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# Necrotizing Enterocolitis in the Full-Term Infant

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## Abstract

Necrotizing enterocolitis in full-term infants is relatively rare. When seen, it is usually associated with perinatal asphyxia, sepsis, or specific forms of congenital heart disease. It can also be associated with endocrinopathies. In this review, a full-term infant was found to have necrotizing enterocolitis and persistent hypoglycemia. Evaluation for hypoglycemia revealed pan-hypopituitarism, and magnetic resonance imaging confirmed this diagnosis. Timely evaluation and early initiation of hormone replacement therapy is essential to minimize long-term morbidities and mortality associated with pan-hypopituitarism. [*Pediatr Ann.* 2015;44(10):e237-e242.]



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An infant girl born at 39 weeks gestation via Cesarean delivery had a birth weight of 3,240 g (50th percentile), length of 50 cm (50th percentile), and head circumference of 35.5 cm (25th to 50th percentile). Her examination was unremarkable except for a slightly jittery infant with tachypnea but clear lung fields, and questionable dysmorphic facies, including mild hypertelorism. APGAR (Appearance, Pulse, Grimace, Activity, Respiration) scores were 1 and 9 at 1 and 5 minutes, respectively, as the infant had an initial cry but she became apneic with a low heart rate. She required positive pressure ventilation for 1 minute and continuous positive airway pressure for 2 minutes, which resulted in improved heart rate, tone, and respiratory effort.

However, the infant was evaluated for persistent tachypnea. Remarkable findings include a blood glucose level that was undetectable within the first hour after birth. She was admitted to the neonatal intensive care unit (NICU) and given an intravenous (IV) bolus of 10% dextrose in water of 2 mL/kg. Her blood glucose level improved, and she was started on maintenance dextrose-containing IV fluids and antibiotics. Her respiratory status improved, so she was started on enteral feeds on day 1 after birth. She had large residuals and emesis with oral feeding attempts. Abdominal radiographs done on day 3 after birth for abdominal distention and emesis were consistent with necrotizing enterocolitis (NEC). She developed worsening hemodynamics requiring vasopressor support, as well as respiratory failure requiring intubation and mechanical ventilation. During exploratory surgery, she was found to have NEC totalis. She was then transferred to a higher-level NICU for further care for persistent pulmonary hypertension (developed postoperatively) at approximately age 2.5 weeks.

## NICU COURSE

Upon transfer, the patient required significant glucose infusion rates of 16 to 18 mg/kg per minute in her parenteral nutrition to maintain euglycemia, and continued to have occasional serum glucose levels in the range of 40

## Necrotizing enterocolitis is an inflammatory disease of the intestine affecting neonates, mostly premature infants.

to 50 mg/dL. She otherwise was able to be extubated to low-flow nasal cannula, with reasonable oxygen saturation values. She was maintained *nil per os* for her NEC, and administered antibiotics for 14 days. She remained well perfused, with reasonable blood pressure values.

## FURTHER EVALUATION

A panel of critical laboratory values was sent when her blood sugar was low on routine testing. Laboratory studies were consistent with panhypopituitarism. More specifically, her pituitary end-organ target hormones were low: free thyroxine (T4) was 0.6 ng/dL (reference range, 0.89-2.2 ng/dL) and cortisol was 1 mcg/dL concurrent with a hypoglycemic episode of a plasma glucose level of 37 mg/dL. On repeat evaluation, her cortisol was undetectable at <0.2 mcg/dL. Insufficient blood was drawn at the time of hypoglycemia to assess a growth hormone level, and hence a random insulin-like growth factor-binding protein 3 was used as a surrogate to assess the growth hormone axis, which was low at 0.6 mg/L (reference range, 0.7-3.6 mg/L). Thus, it was concluded that her anterior pituitary function was compromised. Her urine out-

put became copious at 13.7 mL/kg per hour. The sodium levels did not become overtly elevated, with a sodium level of 136 mmol/L, although the sodium level was confounded by an infusion of total parenteral nutrition and IV fluids. In the context of marked polyuria and apparent compromise of three other pituitary axes, diabetes insipidus was highly suspected and desmopressin acetate was administered with a clinically effective and appropriate antidiuresis. Magnetic resonance imaging (MRI) of the brain was performed and found to be significant for absent anterior pituitary and ectopic posterior pituitary (**Figure 1**). The patient was therefore diagnosed with congenital panhypopituitarism.

