Neonatal Seizures

Soothing a Burning Topic

Matthew D. Thornton, MD, Lei Chen, MD, and Melissa L. Langhan, MD

Abstract: Neonatal seizures are a potentially life-threatening pediatric problem with a variety of causes, such as birth trauma, asphyxia, congenital anomalies, metabolic disturbances, infections, and drug withdrawal or intoxication. Thorough and timely evaluations of such patients are necessary to identify and treat the underlying etiology, therefore reducing potential morbidity and mortality. We review neonatal seizures and hypocalcemia and present the case of a 6-day-old male infant who presented to a tertiary pediatric emergency department with seizure-like episodes. He was found to have markedly low serum calcium, magnesium, and parathyroid hormone concentrations, as well as a significantly elevated serum phosphate concentration. The etiology of these abnormalities was found to be maternal ingestion of extremely high doses of calcium carbonate during the third trimester of her pregnancy, an occurrence that has been reported only once in the literature. Education pertaining to the dangers of excessive calcium carbonate intake during pregnancy may be an important piece of anticipatory guidance for pregnant mothers with symptoms of gastroesophageal reflux, and questioning the mother of a neonate presenting with seizures about such over-the-counter medications may help to elucidate the diagnosis.

Key Words: neonatal seizure, hypocalcemia, calcium carbonate, pregnancy, reflux, hypoparathyroidism, hypomagnesemia

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Neonatal seizures occur in approximately 1.8–3.5/1,000 live births in the United States, making neonates a high-risk pediatric population.[1] These episodes have different etiologies, presentations, electroencephalogram (EEG) patterns, and treatments than seizures in older children. They are medical emergencies with high potential for mortality and neurodevelopmental morbidity.[2,3] An etiology is found for 90% of neonatal seizures. The most common cause is hypoxic-ischemic encephalopathy secondary to perinatal asphyxia, which accounts for approximately two thirds of all neonatal seizures.[3] Other causes, in descending order of incidence, are intracranial hemorrhage, central nervous system infection, malformations of cortical development, and metabolic disturbances such as hypoglycemia, hypocalcemia, and hypomagnesemia.[2] Less common causes include inborn errors of metabolism, benign neonatal convulsions, and drug withdrawal or intoxication. The ability to quickly determine and treat such a cause in the emergency department may save the patient unnecessarily invasive and potentially harmful diagnostic tests, as well as reduce long-term morbidity resulting from the seizures. We present only the second case report of a rare etiology, leading to neonatal hypocalcemia and seizures.

From the Department of Pediatrics, Section of Emergency Medicine, Yale University School of Medicine, New Haven, CT.

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Reprints: Matthew D. Thornton, MD, 100 York Street, Suite 1F, New Haven, CT 06511 (e-mail: matthew.thornton@yale.edu).

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CASE

A 6-day-old white male infant was referred to our pediatric emergency department (PED) from his primary care pediatrician after being seen in her office for the chief complaint of shaking episodes. The patient was reportedly in his mother's arms when he suddenly stared forward and shook for 15 to 30 seconds. The mother noted both upper extremities shaking, but was unsure if his lower extremities were shaking as well. After the incident, the patient fell asleep briefly, but was then acting normally according to the mother. He was brought to his pediatrician's office, where he appeared well and tolerated a feed without difficulty. The patient was subsequently sent to the PED for further evaluation and management.

In the PED, the patient was well appearing; had a temperature of 37.5°C, a heart rate of 132 beats/min, a blood pressure of 75/29 mm Hg, a respiratory rate of 44 breaths/min, and had a pulse oximetry reading of 100% on room air. Pertinent findings on physical examination were jaundice of the face and a mildly increased Moro reflex. The patient had normal suck and grasp reflexes and was moving all extremities equally without focal deficits. Chvostek sign was negative, and there was no clonus or stridor. The anterior fontanelle was flat, and there were no bruises or other external signs of trauma. In addition, there were no dysmorphic features or hepatosplenomegaly.

