Malignant cerebral edema secondary to hyperammonemia in setting of acquired carnitine deficiency

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A 34-year-old woman with a remote history of Roux-en-Y bariatric surgery and pancreatitis with residual sphincter of Oddi dysfunction was hospitalized with 1 week of progressive confusion.

Initial examination was nonlateralizing, but revealed lethargy and asterixis. The initial ammonia level was elevated (362 $\mu\text{mol/L}$ [normal 11–32 $\mu\text{mol/L}$]), whereas liver function tests, hepatitis panel, acetaminophen levels, blood alcohol, drug screen, urinalysis, complete blood count, blood cultures, and comprehensive metabolic panel were normal. Abdominal CT revealed diffuse fatty liver. Within 24 hours, repeat ammonia was >600 $\mu\text{mol/L}$ despite treatment with lactulose. Continuous renal replacement therapy was started with minimal improvement in ammonia levels and progressively worsening mentation requiring intubation. Continuous EEG revealed severe encephalopathy. Head CT revealed diffuse cerebral edema. Follow-up brain MRI corroborated CT findings and revealed transtentorial herniation (figures 1 and 2). Hypertonic saline, mannitol boluses, and extraventricular drain placement all were done for elevated intracranial pressure management without any clinical improvement. Given the patient's history (bariatric surgery and pancreatitis) suggesting an increased risk of malabsorption, along with current refractory idiopathic hyperammonemia, an acquired carnitine deficiency was considered, and empiric supplementation of L-carnitine was initiated, resulting in a dramatic reduction of ammonia levels (to 55 $\mu\text{mol/L}$) 24 hours after supplementation. Total (11 nmol/mL [normal 34–78 nmol/mL]) and free (1 nmol/mL [normal 25–54 nmol/mL]) carnitine levels obtained before empiric treatment returned confirming severe carnitine deficiency. Despite improving ammonia level, clinical deterioration continued, the patient was transitioned to comfort measures, and the patient died 48 hours later.

PRACTICAL IMPLICATIONS

In cases with refractory or potentially life-threatening idiopathic hyperammonemia, consider evaluating for carnitine deficiency and initiating empiric carnitine trial.

Discussion

Carnitine, primarily derived from protein intake, is a required cofactor for long-chain fatty acid metabolism, primarily by trafficking the fatty acids from the cytosol into the mitochondria matrix for beta-oxidation and energy production.¹ In carnitine deficiency, fatty acids accumulate in the cytosol, resulting in inhibition of the urea cycle (via multiple mechanisms), thus impairing ammonia degradation.^{2,3} In addition to stagnating the urea cycle, impaired metabolism of fatty acids also leads to hepatomegaly, hepatic steatosis, and myopathies, with evidence of the former 2 occurring in our patient.¹ As stated above, the majority of carnitine (75%) comes from protein intake; however, when consumption is lacking, the liver is able to produce sufficient amounts using the amino acids methionine and lysine among other cofactors.^{4,5} In patients predisposed to malabsorption (e.g., patients status post-gastric bypass procedures with residual impaired absorption of dietary macronutrients), as was the case in our patient, in addition to carnitine stores becoming deficient, methionine deficiency also readily occurs, given that this essential amino acid,

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Figure 1 Noncontrasted sagittal head CT

Findings consistent with diffuse cerebral edema.

only present in low concentrations in food, cannot be adequately absorbed from the gastrointestinal tract.⁶ As such, carnitine stores are decreased on 2 fronts; exogenous carnitine cannot be absorbed, and endogenous carnitine cannot be produced. Reports first implicating carnitine's role in serum ammonia levels were described in children, but various additional etiologies that result in serum ammonia derangements exist and include hepatic failure, certain drug exposure (including anticonvulsants such as valproic acid and phenytoin), organic acidemias, and urea cycle deficits.^{1,5,7} In our patient, there was no objective evidence that would suggest one of these alternative etiologies as an explanation for her clinical presentation. Given the dramatic decrease in ammonia levels after

only 24 hours of carnitine supplementation, we suspect our patient's development of catastrophic cerebral edema was secondary to an underlying acquired metabolic deficiency in the setting of gastrointestinal malabsorption, most logically carnitine deficiency. Despite the prompt trial of L-carnitine and the dramatic effect on the serum ammonia level, the outcome was still poor. We suspect that although the rapid resolution of serum ammonia occurred, there was not sufficient time to allow equilibration of CNS osmolarity with the newly lowered serum osmolarity, and as a result, the continued elevated intracranial pressure resulted in herniation and patient demise. As illustrated in this unfortunate case, in scenarios of hyperammonemia that lack an obvious etiology and are refractory to standard treatment, one should have a low threshold to assess serum carnitine levels and to trial empiric L-carnitine, especially in life-threatening scenarios, and in so doing reveal a rare, but potentially treatable condition.

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Figure 2 Sagittal T1-weighted brain MRI

Posterior fossa findings consistent with transtentorial herniation as there is a downward shift of brain parenchyma resulting in loss of the prepontine cistern, compression of the fourth ventricle, and herniation of cerebellar tissue through the foramen magnum.

Appendix Authors

Name	Location	Contribution
Daniel Long, DO	Memorial Institute for Neurosciences and Multiple Sclerosis	Initial manuscript draft, review of the literature, and corresponding author
Talal Derani, MD	University of Toledo	Manuscript revisions
Tariq Gheith, MD	Illinois Neurological Institute	Manuscript revisions
Rany Aburashed, DO	Memorial Institute for Neurosciences and Multiple Sclerosis	Manuscript revisions
Ali Saeed, MD	Memorial Institute for Neurosciences and Multiple Sclerosis	Manuscript revision, image review, and review of literature

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