## SUBSEQUENT CLINICAL COURSE

The endocrine team was consulted and the patient was given replacement therapy, including growth hormone, levothyroxine, desmopressin, and hydrocortisone. Her blood sugar normalized on appropriate glucose infusion rates via her TPN. Dosing of her hormone replacement therapy was routinely adjusted per serum hormone level values. The gastroenterology team and surgical team have since been able to optimize her enteral function and nutritional status. At last check, she was maintained on a combination of compressed parental nutrition and gastrostomy tube enteral feedings and she is gaining weight.

## DISCUSSION

### Necrotizing Enterocolitis

NEC is an inflammatory disease of the intestine affecting neonates, mostly premature infants, with an associated 10% to 50% mortality.<sup>1</sup> Fewer than 10% of all cases of NEC occur in full-term neonates.<sup>2</sup> The age of onset of NEC varies inversely with gestational age—that is, premature infants present with NEC later and term infants present with NEC earlier. The pathogenesis is still incompletely understood, but in premature in-

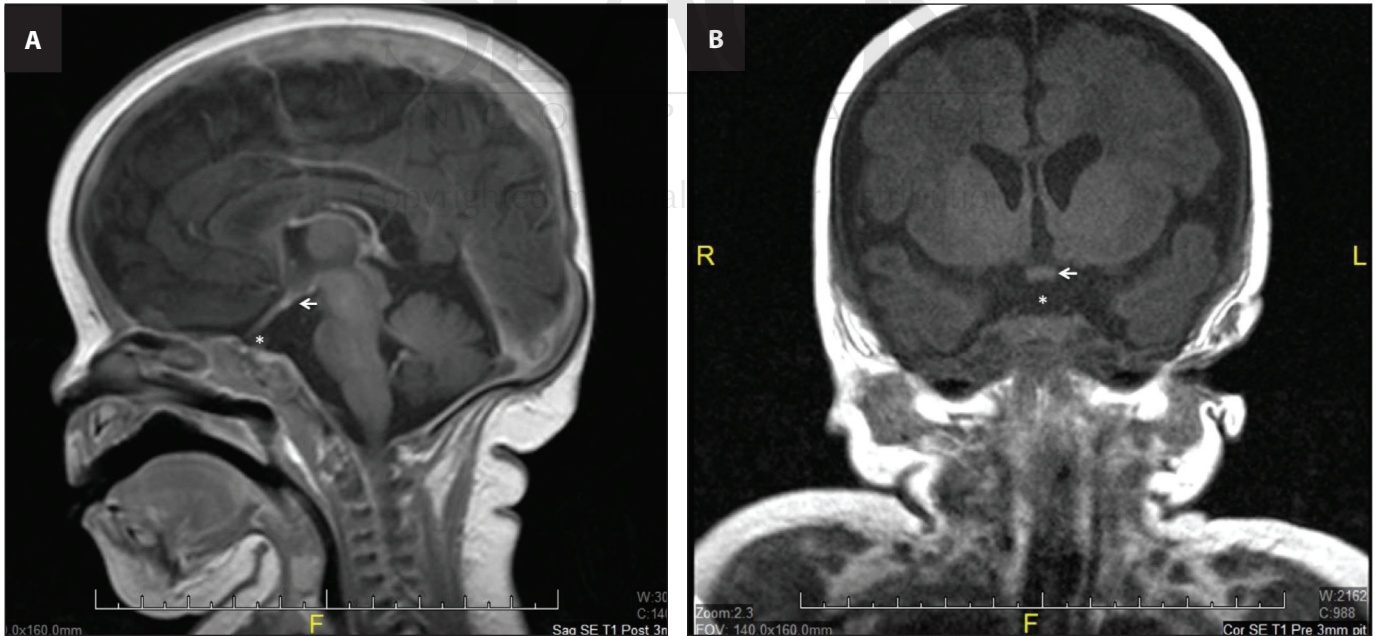


Figure 1. Magnetic resonance imaging scan (T1 weighted) of the brain. (A) Sagittal view showing a flattened sella turcica (asterisk) and ectopic posterior pituitary gland (arrow), which is seen as an area of high-intensity signal. (B) Coronal view showing absent anterior pituitary and infundibulum (asterisk), which should be located beneath the optic chiasm (arrow).

