Food Protein–Induced Enterocolitis Instead of Necrotizing Enterocolitis? A Neonatal Intensive Care Unit Case Series

Mary W. Lenfestey, MD[1], Diomel de la Cruz, MD[2], and Josef Neu, MD[2]

Necrotizing enterocolitis is an important disease in infants born premature. However, other disease entities present with similar signs and symptoms. This series reviews 5 atypical cases initially diagnosed as necrotizing enterocolitis that may be more consistent with food protein–induced enterocolitis. Food protein–induced enterocolitis may be underdiagnosed in this population. *(J Pediatr 2018;200:270-3).*

Necrotizing enterocolitis (NEC) is one of the leading causes of morbidity and mortality in neonates born preterm, with mortality as high as 40%-50%. The course of the disease is variable, ranging from mild to life threatening.[1] Long-lasting effects for those patients who do survive can be debilitating, with correlation of NEC and poor neurodevelopmental outcomes.[2] There is an inverse relationship with gestational age and birth weight, with infants born preterm accounting for >90% of cases.[3] NEC has been noted to occur in 6%-7% of infants of very low birth weight (birth weight <1500 g).[4,5] The disease is multifactorial, involving the premature gastrointestinal tract with immature mucosa and abnormal motility patterns, an immature host immune response, likely gastrointestinal dysbiosis, and the controversial role of advancement of enteral nutrition.[6,7]

The symptoms, laboratory measures, and radiographic findings for NEC are nonspecific. Radiographs of the abdomen may demonstrate pneumatosis intestinalis, pneumoperitoneum, or portal venous gas.[8] Cytopenias, especially neutropenia and thrombocytopenia, are common and correlate with poorer outcomes.[9] Elevated C-reactive protein (CRP) may be noted.[10] A clear definition is lacking, and other disease processes mimic these clinical findings.[11]

We suspect that food protein–induced enterocolitis (FPIES), a non–IgE-mediated syndrome resulting in hypersensitivity to food antigens, is one such entity. Patients with FPIES typically present in the first months of life with vomiting, diarrhea, hematochezia, or lethargy within 1-4 weeks after initial exposure to the triggering antigen. There are both acute and chronic presentations; acute FPIES is seen with intermittent ingestion of the triggering food.[12] Unrecognized FPIES results in chronic symptoms with poor weight gain and failure to thrive; this often occurs with ongoing ingestion of cow's milk or soy proteins.[13] Cow's milk and soy proteins are the 2 most common food triggers.[14] Similar to NEC, FPIES is more common among infants given formula. As with NEC, the presence of transforming growth factor-β and IgA in breastmilk may be protective for infants who are breastfed exclusively.[15-17] Although the pathophysiology of FPIES is not fully understood, data suggest an activation of the innate immune system and T cells with exposure to food antigens.[18,19] Increased levels of tumor necrosis factor-α and decreased expression of transforming growth factor-β receptors also have been noted in the intestinal mucosa in FPIES patients.[20]

The gold standard for diagnosis is an oral food challenge. Although laboratory findings cannot confirm the diagnosis of FPIES alone, some general trends are common in these patients, including leukocytosis with an eosinophil predominance, thrombocytosis, hemoccult positive stools, anemia, hypoalbuminemia, and radiographic findings of intestinalis pneumatosis.[20-22]

To explore the possibility of FPIES masquerading as NEC in the preterm population, all of the cases of diagnosed NEC from 2014 to 2017 within our neonatal intensive care unit (NICU) were reviewed. Of the 56 infants identified, several patients had atypical clinical courses. We propose FPIES as an alternative diagnosis.

Methods

A chart review was completed for the 56 infants diagnosed with NEC in our NICU from 2014 to 2017. Data on clinical presentation and course were collected, including the timing of symptom onset, radiologic and laboratory findings, need for surgical intervention, and relationship of symptoms and feeds. Infants who had evidence of bowel perforation (free air or portal venous gas) or required surgical intervention were presumed to have NEC. There were 5 nonsurgical patients identified with symptoms and courses that were atypical based on age of onset, laboratory findings (absence of leukopenia, presence of eosinophilia), occurrence of multiple episodes, and correlation of symptom onset and resolution with feed changes.

