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A Somnolent Neonate With Hypothermia and Posturing

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Case Presentation

A 2-day-old male infant is transferred to the neonatal intensive care unit with hypothermia and somnolence. He was born at 38 weeks gestation to a 37-year-old gravida 4, para 3 mother via spontaneous vaginal delivery. The pregnancy was notable for maternal history of bipolar disorder and schizophrenia and was complicated by limited access to prenatal care and a history of maternal herpes simplex virus-2 infection (with no active lesions at the time of delivery). Medications used during the pregnancy included alprazolam, quetiapine, and acyclovir. The delivery was uncomplicated. He was appropriate for gestational age (birth weight at 70th percentile, birth length at 73rd percentile, and head circumference at 13th percentile), and Apgar scores were 9 and 9, at 1 and 5 minutes of life, respectively. Physical examination at birth was unremarkable. The infant received routine care in newborn nursery and passed both the hearing screen and congenital heart disease screening. On his second day of life, he was found to be inappropriately nonreactive during his elective circumcision. Measured rectal temperature was 97°F (36°C) despite external warming, and he had intermittent tachypnea. His physical examination was notable for somnolence though muscle tone was appropriate, and the rest of neurological examination was nonfocal. He was transferred to the neonatal intensive care unit where sepsis workup was done, including blood cultures and herpes simplex virus polymerase chain reaction from plasma. No cerebrospinal fluid cultures were obtained despite repeated attempts at a lumbar puncture. Empiric antibiotic and antiviral treatment was initiated with ampicillin, ceftazidime, and acyclovir. Glucose, ionized calcium, complete blood count, urine drug screen, and the rest of liver panel tests, including aspartate transaminase, alanine transaminase, and bilirubin, were within normal limits. Over the next 2 days, he continued to tolerate his feeds by mouth without any difficulty but continued to have a waxing and waning mental status with observed periods of increased somnolence. On day of life 4, the infant developed isolated right upper extremity tonic posturing and intermittent bilateral lower extremity clonus. This prompted further workup, including chemistry and blood gas, which were significant for CO_2 of 17 mmol/L and capillary blood pH of 7.45, and pCO_2 (partial pressure of carbon dioxide) of 28.5 mm Hg. Shortly afterward, the medical team was notified of the abnormal findings on the infant's state newborn screen, specifically elevated citrulline (951 µmol/L, cutoff determined by the state laboratory is >70 µmol/L), concerning for citrullinemia, a urea cycle disorder. Follow-up laboratory results at that time showed elevated ammonia at 331 µmol/L (reference range for age = 54-94 µmol/L).

Final Diagnosis

Citrullinemia type I (CTLN1).

Hospital Course

Emergency treatment was initiated with discontinuation of enteral feeds, high-dextrose intravenous fluids, intravenous ammonia scavenging medications (sodium phenylacetate/sodium benzoate), and arginine infusion.[1] Diagnostic biochemical laboratory results confirmed elevated citrulline (2635 µmol/L, reference range = 2-41 µmol/L), elevated glutamine (2034 µmol/L, reference range = 238-842 µmol/L), and low arginine (6 µmol/L, reference range = 42-132 µmol/L) on plasma amino acids analysis. Urine orotic acid level was normal (0.5 mmol/mol creatinine, reference range = 0.3-2.8 mmol/mol creatinine). Molecular testing detected 2 heterozygous, known pathogenic variants in *ASS1*: a splice variant, c.1194-1G>C, and a missense variant c.836 G>A (p.Arg279Gln), consistent with a diagnosis of CTLN1. Because of the abnormal posturing, a continuous electroencephalography was obtained that showed moderate

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encephalopathy with epileptic activity, and subsequently treatment was started with levetiracetam with adequate seizure control. Since discharge, the patient has been managed with protein-restricted diet, oral ammonia scavenging medication, and arginine supplementation.

Discussion

Citrullinemia Type I

CTLN1 is a urea cycle metabolism defect caused by deficient activity of the enzyme argininosuccinate synthase (encoded by *ASS1*). The urea cycle functions in the liver to detoxify excess nitrogen in the form of ammonia (originating from endogenous and external protein breakdown) to nontoxic urea, which is then excreted in the urine. CTLN1 most commonly presents with hyperammonemia in the neonatal or infantile period ("classic citrullinemia"), but may present later in life, including adult-onset presentation (late-onset CTLN1 is typically associated with milder pathogenic variants and residual enzyme activity). It is inherited in an autosomal-recessive manner.[2] In classic CTLN1, newborns are initially well-appearing, but during the first days of life, they develop hyperammonemia with metabolic decompensation due to protein ingestion in the breast milk or formula that is exacerbated by the inherent neonatal catabolic state. Importantly, the clinical presentation (temperature instability, feeding intolerance, encephalopathy, and tachypnea) is strikingly similar to that of neonatal sepsis. Therefore, urea cycle disorders should always be considered in infants with sepsis-like presentation and no identifiable risk factors. Without treatment, hyperammonemia will result in cerebral edema, which can lead to abnormal posturing, encephalopathy, seizures, coma, and death depending on the level of ammonia and duration. Patients initially exhibit hyperventilation secondary to hyperammonemia but may later progress to hypoventilation and respiratory arrest as pressure on the brainstem increases.[3,4] This abnormal respiration will be typically associated with respiratory alkalosis (sometimes with a compensatory metabolic acidosis). Late-onset presentations may include intermittent hyperammonemic episodes (triggered by acute illness, catabolic states, or increased protein intake), with headache, vomiting, and altered mental status, or developmental delay, seizure disorder, chronic vomiting/feeding intolerance, and aversion to high-protein foods. Hyperammonemia should be considered in the setting of encephalopathy at any age, and an ammonia level should always be measured at the time of acute decompensation.[4] Plasma amino acid analysis is diagnostic and will reveal significant elevations of citrulline and glutamine, and reduced arginine.[2] Genetic testing with *ASS1* sequencing and deletion/duplication analysis can confirm the diagnosis.

Management

Emergency treatment should be initiated as soon as CTLN1 (or hyperammonemia) is suspected.[1-3,5] Management of acute decompensation includes immediate cessation of protein intake, high-dextrose infusion with or without insulin to promote anabolism, ammonia scavenging medications, and hemodialysis for rapid removal of ammonia. The patient's respiratory and neurologic status should be closely monitored, as the risk of increased intracranial pressure is significant. Chronic management of CTLN1 includes (1) protein-restricted diet with nutrition optimized to promote growth and prevent catabolism, (2) repletion of urea cycle intermediates, and (3) administration of ammonia scavenging agents.[1,5] Liver transplantation has been performed in this patient population in an attempt to restore the metabolic defect and to eliminate the risk of recurrent hyperammonemia episodes.[6,7]

Conclusion

Inborn errors of metabolism including organic acidemias, fatty acid oxidation disorders, urea cycle disorders, and cobalamin metabolism defects are rare but potentially treatable causes of altered mental status in the newborn period. Urea cycle defects most typically present in infancy but may have later onset including adult-onset presentations. They should be considered in the differential diagnosis of infants with sepsis-like presentations or in children who present with altered mental status and no identifiable risk factors, as they may be associated with irreversible neurological impairment or death if appropriate treatment is not initiated in a timely manner. Additionally, clinicians should recognize the utility of the newborn screening in reducing mortality and morbidity in inborn errors of metabolism and the importance of close and routine follow-up of results.

Author Contributions

JMN and SK conceived the study and drafted the manuscript, KEG and RM critically revised it, and all authors read and approved the final version.

Declaration of Conflicting Interests

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