infants it is thought to involve dysfunction or immaturity of the gut barrier, with resultant bacterial invasion leading to inflammation and eventual cell necrosis. In full-term infants, different clinical conditions have been identified as risk factors, although they have been not consistently proven. These factors include perinatal hypoxic events/asphyxia, certain congenital heart malformations, polycythemia/thrombotic conditions, endocrinopathies, and perinatal sepsis.<sup>3</sup>

In general, it is accepted that the pathophysiology of NEC is likely multifactorial. It seems that the pathway is initiated by mucosal damage (eg, secondary to infection or asphyxia). From there, increased bacterial translocation across the damaged intestinal epithelium triggers endogenous production of signals such as platelet-activating factor and tissue necrosis factor, which go on to activate inflammatory cascades.<sup>4</sup> What remains to be elucidated is where different clinical factors may play a role in this series of events. For example, are enteral feeding, microbes such as bacteria or viruses, or hypoxic injury simply

the initiator of this pathway? Studies have focused on these factors, as they may be involved in the etiology of NEC.

The clinical presentation of NEC can be highly variable, although classically, infants demonstrate abdominal distention, bloody stools, and/or gastric residuals. Some infants can progress quickly to fulminant shock and death. Laboratory evaluation may show elevated white blood cell count with shift to immature cells, neutropenia, thrombocytopenia, electrolyte abnormalities, and metabolic acidosis. Radiographs may show subtle signs such as nonspecific disorganized bowel gas patterns, or fixed, dilated loops. However, the pathognomic finding of NEC is pneumatosis intestinalis, or air in the bowel walls. In more severe cases, portal venous gas or pneumoperitoneum may be seen. Staging via Bell's classification is based on clinical, laboratory, and radiologic signs, varying from the least severe (stage I) to the worst (stage III).<sup>5</sup> Findings on histology include mucosal edema, inflammation, hemorrhage, coagulation necrosis, and mucosal ulceration, with

the terminal ileum and proximal colon being the most commonly affected sections. The necrosis and inflammation of the intestinal walls seen microscopically correlates with the abdominal distention and sometimes a "bluish" tinge seen on abdominal examination of these infants.

Once diagnosed, initial management includes bowel rest, decompression with a gastric tube, sepsis evaluation, fluid resuscitation, and broad-spectrum antibiotics. Expectant management is appropriate in hemodynamically stable infants. However, severely affected infants often require ventilatory support, vasoactive medications, aggressive fluid resuscitation, and blood product transfusion. Surgical intervention may be required for frank bowel perforation or for worsening clinical status, implying the need for resection of nonviable bowel.

NEC carries significant morbidity and mortality, with 10% to 50% of infants suffering long-term associated morbidities, 15% to 30% suffering mortality, and 20% to 40% of infants requiring surgery.<sup>1,6</sup> Survivors suffer gastrointestinal complications in the short term

with feeding difficulties, and in the long term with poor growth, potential liver disease from parenteral nutrition supplementation, or short gut syndrome.

One of the most frustrating aspects of NEC for clinicians is the lack of biomarkers to predict and diagnose disease, and the lack of definitive treatment. Therefore, prevention of NEC would be the ideal solution for a disease as devastating as NEC. There has been a recent emphasis in NEC research on how to prevent NEC, focusing on a number of factors that have been suggested as important in the pathogenesis of disease. Probiotics have been promising in several large, well-designed studies, but have not yet gained wide acceptance in the United States due to strict US Food and Drug Administration guidelines. The use of human milk feeding, as opposed to formula feeding, also has been promising and its protective effect is likely due to the immunoprotective factors found in breast milk and its ability to promote intestinal colonization.<sup>6</sup>

### **Congenital Hypopituitarism**

The physiological normal range of fasting glucose at all ages is 70 to 100 mg/dL. However, there is no universally agreed upon threshold level of blood glucose considered to be sufficiently low to diagnose hypoglycemia and prompt further evaluation, especially in neonates.<sup>7</sup> Use of a glucometer to test a patient's blood sugar levels (ie, "accuchecks") should be verified by serum glucose testing. Generally, a serum glucose level lower than 40 mg/dL in the neonatal period has been used as a specific cut-off for likely pathology, necessitating further evaluation. Hypoglycemia in the neonatal period can be caused by several disease states, including sepsis or other hypermetabolic states, glycogen storage diseases, fatty acid oxidation disorders, disorders of gluconeogenesis, limited glycogen stores, hyperinsulinism, and deficiencies

of pituitary hormones. Evaluation should be appropriately tailored based on clinical presentation and laboratory findings (**Figure 2**).