The 5 infants with clinical courses atypical for NEC are described to follow. For full details regarding patient description, case summary, and laboratory and imaging findings, please refer to **Tables I** and **II**.

CRP	C-reactive protein
FPIES	Food protein–induced enterocolitis
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit

From the [1]Division of Pediatric Gastroenterology; and [2]Department of Pediatrics, Neonatology, University of Florida, Gainesville, FL

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Table I. Summary of clinical presentation and course for cases A-E

Patient IDs	Gestational age, wk	Other diagnoses	Age at symptom onset (day of life)	Sex	Enteral nutrition*	Presenting symptom(s)
A	35	IUGR, Noonan syndrome, congenital heart disease, airway malacia	2, 29, 39 (35, 39, 41 wk PMA)	Female	Enfamil + EBM, Enfacare formula, Enfamil formula	Distention, increased gastric residual, bloody stools†
B	28	Atrial and ventricular septal defect	45 (34 wk PMA)	Female	Enfamil premature formula	Emesis, bloody stools
C	26	Maternal eclampsia	29, 63, 73 (30, 35, 36 wk PMA)	Female	EBM/DBM + HMF, Similac special care formula, Alimentum	Emesis, bloody stools†
D	29	Severe maternal pre-eclampsia	12, 26, 51 (30, 32, 36 wk PMA)	Female	EBM/DBM + HMF, EBM/DBM + HMF, EBM + Alimentum	Emesis, distention, increased gastric residual, bloody stools†
E	29	Severe maternal pre-eclampsia	12 (31 wk PMA)	Male	EBM/DBM + HMF	Bloody stools

DBM, donor breast milk; *EBM*, expressed mother's milk; *HMF*, human milk fortifier; *IUGR*, intrauterine growth restriction; *PMA*, postmenstrual age.
*Feeds at time of symptom onset.
†For cases with multiple episodes of feeding intolerance, not all symptoms were present with each episode.

Case A

A patient with Noonan syndrome was born at 35 weeks of gestation due to intrauterine growth restriction and nonreassuring fetal heart tones. Primary issues during the hospitalization included congenital heart disease, pulmonary hypertension, and severe tracheobronchomalacia. This patient had 3 notable episodes of feeding intolerance during the hospitalization. At 2 days of age, within 24 hours of initiating feeds with a cow's milk–based formula plus breastmilk, the patient developed large-volume residuals, abdominal distention, and tenderness. After 4 days of bowel rest, feedings were restarted with a cow's milk–based formula. At 29 days of age (39 weeks of postmenstrual age), the patient developed abdominal distention, emesis, and hematochezia with pneumatosis. Feeds were held for 48 hours, after which enteral feeds of the cow's milk–based formula were resumed. At 39 days of age (41 weeks of postmenstrual age), the patient developed loose stools streaked with mucus and blood but was otherwise stable. Blood culture was positive for a methicillin-resistant, gram-positive organism (not *Staphylococcus aureus*, confirmed by polymerase chain reaction), but after further evaluation, the positive culture was felt to be a contaminant. Transpyloric feeds were restarted at 43 days of age with an extensively hydrolyzed casein formula. After transition to the extensively hydrolyzed formula, the patient had no further episodes of hematochezia or feeding intolerance.

Cases B-E are summarized in **Tables I** and **II**. All 5 patients demonstrated clinical courses that were inconsistent with a classic presentation of NEC. Cases A, C, and D demonstrated relapsing courses, with symptoms of feeding intolerance and hematochezia recurring as discrete episodes; the onset of the later episodes occurred outside of the most common window of occurrence for NEC. Although NEC can occur at any time, it is most common near 32 weeks of gestation.[6] The 3 infants described with relapsing courses had continued symptoms from 35 to 41 weeks of postmenstrual age. There seemed to be a correlation of symptoms with attempts to advance or fortify feeds with cow's milk protein containing nutrition for several cases.