Approximately 30 minutes after arrival, the patient had an episode of shaking witnessed only by his parents that spontaneously resolved within 30 seconds. Twenty minutes later, the patient had a third episode, witnessed by his nurse and physician. The episode consisted of approximately 15 seconds of lip smacking, leftward eye deviation, and left upper extremity jerking. There was no postictal state or sleepiness.

Further history revealed a 39-week gestation infant born by repeat cesarean section to a 41-year-old gravida 3, para 3 mother. The pregnancy was complicated by diet-controlled maternal gestational diabetes. Per the mother, her blood glucose measurements were generally 80 to 120 mg/dL with occasional postprandial spikes up to 160 mg/dL. Maternal history also revealed gastroesophageal reflux disease for which she took omeprazole. This was discontinued in the pregnancy's first trimester, as recommended by her obstetrician. She instead took calcium carbonate (Ultra Strength Tums) for symptomatic relief, as well as prenatal vitamins during pregnancy. Prenatal laboratory values were reported as normal, including a negative group B streptococcus screen.

The patient had Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. He spent 2 days in the neonatal intensive care unit for hypoglycemia requiring intravenous dextrose and hyperbilirubinemia secondary to ABO incompatibility that required

less than 24 hours of phototherapy. The patient was discharged home on his third day of life.

The parents reported no prior shaking movements. The patient was breast and bottle feeding every 3 hours with normal output of both urine and stool. His weight on presentation was 4.4 kg (birth weight, 4.2 kg). The day before presentation, the patient had a total bilirubin level of 7 mg/dL.

There was no family history of seizures, strokes, migraines, bleeding disorders, or autoimmune problems. He was being cared for by his parents and his 20-year-old half-brother. The only other person living at home was his 3-year-old sister, who was healthy. The parents denied any history of trauma.

An evaluation to determine the etiology of the seizures was undertaken. Fingerstick glucose measurement after the seizure was 75 mg/dL. Because of difficulty obtaining blood, other results were not immediately available, but specimens were sent to the laboratory. A computed tomography (CT) scan of the brain was performed, while laboratory results were pending. This revealed no evidence of acute intracranial abnormality. Chest radiograph showed an unremarkable cardiothymic silhouette and no consolidations, atelectasis, effusions, or osseous abnormalities. Neurology was consulted and recommended a loading dose of phenobarbital, EEG monitoring, and potentially magnetic resonance imaging and lumbar puncture pending laboratory results and changes in clinical status.

Laboratory results were available shortly after the CT scan and neurology consult. These revealed a normal complete blood count and liver function tests, other than a total bilirubin of 6.44 mg/dL. Serum electrolytes were significant for serum calcium, 5.2 mg/dL (reference range, 8.8–10.2 mg/dL); ionized calcium, 2.8 mg/dL (reference range, 4.48–5.28 mg/dL); magnesium, 1.1 mg/dL (reference range, 1.7–2.6 mg/dL); and phosphate, 10.4 mg/dL (reference range, 2.7–8.0 mg/dL). Other electrolytes were unremarkable. An electrocardiogram revealed no prolongation of the QT interval. The patient's vitamin D and parathyroid hormone (PTH) concentrations were obtained, and the mother underwent measurement of PTH and serum calcium levels. The patient had normal concentrations of both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, but the PTH level was 6 pg/mL (reference range, 10–69 pg/mL). His mother's serum calcium was 9.9 mg/dL, and PTH level was less than 3 pg/mL.

Additional history revealed that the mother ingested up to 20 Ultra Strength Tums per day during her third trimester. Each pill contains 1000 mg of calcium carbonate, of which 400 mg is elemental calcium. She was therefore taking up to 8000 mg of elemental calcium per day. The current recommendation for pregnant or lactating women between the ages of 19 and 50 years is 1000 mg/d.[4]

The patient was admitted to the pediatric intensive care unit, had a central line placed, and was given 2 bolus infusions of calcium gluconate and 1 of magnesium sulfate. He then received an infusion of calcium gluconate and was transitioned to oral calcium glubionate on the fourth hospital day. An EEG performed the day after admission was normal for age without epileptiform activity, and he had no further seizure activity. Serum calcium, phosphate, and magnesium concentrations remained stable. He was discharged on hospital day 5 on oral calcium glubionate and a low phosphate formula. Three weeks after initial presentation, the patient had normal PTH and serum calcium concentrations, and the calcium supplements were discontinued.

