Neonatal Endocrine Emergencies
A Primer for the Emergency Physician

Elizabeth Park, MD\textsuperscript{a}, Nadia M. Pearson, DO\textsuperscript{b}, M. Tyson Pillow, MD, MEd\textsuperscript{a,*}, Alexander Toledo, DO, PharmD\textsuperscript{a}

INTRODUCTION

Neonates have a tendency of presenting discreetly. Neonatal endocrine emergencies are uncommon and may present a particular challenge for diagnosis in the emergency department. In the United States, newborn screening tests are used for early detection and treatment. Each state has a different panel of required screening tests for genetic, metabolic, and congenital issues, some of which are discussed in this article. Most of the screening tests are not immediately available to the emergency care provider. Although many cases are discovered postpartum in the nursery or neonatal intensive care unit, any health care provider who may deal with deliveries and the care of neonates needs to develop an astute sense for these emergencies and the rapid intervention required to offset any permanent neurologic damage from delayed diagnosis. The overlap between endocrine and metabolic emergencies in neonates is significant, but is beyond the scope of this article. This article focuses on the most common and most

KEYWORDS

- Neonatal emergencies
- Hypothyroidism
- Congenital adrenal hyperplasia
- Hypoglycemia
- Jaundice
- Hyponatremia
- Hypocalcemia

KEY POINTS

- Neonatal endocrine emergencies are uncommon and may present a particular challenge for diagnosis in the emergency department.
- The overlap between endocrine and metabolic emergencies in neonates is significant.
- The resuscitation principles for neonates remain the same in any neonatal emergency, such as securing the airway and stabilizing hemodynamics.
- Implementing screening programs more broadly worldwide and improving the current tests remains the challenge for future health care providers and those practicing abroad.

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\textsuperscript{a} Section of Emergency Medicine, Baylor College of Medicine, 1504 Taub Loop Road, Houston, TX 77030, USA; \textsuperscript{b} Department of Emergency Medicine, San Antonio Military Medical Center, 3551 Roger Brooke Drive, San Antonio, TX 78234, USA

* Corresponding author.

E-mail address: tysonpillow@gmail.com

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critical endocrine emergencies encountered in the first 4 weeks of life, including hypo-
glycemia, jaundice, hypothyroidism, congenital adrenal hyperplasia, inborn errors of
metabolism, and common electrolyte disorders.

HYPOGLYCEMIA

Hypoglycemia continues to be the most frequently encountered endocrine abnormal-
ity in neonates. Diagnosis of the hypoglycemic newborn based on physical examina-
tion alone is difficult. Findings can be subtle and nonspecific. Clinical signs of
hypoglycemic include respiratory distress, apnea, lethargy, hypotonia, seizures, jitter-
iness, myoclonus, temperature instability, weak or high-pitched cry, and difficulty with
feeding. These signs could also be the presentation for a multitude of other conditions
such as sepsis, congenital heart disease, prematurity, other metabolic diseases, drug
withdrawal, or increased intracranial pressure.1

A neonate can have transiently low glucose levels that resolve without intervention.
It is part of the normal physiologic process for glucose levels to dip after the first few
hours after birth. Although the mechanism is not completely understood, it is likely
caused by the combination of an abrupt cessation of maternal glucose supply through
the placenta and transition to gluconeogenesis and glycogenolysis. More specifically,
glucacon and cortisol regulate low blood sugar levels by increasing these processes,
which requires some time to take full effect in the neonate.2 The glycemic nadir (as low
as 30 mg/dL) occurs at 1 to 2 hours after birth and slowly rises, reaching adult levels at
3 to 4 days of age.3,4

Routine screening and monitoring of blood glucose concentration is not needed in
healthy term newborn infants after a normal pregnancy and delivery.4 The typical heel-
prick neonatal screening tests are obtained after 24 hours of life. In contrast, the au-
thors recommend that bedside glucose testing be performed for any patients with
complications of delivery, vital sign instability, neurologic findings, maternal history
of endocrine disorders, or any other sign of concern. If there is concern that the
neonate is hypoglycemic before the 24-hour screening tests are drawn, then it should
be obtained immediately. Point-of-care test strip glucose analyzers may vary by 10 to
20 mg/dL especially at the lowest concentrations, therefore laboratory evaluation is
recommended.4 There is no universally accepted definition of hypoglycemia in a
neonate who is otherwise healthy with no risk factors.4,5 An accepted numerical value
of less than 47 mg/dL is often cited in the literature. Hypoglycemia in otherwise healthy
neonates is generally corrected by initiating feedings.2