Abdominal imaging was positive for pneumatosis at some point for 5 of 5 (100%) of cases A-E, as well as 39 of 51 (76.4%) of infants with classic NEC presentations. Other findings noted in the atypical cases included distention of bowel loops and wall thickening. None of the infants presented with free air or portal venous gas, in comparison with 23 of 51 (45%) of infants who clinically presented with classic NEC. For laboratory findings, the only positive blood culture among cases A-E was one obtained in the third episode for case A, which was subsequently evaluated as a contaminant. No other blood cultures were positive. None of the cases felt to have FPIES had elevated CRPs, compared with 27 of 51 (52.9%) of the infants with a more classic NEC presentation. Thrombocytopenia at <24 hours of symptom onset was more predominant in the group with typical NEC presentations, in 26 of 51 infants (50.9%). In contrast, only 1 of 5 (20%) of the atypical cases developed thrombocytopenia.

The group of infants who presented as classic NEC had more leukopenia, with 20 of 51 infants having white blood cell counts <5.0 (10^3/mm^3) at some point within the first 24 hours of symptoms. In cases A-E, only 1 of 5 (20%) patients had a leukocyte count <5.0 (10^3/mm^3), and this was only during 1 of the 3 episodes noted. With respect to cell subtypes, monocytosis was present in both groups; this finding was noted in 4 of 5 (80%) patients with atypical presentations and 34 of 51 (66.6%) with classic presentations. Eosinophilia was noted somewhat more often in the atypical cases, in 2 of 5 (40%) patients, as compared with the classic group in only 6 of 51 patients (11.7%). Albumin was found to be low in 3 of 5 cases (60%), which was comparable with the NEC group (33/51, 64.7%). There were no differences in hemoglobin concentration noted between the 2 groups.

Discussion

We propose that FPIES can mimic NEC in the preterm NICU population. Although there have been a few reports of FPIES in the premature population,[23,24] it may be underdiagnosed in this group of patients. One challenge in the diagnosis of FPIES is the lack of pathognomonic tests and overlap in clinical presentation with both NEC and cow's milk protein intolerance, another allergic process that may present as feeding

