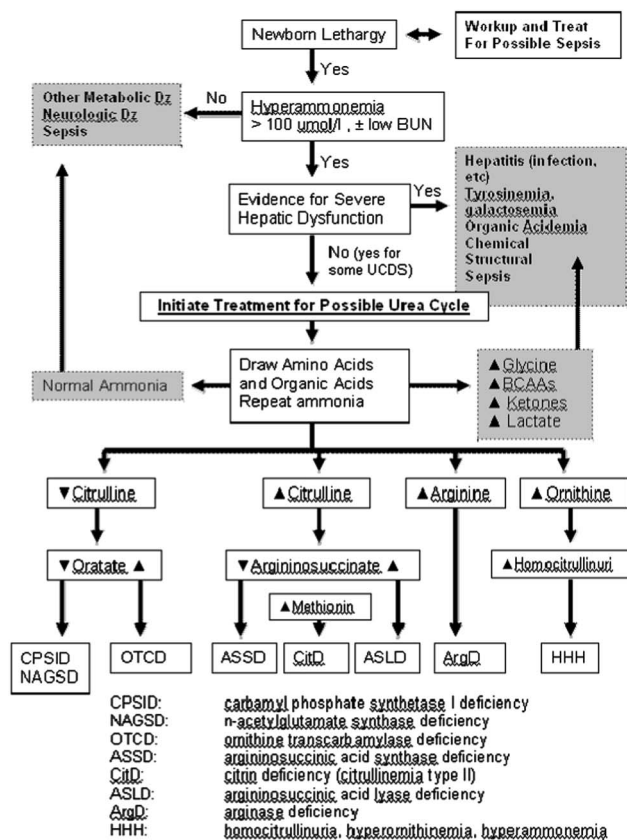


Figure 3: Three step diagnostic work up for hyperammonemia [Rao et al. (2006)].

direct correlation with high urine methionine levels. The patient was diagnosed with HHH syndrome, and a mutation (F188Del) in ornithine transporter 1 (SLC25A15) was found. With dietary protein restriction, his cognitive function improved (Montreal Cognitive Assessment: 24/30), as did his visuospatial skills (Figure 1B). The patient recalled consuming a large amount of milk before unconsciousness. He was discharged home in good condition with instruction to restrict dietary protein to 60 to 65 mg/day and calorie restriction to 2600 to 3500 Kcal/ day with 1 ml fluid/Kcal.

Hyperammonemia is a potentially fatal but treatable condition. Common causes of hyperammonemia include genetic defects in the urea cycle, organic acidemia (urea cycle dysfunction), acute and chronic liver disease, gastrointestinal hemorrhage, and porto-systemic shunting.² HHH syndrome is an autosomal recessive disorder of the urea cycle. Fewer than 100 cases have been reported since its initial description in the 1960s.³ There is a worldwide distribution; however, a founder effect exists in the French-Canadian population from Quebec. In suspected cases, because of ethnicity, molecular analysis for the SLC25A15 F188del mutation, common in French Canadians, should be performed.⁴ Our patient was homozygous for this deletion. The onset for HHH syndrome ranges from the neonatal period to childhood and rarely presents in adulthood, such as in our patient. HHH syndrome might present as chronic neurological symptoms, acute encephalopathy, and liver disease. Presenting as acute

encephalopathy usually raises the suspicion for a metabolic condition. However, the absence of typical early signs of hyperammonemia, including anorexia, vomiting, and asterixis (occurring at ammonia $\geq 60 \mu\text{mol/L}$), makes the diagnosis a challenge in such cases.

Brain MRI showed T2 hyperintensities with diffusion restriction in the cingulate gyrus and insular cortex. This pattern of brain signal change is common and specific in hyperammonemia, irrespective of cause. It is important to be aware of this pattern because it mimics stroke and may delay appropriate management. Magnetic resonance spectroscopy might be useful because of demonstrating an elevated brain glutamine peak.⁵ In any patient presenting with signs of acute encephalopathy, blood ammonia levels should be checked; if hyperammonemia is detected, a three-step diagnostic algorithm can be used to identify the cause (Figure 3).² The treatment of HHH is divided into chronic management to minimize the frequency of hyperammonemic attacks, including protein restriction and ornithine supplementation and acute management of the attacks themselves.

DISCLOSURES

The authors have no disclosures to report.

F. Moein-Afshari

Neurology Department, Faculty of Medicine, University of Saskatchewan, Saskatoon, SK, Canada

N.Z. Mirhosseini

Pure North S'Energy Foundation, Calgary, Alberta, Canada

E.G. Lemire

Neurology Department, Faculty of Medicine, University of Saskatchewan, Saskatoon, SK

C.L. Voll

Neurology Department, Faculty of Medicine, University of Saskatchewan, Saskatoon, SK

REFERENCES

- Mhanni AA, Chan A, Collison M, et al. Hyperornithinemia-hyperammonemia-homocitullinuria syndrome (HHH) presenting with acute fulminant hepatic failure. *J Pediatr Gastroenterol Nutr.* 2008;46:312-5.
- Rao AN, Varma P, Sumitra Dhanya S. Hyperammonemia: diagnostic experience at The Metabolism Laboratory. *Internet J Lab Med.* 2006;1.
- Shih VE, Efron ML, Moser HW. Hyperornithinemia, hyperammonemia, and homocitullinuria. A new disorder of amino acid metabolism associated with myoclonic seizures and mental retardation. *Am J Dis Child.* 1969;117:83-92.
- Gatfield PD, Taller E, Wolfe DM, Haust MD. Hyperornithinemia, hyperammonemia, and homocitullinuria associated with decreased carbamyl phosphate synthetase I activity. *Pediatr Res.* 1975;9:488-97.
- Takanashi J, Barkovich AJ, Cheng SF, Kostiner D, Baker JC, Packman S. Brain MR imaging in acute hyperammonemic encephalopathy arising from late-onset ornithine transcarbamylase deficiency. *AJNR Am J Neuroradiol.* 2003;24:390-3.