Risk factors for prolonged hypoglycemia include having a diabetic mother, the infant
being small for gestational age (SGA) or large for gestational age (LGA), initial respira-
tory distress, or prematurity.2,3 Without the presence of these risk factors, otherwise
healthy singleton pregnancies produce more cases of hypoglycemia when the mother
spiked a fever during labor, the neonates’ family had public rather than private insur-
ance, and if the patient was born earlier while still remaining in the context of being full
term.6 In neonates who are premature or have increased rates of insulin production
baseline secondary to being exposed to high levels of blood glucose during gestation
within a diabetic mother, the episode of hypoglycemia can be more profound.2
Newborn hypoglycemia is most common in an infant born to a diabetic mother (either
type I or II diabetes mellitus [DM], or gestationally induced DM), wherein the infant was
constantly exposed to increased glucose levels from the mother’s blood.2,7 As a
compensation response, the fetus’ beta cells of the pancreas remain in a state of over-
production. When the placental supply is abruptly cut off, it can take hours to days for
the neonatal insulin drive to downregulate.1 During this time, feedings often suffice.
However, intravenous dextrose infusions or further treatment options as discussed later may need to be initiated if an inadequate response is obtained or if the neonate is not able to tolerate oral feeds. In a study done with mothers with type 2 diabetes and gestational diabetes, the neonates whose mothers needed treatment with glyburide or insulin during pregnancy had a higher incidence of hypoglycemia within the first hour of birth. Those women who were treated with diet alone for their diabetes did not produce neonates with hypoglycemia as frequently.

If the blood glucose continues to remain low despite feedings and intravenous dextrose administration, congenital hyperinsulinemia, glycogen storage diseases, disorders of fat oxidation, hypopituitarism, and genetic issues such as Beckwith-Wiedemann, Costello, and mosaic Turner syndrome should be considered and investigated. In such cases, a detailed obstetric and family history along with the ethnic origins of the parents need clarification. Certain obstetric elements may signal that the infant has an inborn error of metabolism, which occurs in 1:1500 births. For example, HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome or acute fatty liver of pregnancy could signal an underlying fatty acid oxidation disorder in the fetus. Any step of carbohydrate or fatty acid metabolism can be affected with an enzyme deficiency and subsequent buildup of substrates that can cause metabolic derangements. Certain ethnic groups to question more extensively for family congenital disorders include Ashkenazi Jews, Old Order Mennonites, Mediterranean races, French Canadians, and Africans.

In terms of the acute setting, diagnosing the exact reason for the hypoglycemia is not as critical as normalizing the value to prevent irreversible neurologic damage. In general, the first line of treatment is initiating breast or bottle feedings. There is currently no evidence that hypoglycemia with no clinical signs harms the neonate or produces lasting neurologic sequelae. However, if clinical signs of hypoglycemia are present and laboratory values confirm the abnormality, then neonates require regular glucose checks and should be transferred to the neonatal intensive care unit for further evaluation and monitoring. Neonates of insulin-dependent mothers need glucose level checks at 1, 2, 3, 6, and 12 hours post partum for normalization. Other tests that concurrently should be checked in these patients include bilirubin levels, hematocrit, and calcium levels. There are no exact guidelines of when a sick-appearing neonate needs tests for investigation into whether hypoglycemia is the primary or secondary cause of the presentation. However, a consideration of risk factors such as maternal comorbidities, the physical examination, and lack of clinical improvement with treatment should trigger the clinician to start the work-up.

There is ongoing debate about when to intervene with asymptomatic hypoglycemic patients and whether or not to start dextrose infusions. Those infants whose blood sugars continue to be less than 50 mg/dL even with oral feedings and have risk factors for remaining in a hyperinsulinemic state should likely be started on dextrose infusions. Target glucose levels are not established as a standard of treatment because the goal is to prevent adverse neurologic outcomes. Dextrose infusions generally start at a bolus of 2 to 3 mL/kg of 10% dextrose solution followed by a drip at 80 to 100 mL/kg/d. If the levels do not respond, then gradual escalation to 30 mg/kg/min has been documented. With concentrations higher than 12.5% dextrose, a central line must be inserted into the patient for protection of peripheral vasculature.

