Clinical Reasoning:

An encephalopathic 3-day-old infant

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SECTION 1

A full-term, 3-day-old infant presented to the emergency department with poor feeding, increased work of breathing, and encephalopathy 1 day after having been discharged from the hospital in good health.

Pregnancy and labor were uneventful, and birth was by spontaneous vaginal delivery. Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. The infant's nursery course was unremarkable. On the evening after discharge, his parents noted he became sleepy and lost interest in feeding over the next 12 hours. The following morning, they noted his breathing was rapid, so they brought him to the emergency room. His general examination at presentation revealed suprasternal retractions, a flat anterior

fontanelle, and an enlarged liver. Neurologic examination was notable for marked encephalopathy; he did not open his eyes or react to stimulation. His suck was weak and poorly coordinated and his gag reflex was absent. He lay in a frog-legged position; however, passive tone was increased in all 4 extremities. There were no spontaneous movements or motor response to noxious stimulation. Deep tendon reflexes were symmetrically brisk without ankle clonus.

Questions for consideration:

1. What is the differential diagnosis for an infant who is initially well but becomes encephalopathic at several days of life?
2. What are the initial steps to evaluate an encephalopathic neonate?

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SECTION 2

The differential diagnosis for encephalopathy in a previously well 3-day-old full-term neonate includes infection (sepsis, meningitis, encephalitis), a vascular event such as a sinovenous thrombosis, nonaccidental trauma, epilepsy leading to nonconvulsive status, and metabolic disturbances secondary either to inborn errors of metabolism or exogenous causes (such as inaccurate preparation of infant formula).

A careful review of the history can help identify infectious risk factors, such as a maternal history of group B streptococcus colonization, prolonged rupture of membranes, or labor complicated by chorioamnionitis. Absence of herpetic lesions does not exclude the diagnosis of herpes simplex virus infection. A bulging fontanelle would suggest elevated intracranial pressure from either infection or intracranial hemorrhage.

Initial laboratory investigations to consider include serum electrolytes, complete blood count, arterial blood gas, lactate, pyruvate, ammonia, transaminases, total and direct bilirubin, coagulation

studies, quantitative amino acids, carnitine levels, and acylcarnitine profile. Urine should be sent for routine urinalysis, urine organic acids, and orotic acid. A sepsis workup, including blood cultures, urine cultures, and CSF analysis, should be pursued. An urgent bedside head ultrasound can evaluate for cerebral hemorrhage. If there is concern for impending herniation or other neurosurgical emergencies, CT can be performed; however, MRI is preferred in children if available and if the patient is stable.

This infant had a noncontrast head CT in the emergency room, which was notable for cerebral edema. Ammonia (venous sample) was markedly elevated at 770 $\mu\text{mol/L}$ (reference $<49 \mu\text{mol/L}$). Arterial blood gas showed a mild respiratory alkalosis. Serum glucose and anion gap were normal.

Questions for consideration:

1. What are the neurologic consequences of hyperammonemia?
2. What is the differential diagnosis for neonatal hyperammonemia?
3. What are the initial treatment steps for neonatal hyperammonemia?

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SECTION 3

Elevated ammonia levels are toxic to the brain. Acute hyperammonemia rapidly leads to encephalopathy, cerebral edema, and, if untreated, death.¹ Cerebral edema is often apparent on neuroimaging and may result from accumulation of glutamine in astrocytes.¹ Neonates typically fare the worst, but significant neurologic injury can occur after hyperammonemic crisis even in previously asymptomatic adults.¹

In a neonate, the differential diagnosis for hyperammonemia includes both inherited (e.g., urea cycle defects) and acquired (e.g., valproate usage) etiologies (table 1). In this infant, the combination of a highly elevated serum ammonia level, respiratory alkalosis, normal serum glucose, and normal anion gap suggested a urea cycle defect.

