An Infant With Seizures and Acidosis

Robert Listernick, MD

CASE REPORT

A 2-month-old girl was admitted for evaluation of decreased oral intake. For 2 days prior to admission, she was noted to have a poor appetite and to have become increasingly sleepy. On the evening of admission, she had a convulsive seizure at another hospital prompting transfer to Children’s Memorial Hospital.

She was the 2.4 kg product of a 36-week gestation to a 27-year-old G1P1 woman. It was a spontaneous vaginal delivery, and there were no perinatal problems. The family history was unremarkable. There was no history of consanguinity.

On examination, she was a hypotonic, lethargic child. Weight was 3.26 kg, below the 5th percentile, length was below the 5th percentile, and head circumference was in the 25th percentile. Review of her growth chart indicated that she had gained no weight over the last month. Vital signs were normal. The general physical examination was normal. On neurologic exam, she had profound hypotonia and a weak cry. Strength was normal. The deep tendon reflexes and cranial nerves were normal. She had a normal gag reflex.

DISCUSSION

Robert Listernick, MD, moderator: As general pediatricians, what should go through our minds when faced with a 2-month-old baby who has stopped eating?

Sharon Unti, MD, residency program director: There is obviously a broad differential diagnosis. My most immediate concern would be an intercurrent illness or sepsis. Once she had a seizure, additional concerns would be a central nervous system (CNS) infection (bacterial or viral, such as Herpes simplex encephalitis) and nonaccidental trauma.

Barbara Burton, MD, geneticist: Metabolic diseases may present with a clinical picture very similar to sepsis. This child may have been encephalopathic from severe acidosis, hyperammonemia, or abnormal plasma amino acids. Careful exploration of the antecedent history might detect clues of longer standing disease such as poor feeding or weight gain.

Doug Nordli, MD, pediatric neurologist: Mental status may be altered by damage to the brainstem or by a diffuse cortical process. Since this child had a normal examination of the cranial nerves, no lateralizing signs, and had a seizure, I would suspect the latter. Such a diffuse cortical injury might have been caused by any of the above conditions, or by a toxic ingestion. Hypotonia in an infant may be a generalized response to a broad number of illnesses, including this child’s obvious malnutrition.

Joe Sullivan, MD, chief pediatric resident: When I first heard the story, I thought about infant botulism. The subacute presentation, poor feeding, weak cry, and hypotonia all fit this diagnosis. If she had been given an aminoglycoside at the outside hospital, this might have precipitated an apneic event and a subsequent hypoxic seizure. Aminoglycosides are known to potentiate the effect of botulinum toxin at the neuromuscular junction. However, her normal cranial nerve exam and deep tendon reflexes don’t fit with diagnosis.

Dr. Listernick: How should this child be evaluated?

Dr. Sullivan: First, she should be evaluated for the possibility of sepsis and given broad-spectrum antibiotics pending culture results. She should also be evaluated for the presence of a CNS infection, including Herpes simplex encephalitis. This should include a lumbar puncture, a test
for herpes viral DNA, EEG, and MRI scan of the head. I would administer intravenous acyclovir until this diagnosis is excluded. Finally, I would perform some basic metabolic screening tests looking for a cause of seizures and encephalopathy, including serum glucose, electrolytes, calcium, and ammonia.

Dr. Listernick: Bacterial cultures of the blood and cerebrospinal fluid were sterile. Results of the lumbar puncture were normal. The test for herpes viral DNA was negative. The MRI scan of the head was normal. Intravenous antibiotics and acyclovir were discontinued once these results were available. The initial EEG was normal. Two days later, subtle clinical seizures were observed; a second EEG showed numerous focal clinical and electroencephalographic seizures arising during sleep and prolonged focal epileptiform discharges arising from the right temporal area, accompanied by right eyelid twitching. Finally, the ammonia, glucose, and calcium were normal. However, she had a persistent non-anion gap metabolic acidosis. Representative electrolytes were: sodium 144 mEq/L, potassium 4.2 mEq/L, chloride 117 mEq/L, bicarbonate 17 mEq/L, serum pH 7.27. The BUN and creatinine were normal.