Congenital hypopituitarism is a rare condition, defined as the underproduction of one or more pituitary hormones (**Table 1**).<sup>8</sup> It may occur as a result of birth trauma and/or asphyxia, as part of a number of midline anatomic defects, or secondary to a genetic mutation involving the anatomic development of the pituitary gland.<sup>9</sup> Because the clinical presentation can be variable (from none to severe nonspecific symptoms), the diagnosis is often delayed. The most common symptoms include hypoglycemia (which may result in life-threatening seizures, apnea, or cyanosis), prolonged jaundice, or dysmorphic features on examination.<sup>10</sup> Dysmorphic features include midline defects, ocular and craniofacial anomalies, and microphallus in males with or without cryptorchidism. Birth size and weight are often normal or moderately reduced. In this patient, hypoglycemia secondary to hypopituitarism may have been an inciting risk factor in her development of NEC,<sup>11</sup> although other factors were likely also contributory because the majority of patients with congenital hypopituitarism do not develop NEC.

Careful evaluation of these patients is critical, as early treatment prevents the morbidity and mortality associated with untreated hormonal abnormalities. Evaluation should include serum testing for hormone levels, but diagnosis based on laboratory evaluations can sometimes be difficult in the neonatal period as age-normative data are lacking.<sup>12</sup> In the newborn period, a growth hormone (GH) level <20 mcg/L during hypoglycemia or after a glucagon stimulation test is definitive. However, with clinical evidence, a single, randomly taken GH level <7 mcg/L in the first week of

life can also be diagnostic.<sup>13</sup> Thyroid function testing and cortisol function should also be assessed. Pituitary gonadotropin levels and sex steroids, perhaps at birth and then during the "mini-puberty" of infancy at age 2 months, may be helpful to aid in early treatment to minimize medical and psychological complications associated with deficiencies resulting in micropenis in males.

Definitive diagnosis can be made by MRI of the brain and pituitary gland, and MRI may also identify associated structural anomalies. Classical congenital hypopituitarism is characterized by the triad of pituitary stalk interruption syndrome: (1) an interrupted or thin pituitary infundibulum, (2) an absent or ectopic posterior pituitary, and (3) anterior pituitary hypoplasia or aplasia.<sup>14</sup> Other associated structural abnormalities may include optic nerve hypoplasia, absent septum pellucidum, agenesis of the corpus callosum, septo-optic dysplasia, and Arnold-Chiari I malformation.<sup>15</sup>

Although the majority of cases (80%-90%) of congenital hypopituitarism are sporadic,<sup>16</sup> specific gene mutations have been found in an increasing number of cases, especially as the identification of genes that are key in pituitary development and hormone production is expanding. A positive family history and significant malformation of the pituitary gland are risk factors that increase the likelihood of finding a specific genetic mutation. Patients with a complex phenotype, including anterior pituitary hormone deficiencies in association with extra-pituitary abnormalities or malformations, generally have defects in transcription factor genes that are expressed in the early development of the forebrain and midline structures. Patients with pure anterior pituitary hormone deficiencies but normal hypothalamo-pituitary morphology

often have mutations of pituitary-specific transcription factors that act late in pituitary development.<sup>17</sup> This categorization underlies the importance of MRI in diagnostic evaluation, as genetic testing can be recommended on the basis of imaging findings.

