Focal intestinal perforation in late preterm and term neonates with hypoxic ischemic encephalopathy

Ryan M. McAdams a,*, Daniel J. Ledbetter b

a Department of Pediatrics, University of Washington and Seattle Children’s Hospital, Seattle, WA, USA
b Department of Surgery, University of Washington and Seattle Children’s Hospital, Seattle, WA, USA

Abstract
Focal intestinal perforation (FIP) is a significant cause of morbidity and mortality in extremely low birth weight neonates. In late preterm or term neonates, birth asphyxia is a risk factor for FIP, although recent reports of FIP in these patients are limited. We describe two cases of FIP, one in a late preterm neonate and one in a term neonate, both associated with hypoxic ischemic encephalopathy. Potential risk factors and pathophysiological mechanisms of FIP in late preterm and term neonates are discussed.

Gastrointestinal perforations without an identifiable cause, commonly referred to as idiopathic-, localized-, spontaneous, or focal intestinal perforations can occur in neonates, children, and adults [1,2]. In preterm neonates, these gastrointestinal perforations typically occur in extremely low birth weight (ELBW) infants, and appear to be associated with specific risk factors such as chorioamnionitis and exposure to postnatal steroids with or without indomethacin treatment [3–5]. In term neonates, although not as common, gastrointestinal perforations have been associated with birth asphyxia [6,7].

Since perforations in neonates are usually associated with specific risk factors it may be preferable to describe the bowel injury as a “focal” intestinal perforation (FIP) [8,9], which alludes to the extent of injury rather than “spontaneous” intestinal perforation, which suggests that these risk factors are only coincidental. Histopathologically, FIP is characterized by focal intestinal perforations with necrosis of the muscularis externa and no ischemic damage [10]. Most of the recent literature on FIP discusses cases in ELBW neonates and reports of late preterm or term neonates with FIP are uncommon. We describe two cases of FIP, one in a late preterm neonate and one in a term neonate, both associated with hypoxic ischemic encephalopathy (HIE).

1. Case 1

A female neonate was born by emergency Caesarean section at 36 weeks and 5 days gestation to a 36-year-old Gravida 2 Para 1 female after a failed attempted vaginal birth after previous Caesarean section. The birth weight was 3075 g (61.6 percentile). The delivery was complicated by placenta accreta with abruption and a difficult extraction because the fetal head was stuck in pelvis for approximately 10 min. At birth, the neonate had no tone or respiratory effort. She received positive pressure bag mask ventilation for 5 min, transitioned to continuous positive airway pressure, and was subsequently intubated and placed on mechanical ventilation. Apgar scores were 2, 4 and 6 at 1, 5 and 10 min, respectively. She developed bilateral pneumothoraces, which were treated with bilateral needle thoracostomy and a left chest tube. She had hypotension requiring dopamine and dobutamine. She received 2 doses of surfactant and was extubated on day of age 2 to room air. She was coagulopathic and received multiple blood product transfusions. An echocardiogram demonstrated an atrial septal defect, patent ductus arteriosus, and muscular ventricular septal defect. An abdominal ultrasound on day of age 5 demonstrated a 3.2 × 1.1 × 1.2 cm hypoechoic area consistent with a hepatic infarct along the anterior/superficial aspect of the right
haptic lobe. Her serum creatinine was elevated at 3.7 mg/dl and her renal US showed intact Doppler flow bilaterally with hydronephrosis. An electrical encephalogram (EEG) showed no seizure activity, but a discontinuous background suggestive of moderate encephalopathy. Although she had HIE, she did not undergo therapeutic hypothermia. On day of age 6 feeds were started with expressed breast milk. On day of age 8 feeds were stopped due to feeding residuals, mucoid stools with frank blood, and abdominal distension. Abdominal radiograph showed free air without pneumatosis intestinalis and she was transferred to our tertiary care facility for surgical management.

On the day of transfer, exploratory laparotomy was performed and a focal perforation in the terminal ileum (5 cm from the ileocecal valve) of about 40% of the circumference of the bowel was the only abnormality noted. Following a small bowel resection (pathology specimen not sent), a primary reanastomosis was performed. Peritoneal culture grew a few *Staphylococcus epidermidis*.