Obviously, there are several issues. Let’s first address the seizures and the encephalopathy.

Dr. Nordli: Neurologic evaluation of a 2-month-old infant may be relatively insensitive from the diagnostic standpoint because one has a limited window into CNS function at this age. EEG in the 2-month-old is similarly insensitive. Infants of this age may have pronounced cortical pathology but have an unremarkable EEG, as this child did originally. The normal background gradient of EEG activity begins to establish itself at 3 months. The second EEG demonstrates that something is irritating the CNS but does not give a clue as to etiology. Because there is no evidence of CNS infection, I would start looking for metabolic disease. As Dr. Burton pointed out, metabolic disease should be one of the first considerations in any infant who has “the dwindles” over several weeks culminating in seizures. This child’s picture is a classic presentation of a metabolic encephalopathy.

Dr. Listernick: What do you make of the persistent non-anion gap metabolic acidosis?

Richard Cohn, MD, pediatric nephrologist: This child has a hyperchloremic acidosis with normal kidney function. Evaluation of the urine electrolytes will help differentiate between renal and nonrenal causes of metabolic acidosis. If the renal tubular function is normal, hydrogen ions are secreted in the distal tubule and bicarbonate is reabsorbed in the proximal tubule. In the normal state, the sum of the urinary concentrations of sodium and potassium is lower than that of chloride. This is called a “negative urinary anion gap”; the missing cation is hydrogen ion in the form of ammonium. In renal acidosis, the sum of the urinary concentrations of sodium and potassium is higher than that of the urine chloride, the so-called “positive urinary anion gap.” The urine pH may be alkaline or acidic in renal tubular acidosis (RTA) depending upon the site of the defect.

Dr. Listernick: The urine sodium was 50 mEq/L, potassium 6 mEq/L, chloride 23 mEq/L, bicarbonate less than 5 mEq/L, and the urine pH was 5.3.

Dr. Cohn: These data are consistent with proximal RTA. This results from a defect in the proximal tubule’s ability to reabsorb bicarbonate. Generally, when the serum bicarbonate level exceeds 17 mEq/L, individuals with proximal RTA do not completely reabsorb bicarbonate in the proximal tubule; the urine will be alkaline despite systemic acidosis. In more severe systemic acidosis, proximal tubular bicarbonate will be completely reabsorbed and the urine pH will be acidic. In contrast, the defect in distal RTA is an inability of the distal tubule to secrete hydrogen ion; as a result, the urine is always alkaline. Isolated RTA generally presents in the first year of life with failure to thrive or linear growth failure. Symptoms may include vomiting, constipation, recurrent dehydration, or poor oral intake.

Dr. Listernick: What is the treatment of proximal RTA?

Dr. Cohn: These children generally need large doses of bicarbonate (or other alkali) to overcome the systemic acidosis and continued bicarbonate wasting. Although proximal RTA can be an isolated condition, it may be part of Fanconi syndrome, a generalized defect in proximal tubular reabsorption, or can be secondary to a number of underlying diseases (including cysti-
nosis, Lowe syndrome, galactosemia, mitochondrial disorders). Because of this child's encephalopathy, we suspected that this was part of an underlying systemic disease. In fact, there was another clue to this child's basic problem. The urine anion gap is very high at 33 due to a "missing anion."

Dr. Listernick: Although she clearly had a nonanion gap acidosis, the encephalopathy and seizures led us to measure the serum lactate. Serum lactic acid levels were uniformly elevated, ranging from 4.8 to 9.2 mEq/L (normal: 0.5-2.2 mEq/L), accounting for the unexplained anion.

Joel Charrow, MD, geneticist: In the evaluation of possible lactic acidosis, one must first make sure that the levels aren't spuriously elevated. Serum lactate levels may be elevated because of ischemia in the forearm during phlebotomy or due to red blood cell anaerobic metabolism in improperly stored blood. It's best to obtain either an arterial or free-flowing venous sample, which is placed in the correct tube on ice as rapidly as possible. Lactic acidosis primarily is found in one of three classes of disorders: organic acidemias, such as methylmalonic or propionic acidemia; disorders of pyruvate metabolism, specifically pyruvate dehydrogenase complex deficiency and pyruvate carboxylase deficiency; or disorders of the energy-producing respiratory chain.