Early treatment with hormone replacement therapy is critical to avoid growth impairment (due to growth hormone deficiency), fatal adrenal crisis (due to cortisol deficiency), or cretinism (due to thyroid hormone deficiency). Adequate replacement of both growth hormone and cortisol may be key to avoidance of hypoglycemia and adverse neurologic sequelae that may ensue in the important early period of critical neurocognitive development. Children with GH deficiency that are untreated may be more than 4 standard deviations below mean height by age 1 year, and may only achieve 70% of growth potential.<sup>17</sup> Periodic evaluation of thyroid and cortisol function is also important. The need for replacement of sex hormones should be assessed based on the individual patient, and becomes especially important at the age of normal pubertal

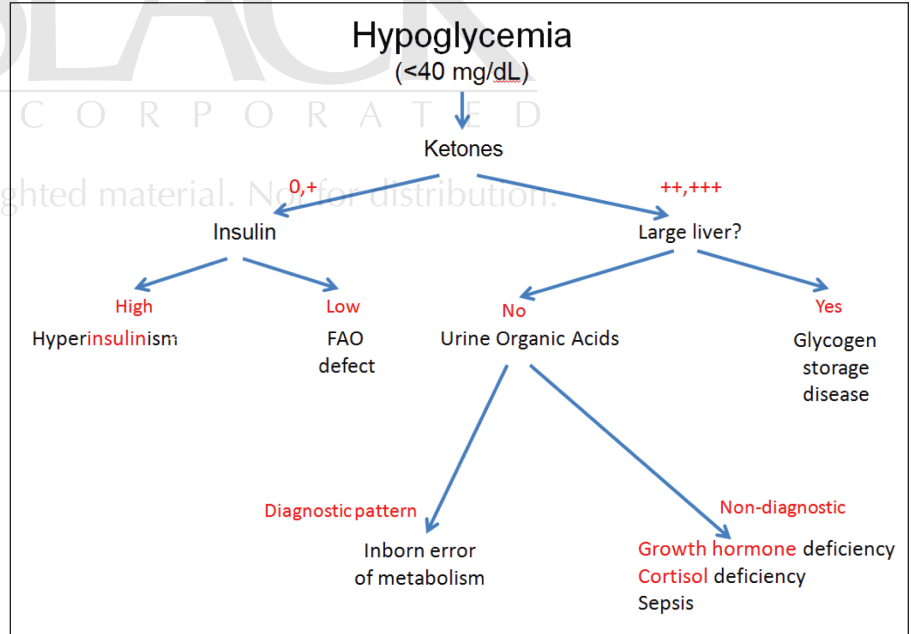


Figure 2. Algorithm for assessment of hypoglycemia. FAO, fatty acid oxidation.

maturation. A short course of testosterone over a few months in infancy or childhood may address the micropenis that ensues from hypogonadism, and replacement of testosterone, and later follicle-stimulating hormone and luteinizing hormone may optimize penile size and sexual and reproductive function in adulthood.<sup>18,19</sup>

**CONCLUSION**

In summary, NEC in a full-term infant is relatively rare and warrants further investigation. There are a number of associated conditions that may predispose a full-term infant to NEC, such as congenital heart disease, metabolic deficiencies, and asphyxia. Given its rarity, careful observation of

TABLE 1.

**Schematic of the Hypothalamic-Pituitary Axis**

Hypothalamus							
Hormone released by hypothalamus	Growth hormone-releasing hormone	Corticotropin-releasing hormone	Thyrotropin-releasing hormone	Prolactin-inhibitory factor	Gonadotropin-releasing hormone	Antidiuretic hormone	Oxytocin
Adenohypophysis					Neurohypophysis		
Hormone released by pituitary	Follicle-stimulating hormone/luteinizing hormone	Adrenocorticotropic hormone	Thyroid-stimulating hormone	Prolactin	Gonadotropin hormone	None	None
Target organ	Gonads	Adrenal cortex	Thyroid	Mammary gland	Liver/cartilage	Kidney	Mammary gland
Hormone/function	Estradiol or testosterone	Cortisol	T4/T3	Milk	Insulin-like growth factor	Urine concentration	Milk let down

Abbreviations: T3, triiodothyronine; T4, thyroxine.

clinical abnormalities in full-term infants with NEC should lead to further investigation for a potential associated risk factor. In the infant discussed in this article, the early and persistent hypoglycemia was a clue to her underlying endocrinopathy, which is a known associated risk factor for NEC in a full-term infant. Although a rare cause of hypoglycemia, congenital hypopituitarism is important to consider as early diagnosis and treatment imparts more favorable outcomes.

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