Postoperatively, she was treated with piperacillin and tazobactam for one week. On day of age 11 she was discharged from the NICU with hospital discharge on day of age 34. At a 5-month-old neurology follow up visit she was noted to have no feeding issues, and a normal gross motor exam.

2. Case 2

A male neonate was born by spontaneous vaginal delivery at 39 weeks and 4 days gestation to a 36-year-old Gravida 1 Para 1 female. The birth weight was 3798 g (71.6 percentile). The pregnancy was complicated by a maternal urine culture positive for Gardnerella that was treated. Other screening labs, including Group B Streptococcus, were negative. The delivery was complicated by shoulder dystocia and maternal fever with ampicillin treatment given 10 min prior to delivery. At birth, the neonate had no respiratory effort so he was intubated and placed on mechanical ventilation. Apgar scores were 2, 5 and 5 at 1, 5 and 10 min, respectively. The neonate had an elevated temperature of 39.3 Celsius and initial laboratory effort so he was intubated and placed on mechanical ventilation. Apgar scores were 2, 5 and 5 at 1, 5 and 10 min, respectively. The neonate had an elevated temperature of 39.3 Celsius and initial blood gas demonstrated a metabolic acidosis with a pH of 7.05, a pCO2 of 22 mm Hg, and base excess of −24. A large right tension pneumothorax and left pneumothorax were noted after intubation. Following bilateral needle thoracostomy, a right chest tube was placed. The neonate was passively cooled and transferred to our tertiary care facility for therapeutic hypothermia, which commenced at 8 h of age for HIE.

The neonate’s white blood cell count was elevated at 78,100 mm−3 and he was placed on ampicillin and cefotaxime for empiric sepsis coverage. A random cortisol level was elevated at >61.5 mcg/dL. The neonate’s clinical course was complicated by a subgaleal hemorrhage, verified by MRI, which was aggressively treated with blood products to correct his coagulopathy. He had hypotension that was treated with a dopamine drip and hydrocortisone (1 mg/kg every 12 h). Clinical seizures, which were noted at 14 h of age and confirmed with an EEG, were treated with phenobarbital. The neonate received 72 h of therapeutic hypothermia for HIE.

On day of age 4, expressed breast milk feeds were started at 5 mL every 3 h. On day of age 6, the neonate developed abdominal distension and abdominal radiograph showed free air without pneumatosis. Exploratory laparotomy was done and a focal perforation at the terminal ileum, 10−15 cm from the ileocecal valve was noted. A 4 cm segmental resection was done and both intestinal ends were brought out the abdominal wall through a single incision as a “double barrel” ileostomy. Peritoneal cultures were negative. Histopathology of the resected bowel demonstrated thinning and loss of the normal muscularis propria accompanied by hemorrhage and ischemic change (Fig. 1). The adjacent bowel was edematous without necrotic tissue.

Postoperatively, the neonate was treated with piperacillin and tazobactam for one week. He was weaned to room air on day of age 9 and feeding was resumed on day of age 12. An ileostomy take-down and ileostomy was performed at 37 days of age. At 2 months of age he was noted to be doing well with no recurrent seizures and no neurological abnormalities on physical exam.

3. Discussion

The first report of a gastrointestinal perforation in a newborn was published by Siebold in 1825 [11]. Many similar cases were subsequently reported in the literature, including Thelander’s review of 83 cases of spontaneous gastrointestinal perforation (excluding known bowel obstruction) published between 1825 and 1939 [12]. In this series, which may have included newborns with necrotizing enterocolitis (NEC), most of the infants were born at term (90.4%; 75 of 83) and mortality was very high (98.8%; 82 of 83 died). Later, Bell reported 60 cases of gastrointestinal perforation, which included 31 cases of NEC, 8 cases due to obstruction, 6 cases related to feeding tube–associated perforations, and 10 cases of spontaneous gastric perforations that occurred within the first five days of age [13]. In this series, which included some term neonates (although specific gestational age details were not available), mortality was only 33%, likely reflecting improvements in diagnosis, perioperative care, anesthesia and antibiotic therapy. In a recent prospective 5-year multicenter analysis by Fisher et al. that included 177,618 very-low-birth-weight (VLBW, 401−1500 g)
neonates born between January 2006 and December 2010 admitted to US hospitals participating in the Vermont Oxford Network, laparotomy-confirmed FIP was diagnosed in 2036 neonates (an incidence of 1.1%) and the mortality rate was 19% [14].

