Bronchoalveolar Carcinoma and Respiratory Failure in HHH Syndrome: A Perfect Storm of Therapeutic Limitations

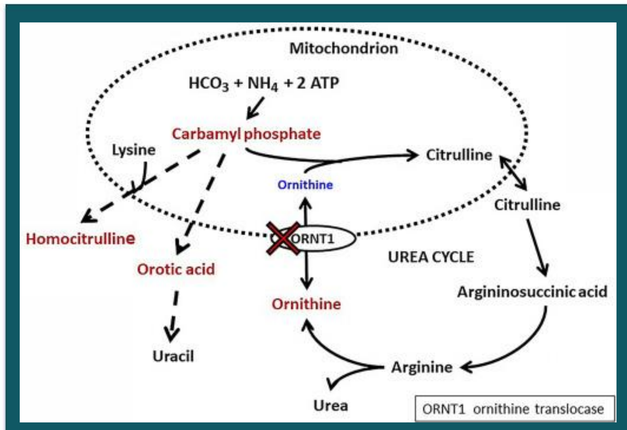
Jeongwon Lee, DO; Arjun Bagai, DO; Sasha Singh, DO; Dhruv Patel, DO; Suresh Duvvada, MD; Rashad Mohmmad Adil, DO; Raju Z Abraham, MD; Samrat Khanna, MD
Riverside Medical Center, Kankakee, Illinois

Background

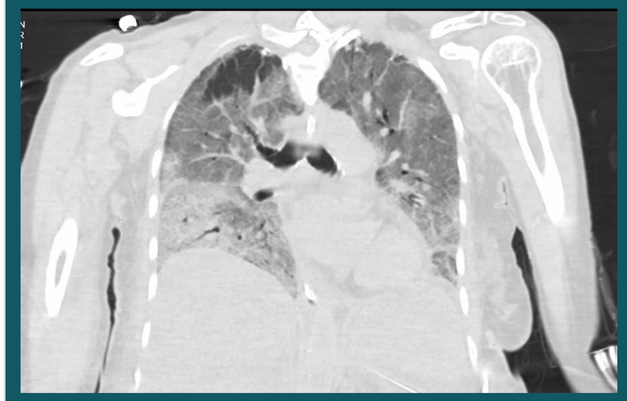
Hyperornithinemia-Hyperammonemia-Homocitrullinuria (HHH) syndrome is a rare autosomal recessive urea cycle disorder with less than 100 cases reported worldwide. The impaired ornithine transport across the inner mitochondrial membrane disrupts the urea cycle, causing hyperammonemia and accumulation of neurotoxic metabolites. We present a challenging case of acute respiratory distress syndrome secondary to a multifocal pneumonia in a patient with HHH syndrome who was later found to have bronchoalveolar carcinoma, illustrating how this rare metabolic disorder complicates standard critical care interventions.

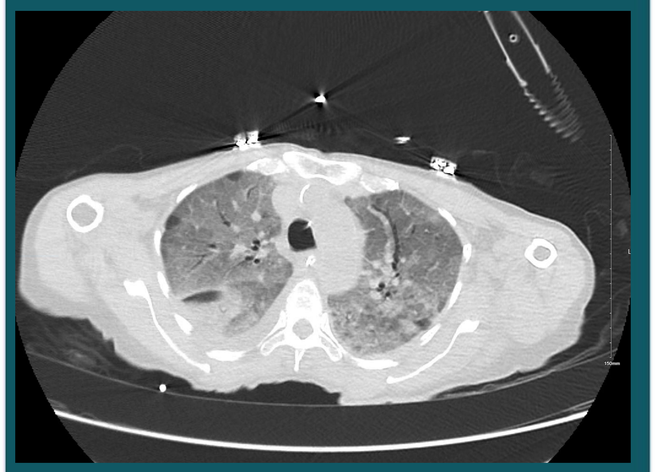
Case Presentation

A 69-year-old woman with HHH syndrome, arginase deficiency, peripheral neuropathy with bilateral foot drop, severe kyphosis, and wheelchair dependence presented with generalized weakness. Chest radiograph demonstrated bilateral mass-like infiltrates, and CT revealed bilateral pneumonic infiltrates predominant in the right upper lobe with small pleural effusions. She developed worsening hypoxic respiratory failure requiring mechanical ventilation within 48 hours. Bronchoscopy revealed bilious secretions throughout the airways, raising concern for chronic aspiration. Extensive infectious workup including respiratory viral panel, urine Legionella and pneumococcal antigens, fungal serologies, and BAL cultures remained unremarkable. BAL cytology unexpectedly revealed adenocarcinoma. Management was severely constrained by her underlying HHH syndrome. Corticosteroids, standard therapy for severe pneumonia and ARDS, posed significant risk for hyperammonemia. Propofol sedation required minimization for concern of worsening mitochondrial dysfunction. Nutritional support required careful balance to prevent catabolism while avoiding nitrogen overload that would overwhelm her already-compromised urea cycle capacity. Despite broad-spectrum antibiotics and aggressive pulmonary pulmonary care, she remained ventilator-dependent with persistent shock. The family eventually elected for comfort-focused care.



Jones, P., Patel, K., & Rakheja, D. (2020). Disorder: Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. A Quick Guide to Metabolic Disease Testing Interpretation, 85–88. https://doi.org/10.1016/b978-0-12-816926-1.00016-x





Conclusions

HHH syndrome creates a unique dilemma in the management of critical illness. Clinical features of HHH include chronic neurocognitive deficits including developmental delay and ataxia, acute encephalopathy from elevated ammonia levels, and chronic liver dysfunction. The defective mitochondrial ornithine transporter ORNT1 transporter prevents ornithine entry into mitochondria, causing cytosolic ornithine accumulation while depleting the mitochondrial ornithine pool necessary for urea synthesis. This renders patients to be exquisitely sensitive to any metabolic stressor as ammonia cannot be further broken down into urea and appropriately excreted. Corticosteroids can induce catabolism of proteins and further induce higher levels of ammonia. Current evidence shows that corticosteroids may also directly downregulate the expression of key enzymes in the urea cycle including carbamoyl-phosphate synthase 1 and argininosuccinate synthase, explaining why steroid-induced hyperammonemia in urea cycle disorders can be more severe than that from other precipitants. Similarly, propofol disrupts mitochondrial electron transport and fatty acid beta-oxidation, reducing the availability of ATP necessary for normal operation of the urea cycle and posing even heightened risk in patients with pre-existing mitochondrial dysfunction. Maintaining adequate nutrition is a vital yet delicate balance as ammonia is a by-product of protein and amino acid degradation. On top of this, neuromuscular complications including dysphagia and impaired airway clearance predisposed the patient to chronic aspiration, which may have contributed to recurrent pulmonary infection. Treatment considered standard of care in critical illness including steroids, sedatives, and aggressive nutritional support may in turn pose life-threatening complications in HHH syndrome, highlighting the importance of a patient-centered, multidisciplinary approach.

Disclosure Information

Nothing to disclose.