DISCUSSION

Emergency medicine physicians are often familiar with common causes of neonatal seizures but may be less knowledgeable about the potential etiologies of hypocalcemia in this age group. For this reason, we will briefly review the etiologies of neonatal seizures and then take a more in-depth look at the differential diagnosis for neonatal hypocalcemia (Table 1).

As previously mentioned, the most common cause of neonatal seizures is hypoxic-ischemic encephalopathy secondary to perinatal asphyxia, which accounts for approximately two thirds of all neonatal seizures.[3] These seizures generally occur within 12 hours of birth, with the remaining having onset at 24 to 48 hours of life.[2,5] These seizures are therefore usually noted before initial discharge from the hospital and rarely present for the first time to the emergency department.

Seizures due to subarachnoid, intraparenchymal, or subdural hemorrhage can be seen in term neonates. Most seizures due to intracranial hemorrhage from birth trauma occur from days of life 2 to 7.[5] Well infants who seize on day of life 2 to 3 often have subarachnoid hemorrhage as the cause.[5] Neurosonography is an excellent tool for detection of intraventricular and parenchymal hemorrhage, but there must be a radiologist with experience in pediatric neurosonography readily available for this to be useful. Furthermore, an ultrasound would be unable to detect a subdural or subarachnoid hemorrhage.[5] It is important for the emergency medicine physician to keep in mind that neonates are at risk for nonaccidental trauma that could lead to intracranial hemorrhage. A head CT is indicated if preliminary tests are nondiagnostic, or there are any signs of trauma.[5]

Central nervous system infections are an important etiology to consider when evaluating a neonate with seizures. If the cause of neonatal seizures is unknown, meningitis should always be considered. Both bacterial and viral infections of the central nervous system in neonates can lead to seizures. The most common bacterial causes are group B streptococcus and *Escherichia coli*.[2] Meningoencephalitis secondary to intrauterine infections such as toxoplasmosis, herpes simplex,

TABLE 1. Potential Causes of Neonatal Hypocalcemia

Etiology	Serum Calcium Concentration	Serum Phosphate Concentration	Serum PTH Concentration	Serum Magnesium Concentration
Increased phosphate load	↓	↑	Normal or ↑	Normal or ↓
Hypomagnesemia	↓	Normal or ↑	Normal or ↓	↓
Vitamin D deficiency	Normal or ↓	Normal or ↓	↑ or Normal	Normal or ↓
Hypoparathyroidism	↓	↑	↓	Normal or ↓
Pseudohypoparathyroidism/ PTH resistance	Normal or ↓	↑	↑	Normal

coxsackievirus, or cytomegalovirus may also lead to seizures in neonates.[2,5] Obtaining a detailed maternal history and the results of her prenatal laboratory tests, when possible, may provide clues to these diagnoses.

Metabolic disturbances such as hypoglycemia, hypocalcemia, and hypomagnesemia should be included in the differential diagnosis of a neonate with seizures. Although they are not as common as many other causes, they are often readily treatable. When metabolic disturbances are the primary cause of neonatal seizures and are treated appropriately, they are rarely associated with significant long-term consequences.[2]

Less common causes include inborn errors of metabolism, benign neonatal convulsions, and drug withdrawal or intoxication. A thorough family history, including questioning about any parental consanguinity or death in other infants, may provide information about the possibility of inborn errors of metabolism. If possible, obtaining results of the newborn metabolic screen can also be helpful. Neonates with intrauterine exposure to chronic opioids, alcohol, benzodiazepines, or barbiturates may suffer from a withdrawal syndrome that may include seizures during the first week of life.[6]

Neonatal hypocalcemia causing seizures, such as was seen in our patient, is a rare condition that requires prompt recognition and treatment. During the third trimester, umbilical cord blood contains a significantly higher level of total calcium than maternal serum, as calcium is actively transferred from the mother to the fetus. Thus, in late pregnancy, the fetus is hypercalcemic with respect to its mother.[7] During the first 48 hours after birth, neonatal serum calcium decreases, while PTH increases.[7] Normal levels of serum calcium are achieved by 72 hours.[8] There are, however, many potential scenarios that can disrupt this normal balance.