Although survival of FIP has dramatically increased over the past century, particularly in smaller, more premature neonates, the etiology of FIP in neonates remains incompletely understood. Currently, FIP is mainly seen in ELBW neonates and has been associated with exposure to postnatal steroids within the first week of age and early use of indomethacin, chorioamnionitis, stress with an elevated cortisol level, and infection (particularly with Candida and S. epidermidis) [15]. Attridge et al., using a national data set, described two forms of FIP that differ in both time of presentation and gestational age with ELBW (median 25 weeks' gestation, median birth weight 0.775 kg) neonates presenting at 7 days of age (median), whereas older preterm (median 31 weeks' gestation, median birth weight 1.401 kg) neonates typically present within 3 days of age [4]. Gordon has proposed that in ELBW neonates who acquire FIP between days 4–14, perforation occurs after postnatal steroid treatment (alone or in combination with indomethacin), which induces ileal mucosal hyperplasia and submucosal thinning [10]. These changes likely make the ileal wall more vulnerable to focal necrosis and perforation once bowel motility resumes (proximal to distal) and ileal wall tension increases with peristalsis and luminal distention.

Unlike ELBW neonates, the pathophysiologic mechanisms related to FIP in late preterm and term neonates are not clear. The neonate in Case 2 had an elevated cortisol level and was treated with hydrocortisone for hypotension for 4 days before he was diagnosed with FIP. Cortisol levels were not checked in the neonate in Case 1. Whether high endogenous cortisol levels or exposure to postnatal steroids have similar affects on the ileal wall in term neonates as in preterm neonates needs further study. Neither of the neonates was treated with indomethacin. Both neonates were hypotensive, which may have compromised mesenteric perfusion and contributed to the development of FIP. Additionally, both neonates were fed prior to the occurrence of their perforations. While term infants may share risk factors for NEC and FIP, such as birth asphyxia, the distinct intestinal histopathology is consistent with disparate entities similar to the different bowel injury patterns seen in preterm neonates.

Asphyxia has been recognized as a risk factor for FIP [6]. Lloyd reported that birth asphyxia was present in 80% of the cases of his analysis of 83 neonates with gastrointestinal perforation, 50 of whom died (43 had autopsies performed) [16]. Based on review of 402 cases of gastrointestinal perforation in neonates, which did not describe their gestational age or birth weight, he proposed that in the setting of asphyxia, the mammalian Diving Reflex is activated with subsequent preferential circulation to the heart and brain with shunting of blood from the mesenteric, renal, and peripheral vascular beds. This inherent circulatory stress response has been speculated to result in localized gut ischemia that may lead to FIP. Prabhakar et al., in a retrospective analysis from a single center in India, reported gastrointestinal perforation in 27 neonates (18 born at home, 3 preterm, and 22 low birth weight) of which 3 hospital-born neonates had known birth asphyxia [7].

4. Conclusion
Late preterm and term neonates with HIE are at risk for FIP. The pathogenesis of FIP in these patients remains unclear, but may be related to localized bowel weakening due to mesenteric hypoperfusion during a period of asphyxia, or other variables such as increased endogenous or exogenous steroid exposure. Monitoring cortisol levels, judicious use of steroids, and observant initiation of feeds is recommended in infants with HIE.

Disclosures
This manuscript does not contain patient studies or patient identifying information.

Conflicts of interest
The authors have no conflict-of-interest, financial support, or other potential conflicts of interest to declare.

Acknowledgment

We would like to thank Dr. Bonnie Cole for providing the histology images.

References