There are a variety of reasons why the neonate may fail to maintain adequate glucose levels. Further treatment options that can be explored include glucagon, steroids, diazoxide, and octreotide depending on the presumed cause of the hypoglycemia. Sometimes surgical management is required for certain types of insulin-secreting adenomas, whereas others can be medically managed. Diazoxide works at the
level of the beta islet cells to close the channels that regulate insulin secretion. Diazoxide is a benzothiazine derivative and works within 1 hour of administration. Dosages start at 10 to 15 mg/kg/d and are given for about 5 to 8 days. If diazoxide fails to achieve normalization of levels, then octreotide, a somatostatin analogue, is initiated. Octreotide inhibits the secretion of insulin in a more direct fashion but also has a shorter duration of action. If hypoglycemia is not caused by hyperinsulinemia, then glucagon is usually introduced. Intravenous dosing starts from 3 µg/kg to 20 µg/kg and is given continuously for 1 day. Other treatments that may be attempted but are not proved to show dependable results include glucocorticoids and nifedipine.

It is important to note the outcomes of neonates who receive a delayed diagnosis and initiation of treatment of hypoglycemia. In one study that performed magnetic resonance imaging (MRI) scans of babies at least 18 months after symptomatic neonatal hypoglycemia, 95% had signs of white matter damage and, of those, 43% had severe signs. Other findings discovered on MRI included evidence of stroke and hemorrhage. In another study, 30% of the patients with congenital hyperinsulinemia who received medical therapy did not achieve milestones of development appropriately. Those who failed medical therapy and needed surgical intervention fared worse.

In hypoglycemia of the newborn or older infant, consideration of other causes and differential diagnoses is of the utmost importance. In the approach to a generalized work-up for hypoglycemia in an older child or adult, inadequate intake, poor absorption, increased usage, disordered processing, or usage of glucose still applies. Considering sepsis and initiating appropriate work-up are important in the setting of maternal fever during delivery, neonate with sick contacts, febrile neonate, neonate with altered mental status, and neonate with neurologic changes, in addition to the signs and symptoms listed previously for hypoglycemia. It is important to ensure careful maternal history of a breastfeeding mother to include medications and or drug use that also may cause hypoglycemia in an infant less than 30 days of age. This history elicited to search for causes of inadequate intake should include how often and how long the infant is feeding on each breast, appropriate latch, maternal assessment of milk production, and growth of infant from birth weight. If the infant is formula fed, appropriate mixing of the formula is important in this assessment because inappropriate mixing can also lead to other electrolyte derangements. Poor absorption in an infant with hypoglycemia may manifest with a history of inadequate weight gain despite adequate feeding, or excessive loss such as diarrhea. According to the American Academy of Pediatrics, an infant can lose up to 10% of body weight after birth, but should recover by about a week of age. Assessing these historical facts helps guide the work-up of an infant with a presentation of frank hypoglycemia.

HYPOTHYROIDISM

The second most common endocrine emergency in neonates after hypoglycemia is hypothyroidism, which is another disorder that requires prompt diagnosis and treatment to improve prognosis and reduce the chances of developmental delay. Although the incidence of neonatal hypothyroidism varies by country, congenital hypothyroidism in the United States occurs in 1 in 2000 to 1 in 4000 live births. Congenital hypothyroidism is classified into primary and secondary as well as permanent and transient cases. Thyroid dysgenesis accounts for 85% of permanent primary congenital hypothyroidism, whereas inborn errors of thyroid hormone biosynthesis account for 10% to 15% of cases. Secondary cases are often associated with congenital hypopituitarism rather than isolated thyroid-stimulating hormone (TSH) deficiency. As
with hypoglycemia, there can be multiple causes, but, in the acute care setting, identifying the abnormality and initiating treatment is of critical importance.

Screening methods were introduced because hypothyroid neonates are largely asymptomatic at birth. Screening for hypothyroidism, which began in the early 1970s, has reduced cases of mental retardation. When signs and symptoms do present, usually around 6 weeks of age, they can include poor feeding, constipation, an increased need for sleep, greater than average weight, and jaundice. On physical examination, some findings signaling the need for further evaluation include large, puffy facies; macroglossia; hypotonia; or a distended abdomen, sometimes with an umbilical hernia. The mother’s history may also provide clues to further investigate the neonate for hypothyroidism. A maternal history of taking antithyroid medications, autoimmune disorders, or residing in a country with high incidence of iodine deficiency is helpful in diagnosing the neonate. There may also be a history of thyroid problems in the family, such as thyroid dysgenesis, for which a genetic linkage has been shown. Central hypopituitarism is often associated with congenital midline defects such as cleft palate.