Hypocalcemia is defined as total serum calcium of less than 7 mg/dL in term infants.[8] Early hypocalcemia presents within 72 hours of birth and is commonly seen with prematurity, infants of diabetic mothers, perinatal asphyxia, and intrauterine growth restriction.[9] Proposed mechanisms of hypocalcemia in infants of diabetic mothers include increased calcium demands of macrosomic infants and hypomagnesemia inducing functional hypoparathyroidism and hypocalcemia. These patients typically present with symptoms in the first 48 to 72 hours after birth.[9,10] Because our patient did not have symptomatic hypocalcemia until day 6 of life, this would be unlikely.

Late hypocalcemia is defined as hypocalcemia occurring after the third day of life. This is a rare condition and typically presents at the end of the first week. Common causes include increased phosphate load, hypomagnesemia, vitamin D deficiency, PTH resistance, hypoparathyroidism, metabolic syndromes, and iatrogenic causes.[9]

Our patient's low serum calcium, PTH, and magnesium concentrations, as well as hyperphosphatemia, all point toward a diagnosis of hypoparathyroidism. Classically, excess phosphate intake leading to hypoparathyroidism has been observed in patients with near-normal serum calcium levels receiving cow's milk or cow's milk–based formula with a high phosphate concentration. These formulas are no longer standard in the United States.[9] Our patient received breast milk and formula without high phosphate content, which rules out this potential etiology.

Vitamin D deficiency causes hypocalcemia associated with hypophosphatemia due to an intact PTH response of the kidneys.[9] Because our patient had normal vitamin D, high phosphate, and low PTH concentrations, this is unlikely. Another diagnosis that can be excluded by laboratory findings is neonatal pseudohypoparathyroidism, in which there is increased PTH due to insensitivity to the biological activity of PTH.[11]

Primary hypoparathyroidism can result from hypoplasia or aplasia of the parathyroid glands secondary to DiGeorge syndrome. Given no characteristic findings (abnormal facies, low-set ears, cleft palate) and a normal cardiothymic silhouette on chest radiograph, however, this was improbable. Thus, secondary hypoparathyroidism was the most likely diagnosis. This is predominantly caused by maternal hyperparathyroidism, which was ruled out by the mother's extremely low PTH. Secondary hypoparathyroidism resulting from excessive maternal calcium carbonate ingestion would explain the low neonatal and maternal PTH.

Robertson[12] reported a similar case of neonatal hypocalcemia secondary to maternal calcium carbonate ingestion. He hypothesized that large doses of the medication caused hypercalcemia and temporary suppression of fetal parathyroid function, resulting in hypocalcemia and seizures.[12] Given our patient's history and laboratory data, we agree that these proposed mechanisms best explain his hypocalcemic seizures. No maternal laboratory results were obtained for Robertson's[12] patient, but he believed that measurements would have shown modest hypercalcemia and mild PTH suppression. Our patient's mother had a serum calcium that was within the reference range, but we postulate that she likely had hypercalcemia in the third trimester, before decreasing her calcium carbonate intake after giving birth. The maternal PTH of less than 3 mg/dL illustrates that excessive intake of calcium carbonate can in fact lead to significant PTH suppression.

In summary, hypocalcemia is a rare, but treatable, cause of neonatal seizures. Although rarely documented, excessive maternal intake of calcium carbonate during the third trimester can cause suppression of neonatal parathyroid function and potentially symptomatic hypocalcemia. Anticipatory guidance should be given to pregnant women with symptoms of gastroesophageal reflux to prevent potentially detrimental outcomes. In addition, physicians caring for neonates presenting with seizures should question mothers about their use of over-the-counter medications such as calcium carbonate to help expedite diagnosis and treatment.

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