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Severe Hyperammonemia in a Neonate: An Alternate Ending

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PRESENTATION

A male infant is born at 38 weeks 3 days gestational age to a gravida 5, para 1 woman via spontaneous vaginal delivery, after a pregnancy complicated by maternal preeclampsia. Maternal history is significant for 2 early miscarriages and an ectopic pregnancy. All prenatal laboratory findings, including maternal immunoglobulin G for herpes simplex virus (HSV), had been normal or negative. The family history is unremarkable. The infant requires normal newborn care and is discharged from the hospital on day 2 after birth. His parents note that he had been sleepy and a poor feeder. He is hypothermic and tachypneic at his first newborn visit to the pediatrician and is immediately referred to the emergency department.

Septic evaluation reveals HSV in both serum and cerebrospinal fluid. Ammonia concentration is normal and his complete blood cell count reveals leukopenia. Initial treatment includes acyclovir, cefotaxime, and ampicillin, narrowed within 48 hours to acyclovir monotherapy. His condition rapidly declines and he develops respiratory failure on hospital day (HOD) 1. The ammonia concentration is within the normal range (39 $\mu\text{g/dL}$ [28 $\mu\text{mol/L}$]). Feeding is initiated on HOD 2 with a subsequent rise in the ammonia concentration (113 $\mu\text{g/dL}$ [81 $\mu\text{mol/L}$]). Despite the cessation of feeding and initiation of moderate glucose infusion rate, the ammonia concentration rises to 538 $\mu\text{g/dL}$ (384 $\mu\text{mol/L}$) by HOD 4. The patient is transferred to a different hospital for metabolic consultation.

DISCUSSION

Increased glucose infusion rate along with a bolus of sodium benzoate and sodium phenylacetate did not sufficiently improve this infant's hyperammonemia. Continuous renal replacement therapy (CRRT) was initiated when the ammonia concentration exceeded 700 $\mu\text{g/dL}$ (500 $\mu\text{mol/L}$). The highest measured ammonia concentration was over 1,400 $\mu\text{g/dL}$ (1,000 $\mu\text{mol/L}$). The patient's hyperammonemia initially improved with CRRT but quickly rebounded after stopping therapy, requiring further CRRT. CRRT was gradually weaned, and protein supplementation was slowly introduced through total parenteral nutrition, and the patient had no additional issues with hyperammonemia.

In this case, a history of poor feeding, sleepiness, hyperammonemia developing after feeding, hyperammonemia out of proportion with liver dysfunction, and the degree of elevated ammonia concentration raised suspicion for proximal urea cycle defects. Proximal urea cycle defects are included on US newborn screening, and can be missed. The ultimate resolution of the hyperammonemia, even after initiation of protein-based feeds, made these diagnoses unlikely. Initial liver function tests, coagulation studies, newborn screening, and abdominal ultrasonography were normal. The patient had no lacticemia, hypoglycemia, ketonuria, or acidosis. Initial acylcarnitine profile, plasma amino acids, urine orotic acid, and urine organic acids, all measured before the infusion of sodium benzoate and sodium phenylacetate, resulted in no diagnostic pattern. Given the severity of the child's condition, rapid whole exome sequencing was performed and was also negative. Ultimately, the hyperammonemia was attributed to disseminated HSV infection, including severe HSV pneumonitis, similar to a previously reported case. (1)

This infant's hospital course was complicated by severe respiratory failure and acute respiratory distress syndrome necessitating high-frequency oscillator ventilation. He also suffered bilateral pneumothoraces requiring the placement of multiple chest tubes. Due to refractory air leak, despite maximal medical management including chest tubes, paralysis, and high frequency jet ventilation, the patient was placed on venoarterial extra corporeal membrane oxygenation (ECMO). Pneumothoraces resolved, and after 13 days, the patient underwent successful decannulation. He was weaned off respiratory support, and transitioned from parenteral to enteral nutrition. After ECMO, magnetic resonance imaging showed normal brain parenchyma with a small focus of extra-axial blood products over the left frontal lobe. The infant was discharged from the hospital. On follow-up at 9 months of age, the infant was feeding orally and growing well. ECMO was not available for the previously reported case, which was fatal. (1)

Ammonia is a byproduct of protein metabolism that, when elevated, can present with signs and symptoms of neurotoxicity. In a neonate, these include poor feeding, vomiting, lethargy, seizures, and encephalopathy and can mimic sepsis. (2)(3) Hyperammonemia may be precipitated by illness, such as sepsis, prematurity, liver immaturity, or inborn error of metabolism. Inborn errors of metabolism include primary urea cycle defect or secondary hyperammonemia in organic acidurias, mitochondrial disease, or substrate deficiencies. (2) Hyperammonemia is diagnosed using a free-flowing blood sample placed on ice. (4) The underlying cause for the hyperammonemia should be determined simultaneously with treatments aimed at lowering the ammonia level in the patient. Laboratory evaluation should include plasma glucose, complete metabolic panel, coagulation factors, plasma acylcarnitines, plasma amino acids, urine organic acids, and urine orotic acid. (4) An evaluation for infection and liver imaging may also be clinically indicated.

Regardless of the origin, prompt management of hyperammonemia in the newborn is important for neurodevelopmental outcomes. (5)(6) Early in a disease process, the different etiologic factors may be indistinguishable. (2) Initial medical management includes decreasing ammonia production and increasing ammonia removal. (4) Preventing catabolism with high-dextrose intravenous fluids with a target glucose infusion rate of 8 to 10 mg/kg per minute and limiting protein intake may help to decrease the production of ammonia. Protein

intake should be restricted for more than 24 to 48 hours because excessive protein restriction may lead to catabolism of endogenous protein. Nitrogen scavengers, such as sodium phenylbutyrate and sodium benzoate, will aid in the removal of ammonia. Amino acid supplementation may be helpful in primary urea cycle defects. The usefulness of dialysis in the treatment of hyperammonemia has been studied in patients with inborn errors of metabolism and sepsis. (1)(6)(7) (8) Indications for dialysis include blood ammonia levels of 400 to 500 $\mu\text{mol/L}$ in neonates and insufficient response to medical management, though others have used thresholds of 280 $\mu\text{g/dL}$ (200 $\mu\text{mol/L}$). (4)(9) In the management of hyperammonemia, it is extremely important to be cognizant of one's resources, because timely transfer of the neonate to a metabolic center or larger children's hospital with access to ammonia scavengers and dialysis may be necessary. Early consultation with a metabolic physician is recommended.

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Lessons for the Clinician

- Always consider hyperammonemia in the evaluation for neonatal sepsis, especially in the setting of poor feeding, vomiting, lethargy, seizures, and encephalopathy.
- Early management of hyperammonemia is crucial for improved neurodevelopmental outcomes and transfer to a metabolic center or larger children's hospital may be necessary.
- Lung rest strategies via extracorporeal membrane oxygenation are a potential solution for refractory air leak in a neonate.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and differential diagnosis of metabolic encephalopathy.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle.
- Recognize the clinical and laboratory manifestations of metabolic acidosis and metabolic alkalosis in infants.
- Know the causes and differential diagnosis of metabolic acidosis and metabolic alkalosis in infants.