In neonatal hypothyroidism, there are special considerations that need to be factored into the clinician’s interpretation of results and diagnosis of the disorder. In normal neonatal physiology, thyroid hormone levels do not remain constant during the infants’ first days of life and these levels depend on the gestational age of the patient. In a healthy full-term infant the TSH is increased for the first few days of life, which is when the thyroid screening tests are obtained. The levels normalize within the first month of life, which is when a patient is brought in for retest to confirm the diagnosis or to determine whether it was a transiently high level. In premature neonates, the TSH is increased compared with that of full-term babies and must be interpreted in relation to reference ranges according to their gestational age.

There has been much research into the timing and the type of screening test for hypothyroidism. Debate as to whether to use only TSH or a combination of TSH and T4 for screening and when the levels should be drawn and the cutoff levels for treatment have been ongoing. The most recent research suggests that checking TSH levels with the rest of the screening tests after birth and again within the first 30 days of life detects the greatest number of hypothyroidism cases. When the patient is discharged before a second screen can be done, the caretaker needs to follow up for a retest. This method achieved the highest rates for identifying hypothyroid cases, at 2.6 per 1000 births. By using only the first screening test, only half of the cases would be identified. For very low birth weight patients, most cases were detected with this screening method.

It may be impossible to determine whether a persistently increased TSH level is transient, but because the effects to the development of the infant of withholding treatment can be so severe, the standard is to treat the patient for hypothyroidism for the first 3 years of life after a positive screening. Treatment starts immediately with levothyroxine 10 to 15 μg/kg/d. In the acute setting, the levothyroxine needs to be uptitrated as soon as possible until T4 levels are more than 130 mmol/L (10 μg/dL) and TSH levels are also within the reference range. After this initial stabilization of levels, they may rechecked every month for the first 6 months of life to ensure adequate dosing.

The prognosis of those infants who are started on therapy within the first 30 days of life is good. Studies have shown that they perform similarly to their peers on cognitive tests in grade school. Factors that may influence this outcome depend on the severity of the hypothyroidism and the time of initiating treatment (after 30 days of life) as well as not starting the dose of medications at a high enough level.
screening tests were routine in developed countries, congenital hypothyroidism was the most common cause of mental retardation. Only about 25% of the world has mandatory newborn screening programs and a world health initiative may be underway to increase the screening in other countries, especially in those areas with endemic iodine deficiency.\textsuperscript{16}

\section*{Hyperbilirubinemia}

Emergency department (ED) physicians are certain to encounter infants presenting with jaundice, because 60% of newborns have some degree of jaundice.\textsuperscript{17} Infants often even present to the emergency setting for a routine postnatal bilirubin check because the primary care providers and/or laboratories are unavailable. Bilirubin is produced by the breakdown of hemoglobin. In its unconjugated state, it can be bound to albumin in the blood, or in a free, water-insoluble state. When unconjugated, it is difficult to excrete and can cause central nervous system toxicity. This toxicity is still commonly referred to as kernicterus, but more recently has been termed bilirubin-induced neurologic dysfunction.\textsuperscript{18} As bilirubin passes through the liver, it is conjugated to a water-soluble form that may be easily excreted. This process is the same in newborns as in adults; however, lower enzyme levels and lower amounts of binding substrate predispose them to jaundice more easily. Determining the type of hyperbilirubinemia is the first step in the diagnosis and management in these infants.

\subsection*{Unconjugated Hyperbilirubinemia}

The diagnosis of unconjugated hyperbilirubinemia can range from normal physiologic processes to rare, life-threatening diseases. Even physiologic processes may, rarely, precipitate toxic levels of hyperbilirubinemia. Risk factors for more serious causes of jaundice include prematurity, jaundice within the first 24 hours of life, rapid rate of increase of bilirubin (>0.5 mg/dL/h), anemia, or hepatosplenomegaly.\textsuperscript{19,20} The ED physician must realize that it is important to correlate levels with the clinical presentation.

Physiologic jaundice occurs when normal bilirubin released by the breakdown of hemoglobin transiently overwhelms the neonate’s ability to conjugate and excrete it. Levels are usually around 12 mg/dL in a term infant at 72 hours.\textsuperscript{19} This type of jaundice usually occurs at about 1 to 2 weeks of life. Two other presentations that should be distinguished are breast feeding failure jaundice (caused by dehydration) and so-called breast milk jaundice (a poorly understood phenomenon seen with breast milk). Breast feeding jaundice is caused by inadequate feeding and therefore inadequate excretion of bound bilirubin through the gastrointestinal tract. Breast milk jaundice is a diagnosis of exclusion, can be familial, and can last longer (months).