Dr. Listernick: Can these disorders be distinguished clinically?

Dr. Charrow: The clinical syndromes have tremendous overlap. For this reason it's important to undertake a very systematic comprehensive approach in the evaluation of lactic acidosis so that nothing is overlooked. Pyruvate dehydrogenase complex deficiency can present with either minimal lactic acidosis or with severe life-threatening acidosis, with lactate levels between 20 to 30 mEq/L (normal 1.5-3.0 mEq/L). Many of these disorders may have associated neurologic symptoms such as hypotonia, developmental delay, or seizures. Pyruvate carboxylase deficiency may be associated with hypoglycemia. Disorders of the energy-producing respiratory chain should be suspected whenever multiple organ systems are affected.

Dr. Listernick: What are the respiratory chain disorders?

Dr. Charrow: The respiratory chain includes groups of proteins that produce energy for the cells. Although mitochondrial genes encode some of its components, nuclear genes also encode many respiratory chain proteins. We can identify abnormalities of mitochondrial DNA in peripheral white blood cells. Unfortunately, only a few nuclear-encoded respiratory chain genes have been identified. If we are unable to identify a mitochondrial deletion or mutation, the next step would be to perform a skin or muscle biopsy. A functional assessment of the respiratory chain can be performed on either cultured fibroblasts or muscle cells.

Dr. Listernick: When should clinicians suspect one of the mitochondrial disorders?

Dr. Charrow: These disorders should be thought of whenever there's lactic acidemia or involvement of multiple highly energy dependent systems, including brain, skeletal muscle, heart, kidney, and liver.

Dr. Nordli: Most of these disorders affect the CNS at some time. A common manifestation of depleted energy reserves is encephalopathy punctuated by seizures.

Dr. Cohn: Would magnetic resonance spectroscopy (MRS) be helpful in establishing the diagnosis?

Dr. Nordli: In many of these syndromes, MRS demonstrates marked elevation of lactate, particularly during crises. Alternatively, one could directly measure cerebrospinal fluid lactate levels.

Dr. Listernick: The infant was discharged to home to receive nasogastric feedings. She required extremely large doses of bicarbonate in order to maintain normal serum bicarbonate levels. Several weeks after discharge, we learned that she had the NARP (neurologic disease, ataxia, retinitis pigmentosa) mitochondrial mutation.

Dr. Charrow: There are a number of eponyms for the mitochondrial disorders including NARP, MELAS (mitochondrial encephalomyopathy, lactic acidemia, stroke), MERRF (myoclonic epilepsy, ragged red fibers), and Leigh disease (subacute necrotizing encephalopathy). These phenotypes were described long before the specific mutations had been identified. Over time, we've come to realize that there is a rather broad range

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of clinical disease associated with a specific genotype. For example, this infant began having brief apneic events at home after being discharged. She became increasingly encephalopathic and died. What genetic counseling can we offer this family about their risk of having a similarly affected child in the future?

**Dr. Charrow:** Genetic counseling for mitochondrial disorders is extremely difficult. Within every cell there are multiple mitochondria, and within every mitochondrion, there are multiple copies of the mitochondrial chromosome. The proportion of mitochondria within each cell that have the abnormal gene may vary greatly. When the proportion of mutated genes exceeds a certain unknown threshold in a particular tissue, organ dysfunction may occur. The variation from tissue to tissue of abnormal mitochondria explains the enormous clinical heterogeneity of these diseases.

The mother may carry the mitochondrial mutation and be at risk for a late-onset form of the disease. Alternatively, she may have a more favorable balance of mutated and wild-type mitochondrial genes. In addition, we have no way of predicting what the burden of the mutation will be on future children.

Even if prenatal diagnosis were attempted successfully, we would have no way of predicting the child’s phenotype.

**Dr. Listernick:** That’s truly depressing. Thank you everybody.

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