The acute management of hyperammonemic crisis involves 1) preventing further ammonia production by discontinuing protein intake and 2) urgent removal of accumulated ammonia via dialysis and administration of sodium benzoate and sodium phenylacetate.¹ These medications may improve survival by providing an alternative pathway for ammonia precursors to be excreted in the urine.² Generous fluid intake can also support urinary ammonia excretion. Encephalopathy makes seizures difficult to de-

Table 1 Differential for hyperammonemia in a newborn^{1,9,10}

Diagnosis	Initial laboratory or clinical findings
Urea cycle defect	Normal serum glucose and bicarbonate (no anion gap); respiratory alkalosis often present
Organic acidurias	Lactic acidosis
Disorder of pyruvate metabolism	Lactic acidosis
Disorder of fatty acid metabolism	Nonketotic hypoglycemia ^a
Transient hyperammonemia of the newborn	Premature infant with respiratory distress
Secondary or exogenous causes	Renal or hepatic failure (severe), valproate usage

^a It is essential to draw serum glucose prior to starting dextrose containing fluids or this diagnosis can be missed.

Table 2 Biochemical pattern of specific urea cycle defects

Deficient enzyme	Amino acids	Organic acids
OTC	Low or undetectable citrulline Low arginine	High orotic acid
CPSI	Low or undetectable citrulline Low arginine	Low orotic acid
NAGS	Low arginine	
ASS	Very high citrulline Low arginine	High orotic acid
ASL	High citrulline High argininosuccinic acid	High orotic acid Very high argininosuccinic acid
Arginase	Very high arginine	

Abbreviations: ASL = argininosuccinic acid lyase; ASS = argininosuccinic acid synthetase; CPSI = carbamoyl phosphate synthetase I; NAGS = *N*-acetylglutamate synthetase; OTC = ornithine transcarbamylase.

tect clinically and therefore continuous EEG is helpful. Consultation with a metabolic expert should be sought urgently to assist with management.

When this infant arrived at our tertiary care facility, EEG showed intermittent multifocal seizures. He was treated with phenobarbital. His ammonia peaked at $>1,000 \mu\text{mol/L}$. He was treated urgently with sodium benzoate, sodium phenylacetate, and hemodialysis. His metabolic labs revealed a low citrulline, high orotic acid, high glutamine and alanine, and normal arginine. This biochemical profile was diagnostic for ornithine transcarbamylase (OTC) deficiency, a urea cycle defect (table 2). There was no maternal history of protein intolerance, nor was there a family history of recurrent miscarriages, sudden unexplained death, or parental consanguinity.

Questions for consideration:

1. What is the purpose of the urea cycle and how do neonates with a urea cycle defect present?
2. What are the predictors of survival and neurologic outcome after an episode of neonatal hyperammonemia?
3. What are the genetics of OTC deficiency?

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Figure The urea cycle

ASL = argininosuccinic acid lyase; ASS = argininosuccinic acid synthetase; CPSI = carbamoyl phosphate synthetase I; NAGS = N-acetylglutamate synthetase; OTC = ornithine transcarbamylase.

SECTION 4

The urea cycle removes excess nitrogen by conversion into water-soluble urea for renal excretion (figure). A deficiency in any one of the 6 enzymes involved can constitute a urea cycle defect.¹ The inheritance pattern is autosomal recessive, except for OTC, which is X-linked. Alternatively, a patient may have a de novo mutation.¹ Elevated ammonia is the hallmark of a urea cycle defect.¹

Presentation in the neonatal period suggests a complete enzyme deficiency, while patients with partial deficiencies may only come to attention in adulthood. Neonates present with encephalopathy, seizures, hypotonia, and poor feeding after protein intake in the form of milk or formula.

To diagnose the specific urea cycle defect, plasma amino acids, urine organic acids, and urine orotic acid should be ordered (table 2).