During the work-up of a jaundiced infant, physiologic jaundice remains a diagnosis of exclusion. In the neonate, jaundice may be secondary to another disease process or a part of a more complicated disease process. Significant dehydration, cephalohematomas, hemolysis, and sepsis may be causative factors of the jaundice. Other causes include inborn errors of metabolism, congenital hyperthyroidism, and Crigler-Najjar syndrome. Table 1 lists potential causes of unconjugated hyperbilirubinemia.

The work-up of the jaundiced infant begins with a thorough history and physical examination. Box 1 lists risk factors for severe hyperbilirubinemia. In the well-appearing infant, bilirubin and hemoglobin may be checked. The indirect bilirubin level is plotted on a nomogram and risk of disease is based on the level versus the age of the infant in hours. There are many different calculators that can also be used. One of the common Internet-based calculators is www.bilitool.org. Given a normal hemoglobin and no other worrisome history or symptoms of other acute illness, follow-up can be arranged
based on the infant’s risk of developing worsening hyperbilirubinemia. Breast feeding is generally continued unless breast milk jaundice is the suspected cause of hyperbilirubinemia. In this case, feedings may be discontinued transiently if bilirubin levels are greater than 17 to 20 mg/dL, in conjunction with admission for phototherapy. However, a full work-up should ensue because discontinuation of breastfeeding is usually not necessary. For patients with indirect bilirubin levels that require treatment, the mainstay is phototherapy and ensuring adequate hydration. A patient may, rarely,
fail to respond to phototherapy, and exchange transfusion with or without intensive phototherapy can be considered.

If the patient is toxic or ill appearing, then the treatment priority is given to the potential underlying disease. Most commonly, these patients undergo a sepsis work-up and other studies as appropriate in addition to phototherapy. These patients may get a complete blood count with peripheral smear, Coombs test, analysis of maternal and fetal blood types, and urine analysis and culture. Glucose-6-phosphate dehydrogenase levels should be checked if the patient does not respond to phototherapy or is suspected based on background.

**Conjugated Hyperbilirubinemia**

Conjugated hyperbilirubinemia does not carry the neurologic risk of unconjugated hyperbilirubinemia, but is a herald of serious disorders. As such, the work-up is directed at identifying and treating underlying disorders. Table 2 lists the differential diagnoses, most notably sepsis, inborn errors of metabolism, and biliary disorders. Therefore, the work-up commonly includes a full septic work-up (including a TORCH [toxoplasmosis, other (syphilis, varicella, parvovirus B19), rubella, cytomegalovirus, herpes] panel), blood gas, lactate, complete liver function panel, ammonia, electrolytes, blood urea nitrogen, and creatinine. In certain cases, it may expand to include urine for reducing substances, alpha1-antitrypsin, sweat chloride, abdominal imaging, and other tests as needed. Treatment and prognosis depend on the underlying diagnosis.

**ELECTROLYTES**

There are a few electrolyte disturbances that, in addition to hypoglycemia, need to be considered as potential causes of seizure presentation in the neonate. Both calcium and sodium derangements can be the causative disturbance for a variety of underlying reasons.

**Hyponatremia**

Hyponatremia (serum sodium <130 mEq/L) is second only to febrile seizure as a cause for first-time seizure in an infant.21 The incidence of symptomatic hyponatremia in

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<th>Table 2</th>
<th>Causes of conjugated hyperbilirubinemia</th>
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| Common causes | Sepsis  
TORCH infections:  
• Toxoplasmosis  
• Other (syphilis, varicella, parvovirus B19)  
• Rubella  
• Cytomegalovirus  
• Herpes |
| Rare causes | Biliary atresia  
Inborn errors of metabolism  
Cystic fibrosis  
Alpha1-antitrypsin deficiency  
Neonatal iron storage diseases  
Alagille syndrome  
Hepatic infarction  
Byler disease |

children is not known because of a lack of prospective studies. However, one retrospective review found that approximately 22% of children who were admitted to the hospital had hyponatremia, and symptomatic hyponatremia was found in 10% of children less than 2 years of age presenting to the ED with seizures. During infancy, common presentations to the ED include gastrointestinal losses and water intoxication. Neonates (who lacks the ability to concentrate their urine) frequently receive free water or inappropriately diluted formula from their parents, leading to hyponatremia. Symptoms include not only seizure but also lethargy, muscle cramping, decreased reflexes, and acute respiratory failure. They may also have hypothermia and hyperglycemia.

Pediatric hyponatremia, as in adults, is classified based on total body water content. In general, significant symptoms do not appear until the sodium is less than 120 mEq/L, but may be present with rapid decreases in the normal range. Of those children with hyponatremia, 53% to 78% with serum sodium less than 125 mEq/L developed symptomatic hyponatremia. As mentioned earlier, receiving free water from parents is a common cause, and bottle-fed infants are at increased risk. Other causes include syndrome of inappropriate antidiuretic hormone (SIADH), congenital adrenal hyperplasia, congestive heart failure, cirrhosis, and nephrosis. Special attention to, and close monitoring of, serum sodium level in any child at risk for hyponatremia or with any of the conditions discussed earlier is necessary to prevent serious neurologic complications.

In general, use of intravenous fluids in the pediatric population should be considered an invasive treatment, and should have the same amount of care and attention applied as when administering any other medication. Children may be at higher risk for development of cerebral edema because of the physiologic nature of a higher ratio of brain volume to skull size.

Symptomatic hyponatremia (seizure, coma, or signs of herniation) should always be aggressively treated with the use of hypertonic 3% saline. The serum sodium level should be increased by approximately 1 mEq/L per hour until the patient is seizure free, the serum sodium has corrected to 125 to 130 mEq/L, or the serum sodium level has increased by 10 mEq/L. In infants, this can be accomplished by the following equation: volume of 3% saline = 10 mEq/L × body weight (kg) × 0.6 (extracellular fluid space). Another common regimen for a bolus is 3 to 5 mL/kg of 3% saline solution run over 30 to 60 minutes. The optimal rate of correction of serum sodium seems to be between 15 and 20 mEq/L over the first 48 hours, because patients with this range of correction have lower rates of mortality and better neurologic outcome compared with those with slower correction. In less symptomatic patients, water restriction treats hyponatremia caused by water intoxication and SIADH. In hypovolemia, resuscitation fluids should be carefully calculated to increase the serum sodium appropriately while replacing volume. Diuretics may be necessary in hypervolemic hyponatremic states.

**Hypocalcemia**

Serum levels of calcium usually decline in the postnatal time period, but there are 2 noted time frames for clinically significant hypocalcemia: early postnatal (within a few days) and late postnatal (5–10 days after birth). In a recent study, Thomas and colleagues reported a retrospective chart review of infants presenting to 2 large medical centers in Texas with the diagnosis of moderate to severe hypocalcemia. The definition used for severe hypocalcemia was an ionized calcium of less than 4 mg/dL with the leading presentation of seizures consistent with tetany in all but 2 of the included infants. Infants excluded from the sample had hypocalcemia associated
with other entities such as prematurity, congenital heart disease, DiGeorge syndrome, sepsis, renal disease, or other neurologic or gastrointestinal manifestation. In this group it was also noted that several subjects had low levels of magnesium as well as phosphorus that needed to be corrected as well. Initial management of seizure with known calcium levels less than 7 mg/dL can be treated with 100 to 300 mg/kg of calcium gluconate given intravenously. Further evaluation as an inpatient in addition to broad emergent work-up should specifically include levels of 25-hydroxy-vitamin D as well as intact parathyroid hormone levels.

**CONGENITAL ADRENAL HYPERPLASIA**

Although congenital adrenal hyperplasia (CAH) is not a common neonatal endocrine disorder, it is still screened for in the United States and other countries. Obvious physical examination findings on birth are helpful in diagnosing this rare and potentially fatal disorder but are not always present. Patients are subdivided into classic and nonclassic types, which present with obvious versus more subtle clinical findings, respectively. Classic CAH is more severe. The classic presentation is a neonate, usually 2 weeks after birth, who is atypically somnolent, vomiting, feeding poorly, and showing signs of dehydration such as a depressed fontanel and decreased skin turgor. This presentation, as is often the case with neonates, still raises a broad differential diagnosis. However, in the critically ill neonate, a basic metabolic panel to check for the typical electrolyte abnormalities of hyponatremia and hyperkalemia is warranted. On physical examination of the female neonate, ambiguous genitalia may include a sizable clitoris and fused labia majora. Intact uterus and fallopian tubes with no anatomic abnormalities are evident on subsequent ultrasonography. With severe cases of CAH, girls may initially be assigned as boys immediately after birth because the genitalia may be more similar to those of a boy. True male babies appear normal at birth with no signs of ambiguous genitalia, but may have some enlargement of the penis and testes along with skin hyperpigmentation. The nonclassic form of CAH does not produce high enough levels of androgens to virilize girls, therefore findings on physical examination may be absent.