The survival rate for acute neonatal hyperammonemia due to a urea cycle defect is 73%, significantly lower than the 98% survival rate of older patients.² Coma at admission is a negative prognostic indicator for survival, as is having a peak ammonia level $>1,000 \mu\text{mol/L}$.²

In one study, neurodevelopmental deficit after the initial hyperammonemic crisis related to the peak ammonia concentration; those neonates with ammonia levels greater than $350 \mu\text{mol/L}$ had severe deficits or died.³ Only those whose peak ammonia level was $<180 \mu\text{mol/L}$ did not develop neurocognitive impairment.³ In another study, long-term neurologic sequelae related to the duration of hyperammonemia but not the peak level.⁴

OTC deficiency is the most common urea cycle defect, with an incidence of 1 in 14,000.⁵ It accounts for almost half of all neonatal onset cases.³ Males typically present in the neonatal period and have a higher mortality.² Female heterozygotes can become symptomatic, with severity and timing dependent on the pattern of hepatic lyonization. Neonatal presentation is associated with poor neurologic outcome.¹ Orthotopic liver transplant can be curative, but will not reverse neurologic injury already sustained.¹

Question for consideration:

1. What screening mechanisms are in place to prevent neonatal hyperammonemic crisis?

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SECTION 5

Current extended newborn screening panels use tandem mass spectrometry to detect abnormal concentrations of analytes associated with 2 of the 6 urea cycle defects: argininosuccinic acid synthetase and argininosuccinic acid lyase deficiencies. Arginase deficiency, the most clinically subtle of the urea cycle defects, has also been detected by these methods, but newborn screening may not reliably detect partial defects.⁶ The tandem mass spectrometry used in newborn screening does not directly detect OTC, carbamoyl phosphate synthetase I, or *N*-acetylglutamate synthetase deficiencies⁷; however, specific biochemical abnormalities on the newborn screen can point toward a diagnosis.

Newborn screening results can take several weeks to be reported. Because newborns are typically discharged from the hospital on the first or second day of life, symptoms usually do not develop until the infant is home. Thus, newborn screening may not detect a urea cycle defect early enough to prevent all neonatal hyperammonemic crises and, instead, clinicians must remain astute to the nonspecific symptoms of hyperammonemia in a newborn.⁷

If there is a known family history of a urea cycle disorder, prenatal testing is available.⁸ Infants with OTC deficiency may have a more favorable neurologic outcome if hyperammonemic crisis is prevented by early detection.⁷

Newborn screening results in this infant were diagnostic for OTC deficiency. The patient was discharged home on day of life 39. At that time, he was seizure-free and his feeding was improving. His neurocognitive development will be followed closely. Molecular genetic testing and enzyme testing had not yet been sent. The mother plans to be tested to see if she is an OTC mutation carrier (vs a sporadic mutation in the infant), as this could have family planning or screening implications for multiple family members.

DISCUSSION

This case underscores the importance of considering hyperammonemia in the differential for a sick neonate. Diagnosis of a urea cycle defect is often delayed as these infants are frequently initially mistakenly assumed to be septic. The key diagnostic clue is that this breastfed infant deteriorated after starting to feed (and therefore ingesting protein), as maternal milk supply typically comes in on the second or third day postpartum.

In infants with acute hyperammonemia, immediate cessation of protein intake and implementation of ammonia-lowering therapy are critical, while further diagnostic testing is ongoing, as peak ammonia level and duration of hyperammonemia are correlated with neurologic outcome.

Neuroprotective strategies during hyperammonemic crises, such as therapeutic hypothermia, or the administration of medications that act at the NMDA receptor to block excitotoxicity, are under investigation.⁷

AUTHOR CONTRIBUTIONS

Dr. Gelfand developed the study concept and analysis/interpretation of data and participated in drafting/revising the manuscript. A. Szniewajs participated in drafting/revising the manuscript. Dr. Glass participated in drafting/revising the manuscript. Dr. Jelin participated in drafting/revising the manuscript. Dr. Sherr participated in drafting/revising the manuscript, study concept or design, analysis or interpretation of data, and study supervision.

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DISCLOSURE

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