The classic form occurs in about 1 in 16,000 births worldwide, whereas the incidence of the nonclassic form may vary according to the population. For instance, in the United States, the nonclassic form was positively screened for in 1 in 130,000 births. The incidence of the disease is closer to 1 in 2000, so the screening test does not pick up all forms of the mild disease. However, in other white populations in eastern Europe, for example, it may be more common, affecting up to 1% to 2% of the population because of the carrier population. Certain other groups such as the Yupic Eskimos in Alaska, Philippinos, Brazilians, and those living on an island in France called La Reunion are known to have the most cases.

In the steroid synthesis pathway, which occurs within the adrenal cortex, cholesterol is converted to many intermediates with the sex hormones, cortisol, and aldosterone being the desired products in normal physiology. CAH is an autosomal recessive disorder in which one of the 5 enzymes in the pathway to create cortisol is defective with a buildup of undesired products that can cause side effects such as virilization in female neonates, hemodynamic instability, and electrolyte abnormalities. The common pathophysiology that occurs with this group of enzyme deficiencies is a deficiency in aldosterone. Sodium channels cannot regulate fluid balance properly, thus leading to hypotension. Certain intermediates that build up can even serve as antagonists to aldosterone, exacerbating the state. Sodium cannot get into the intravascular space effectively without aldosterone regulation. Potassium, also part of the exchange
process in sodium channels, cannot be excreted, leading to hyperkalemia. These neonates are also deficient in cortisol, which is integral for the regulation of blood pressure, fluid status, and glucose levels. Renin levels increase in an attempt to compensate. The most common enzyme deficiency in this group of disorders is the 21-hydroxylase deficiency, which comprises 90% of cases. This enzyme converts 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol, which is eventually converted to cortisol and another precursor that is converted to aldosterone. Without the proper levels of cortisol and aldosterone, these patients present with symptoms of adrenal insufficiency and metabolic derangements: hypotension, hyponatremia, hyperkalemia, and altered mental status. If not detected early these patients often present in florid shock.

In the United States, along with many other countries, CAH is tested for in the panel of newborn screening tests. It has been used as part of the screening tests since 1977. Once the newborn screen returns with an abnormal result, the health care provider must decide whether patients have CAH if they are not showing symptoms of salt wasting. Subsequent laboratory tests for 17-OHP levels, the intermediate that would be increased in 21-hydroxylase deficiency, are sent. The test is done either as an enzyme-linked immunosorbent assay (ELISA) or by mass spectrometry, which is more accurate and reduces the rate false-positives compared with ELISA. Diagnosis is more difficult in premature neonates and those with other comorbidities because stress hormones may be high, which can cause a transient increase in this screening test. The diagnosis is further complicated because levels of 17-OHP are increased in the first few days of life. Because many healthy babies are discharged from the hospital within this time, if a newborn screen is drawn early, then there is a greater chance for false-positives. Studies show that, for every case of CAH identified through screening tests, another 200 babies undergo further testing, ultimately not being true-positives. The current methods of screening for CAH show a poor positive predictive value at 0.53% to 1%. A method to improve the screening accuracy is by correlating the levels according to gestational age. If the initial level is increased, then it is repeated. If this repeat is still increased, then the patient can be diagnosed by a pediatric endocrinologist with a cosyntropin stimulation test, which must be done after the first 24 hours of life. If there is clinical suspicion that the patient has CAH, then health care providers can go straight to the stimulation test without another repeat level. False-negative cases also occur. About 10% of classic CAH cases have low initial levels of 17-OHP.

The decision to treat a patient for CAH depends on the suspicion that the patient has the condition. Treatment is not benign and patients may develop side effects from steroids such as Cushing syndrome, hyperglycemia, or cataracts. The consensus is that, if the patient has physical signs of CAH and is unstable, then it is reasonable to start intravenous normal saline infusion and steroid therapy for adrenal insufficiency. Once diagnosis is made, treatment begins with hydrocortisone at 20 mg/m² daily divided into 3 equal doses per day and fludrocortisone 0.1 mg per day. If the neonate is decompensating, then additional 0.9% NaCl boluses, high doses of intravenous hydrocortisone (100 mg/m² daily), and fludrocortisone 0.1 mg twice a day should be started. The dose for hydrocortisone should be increased only to the point at which the patient suppresses androgen excess and can still achieve proper growth, not until the levels of 17-OHP are within normal values. Also, after the acute crisis is controlled, the patient is switched to oral fludrocortisone and oral sodium chloride supplements. In nonclassic CAH, treatment is not recommended until symptoms develop. Other recommendations for follow-up of nonclassic CAH cases are covered in the pediatric endocrinology literature.
INBORN ERRORS OF METABOLISM

Although a full discussion of inborn errors of metabolism is beyond the scope of this article, the emergency physician should be familiar with a few key aspects of these diseases and their emergent presentations. In general, there are 3 main mechanisms of illness:

1. Accumulation of toxic small molecules
2. Energy deficiency
3. Chronic accumulation of large molecules

The common thread between these three pathways is a genetic mutation that leads to protein malfunction and a blocked metabolic pathway. Also common among each is seizures, stroke, lethargy, encephalopathy, and abnormal tone. Abnormal odors may be present in small molecule and energy metabolism, but are rare as presenting clinical symptoms. In general, the accumulation of toxic intermediates (usually acids) takes place between day 2 and 5 of life, thus a newborn appears normal and does not have signs or symptoms immediately after birth. In utero, the placenta removes the toxic metabolites. Severe metabolic acidosis is a common feature in this category and can also be accompanied by hyperpnea/tachypnea, hyperammonemia, and altered mental status. A more common presentation of encephalopathy associated with an undiagnosed inborn error is central apnea and respiratory distress. Sepsis in an infant with an undiagnosed inborn error of metabolism progresses to shock more rapidly and should be considered in the differential diagnosis in the setting of poor feeding, recurrent vomiting, seizures, abnormal muscle tone, lethargy, or acute life-threatening event. Untreated, accumulation of toxins with noted encephalopathy quickly leads to coma, multisystem organ failure, and death.

Mitochondrial disorders are the prototypic disorders of energy deficiency. Unlike the accumulation of toxic intermediates, the placenta is not protective, and the fetus may develop birth defects, abnormal facies, and other prenatal problems. Seizures, cardiomyopathy, and hepatocellular disease are common hallmarks leading to lactic acidosis, multisystem organ failure, and death.

Accumulation of large molecules results in a chronic disease process that rarely presents emergently. Instead, the severity of disease is related to location and amount of stored material. Joint contractures, valvular disease, cataracts, and neurologic problems are common.

The work-up of potential inborn errors of metabolism is extensive and specific to the suspected disease process. Focus is placed on small toxic molecules (ammonia), and energy deficiency (hypoglycemia) because these present emergently and a prolonged state of coma caused by these entities directly correlates with nonreversible neuronal damage. Screening tests may include complete blood count, electrolytes, blood urea nitrogen, creatinine, arterial or venous blood gas, ammonia, lactate, urine analysis, liver function tests, coagulation studies, and potentially creatinine kinase. An increased anion gap is the most sensitive and specific sign of an organic acidemia (>20 is highly abnormal) and increased ammonia (>150–200 µM) is the hallmark of a urea cycle defect. It is always advised that early consultation with a metabolic specialist can help to determine when and whether specialty laboratory testing is indicated.

The mainstay of therapy is dextrose infusion because this provides energy and increases endogenous insulin production, thereby preventing catabolism. Consideration must also be given to the need for bicarbonate therapy; the management and
further prevention of cerebral edema; and, in rare instances, simultaneous insulin and dextrose administration. In cases of significant impairment caused by hyperammonemia, hemodialysis may be considered in consultation with a nephrologist. This care is beyond the scope of normal emergency medicine practice, so prompt transfer to a pediatric facility after stabilization is critical.

SUMMARY

The resuscitation principles for neonates remain the same in any neonatal emergency, such as securing the airway and stabilizing hemodynamics. However, stabilizing endocrine disorders can be challenging because they can affect several organ systems simultaneously, and have various presentations (which may or may not be subtle), making diagnosis difficult without laboratory studies and clinical acumen. Screening tests have improved significantly in the past few decades and have become standard of practice in many areas of the world. Although not all-inclusive, their implementation has significantly reduced morbidity and mortality in neonates. Implementing screening programs more broadly worldwide and improving the current tests remains the challenge for future health care providers and those practicing abroad. With further attention and study into these disorders and the best treatment practices, these patients can be given the best outcomes.

REFERENCES

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