Table II. Detailed laboratory and imaging summary for cases A-E

Cases	WBC	WBC at 24 h	Monocytes (normal <10%)	Monocytes at 24 h	Eosinophils (normal <8%)	Eosinophils at 24 h	Platelets	Platelets at 24 h	Hemoglobin	Hemoglobin at 24 h	Albumin (normal 3.5-5 g/dL)	CRP (normal <4.9 mg/L)	Blood culture	Imaging (radiograph)
A-1	9300 mm^3 (9.3×10^9/L)	7700 mm^3 (7.7×10^9/L)	10%	3%	0%	0%	47×10^3/mm^3 (47×10^9/L)	55×10^3/mm^3 (55×10^9/L)	17.1 g/dL (171 g/L)	16.4 g/dL (164 g/L)	3.5 g/dL (35 g/L)	1.8 mg/L (17.1 nmol/L)	Negative	Gaseous distention of bowel loops
A-2	12 200 mm^3 (12.2×10^9/L)	18 200 mm^3 (18.2×10^9/L)	8%	14%	2%	1%	148×10^3/mm^3 (148×10^9/L)	155×10^3/mm^3 (155×10^9/L)	16.9 g/dL (169 g/L)	17 g/dL (170 g/L)	4.4 g/dL (44 g/L)	0.9 mg/L (8.6 nmol/L)	-	Pneumatosis
A-3	15 100 mm^3 (15.1×10^9/L)	10 000 mm^3 (10×10^9/L)	4%	45%	4%	4%	232×10^3/mm^3 (232×10^9/L)	188×10^3/mm^3 (188×10^9/L)	13.5 g/dL (135 g/L)	12.3 g/dL (123 g/L)	3.8 g/dL (38 g/L)	0.6 mg/L (5.7 nmol/L)	+ Methicillin-resistant gram-positive organism (not MRSA)*	Pneumatosis
B	15 300 mm^3 (15.3×10^9/L)	10 100 mm^3 (10.1×10^9/L)	8%	5%	0%	3%	598×10^3/mm^3 (598×10^9/L)	360×10^3/mm^3 (360×10^9/L)	10.7 g/dL (107 g/L)	14.6 g/dL (146 g/L)	4.5 g/dL (45 g/L)	0.5 mg/L (4.6 nmol/L)	Negative	Pneumatosis
C-1	6300 mm^3 (6.3×10^9/L)	—	6%	—	4%	—	162×10^3/mm^3 (162×10^9/L)	—	12.8 g/dL (128 g/L)	—	3.8 g/dL (38 g/L)	0.7 mg/L (6.7 nmol/L)	Negative	Pneumatosis
C-2	—	11 000 mm^3 (11×10^9/L)	—	12%	—	33%	—	206×10^3/mm^3 (206×10^9/L)	—	9.6 g/dL (96 g/L)	3.7 g/dL (37 g/L)	0.6 mg/L (5.7 nmol/L)	Negative	Wall thickening
C-3	15 000 mm^3 (15.0×10^9/L)	11 500 mm^3 (11.5×10^9/L)	6%	10%	24%	27%	224×10^3/mm^3 (224×10^9/L)	209×10^3/mm^3 (209×10^9/L)	7.6 g/dL (76 g/L)	7.5 g/dL (75 g/L)	3.4 g/dL (34 g/L)	4.6 mg/L (43.8 nmol/L)	Negative	Pneumatosis
D-1	7200 mm^3 (7.2×10^9/L)	—	6%	—	0%	—	250×10^3/mm^3 (250×10^9/L)	—	8.2 g/dL (82 g/L)	—	3.4 g/dL (34 g/L)	0.3 mg/L (2.86 nmol/L)	Negative	Gaseous distention of bowel loops
D-2	3100 mm^3 (3.1×10^9/L)	7700 mm^3 (7.7×10^9/L)	24%	13%	0%	2%	244×10^3/mm^3 (244×10^9/L)	285×10^3/mm^3 (285×10^9/L)	11.3 g/dL (113 g/L)	10.5 g/dL (105 g/L)	3.4 g/dL (34 g/L)	29.4 mg/L (280 nmol/L)	Negative	Pneumatosis
D-3	6700 mm^3 (6.7×10^9/L)	7300 mm^3 (7.3×10^9/L)	3%	13%	4%	10%	262×10^3/mm^3 (262×10^9/L)	229×10^3/mm^3 (229×10^9/L)	6.9 g/dL (69 g/L)	11.8 g/dL (118 g/L)	3.7 g/dL (37 g/L)	0.2 mg/L (1.9 nmol/L)	Negative	Pneumatosis
E	13 300 mm^3 (13.3×10^9/L)	—	17%	—	1%	—	235×10^3/mm^3 (235×10^9/L)	—	14.5 g/dL (145 g/L)	—	2.9 g/dL (29 g/L)	1.9 mg/L (18.1 nmol/L)	Negative	Pneumatosis

MRSA, methicillin-resistant *Staphylococcus aureus*; *WBC*, white blood cells.
*Felt to be a contaminant; a repeat blood culture was obtained. The repeat culture was collected after ampicillin therapy (to which the initial organism was tested as resistant) and was negative.

intolerance and hematochezia in infants.[12] Although review of cow's milk protein intolerance is outside of the scope of this series, it is important to note that patients are generally well appearing with adequate growth; radiologic images may demonstrate bowel wall thickening, but pneumatosis is uncommon in contrast to infants with FPIES. The cases described had clinical findings that were felt to be more consistent with the diagnosis of FPIES; oral food challenges, the gold standard for diagnosis, are seldom undertaken in this population; thus, diagnosis is most often based on clinical suspicion.

However, there are some differences that may provide a point of reference for clinicians attempting to discern the processes. The literature cites cases of both diseases having pneumatosis, low albumin, anemia, inflammatory marker elevations, and abnormalities in both total white blood cell count and the differential.[8,9,20-22] Reviews of FPIES often note thrombocytosis and leukocytosis, as compared with the leukopenia and thrombocytopenia in severe cases of NEC. The cases described in this series of neonates born preterm were diagnosed as NEC, but it can be argued that their clinical courses are more consistent with FPIES. When comparing these patients with the entire set of patients with NEC, they had less leukopenia, more eosinophilia, less thrombocytopenia, and were less likely to have an elevated CRP. Interestingly, all 5 of the patients reviewed had resolution of symptoms with modification of diet to an extensively hydrolyzed or an amino acid-based formula. Two of the patients did have congenital heart disease, which may predispose to feeding intolerance.

It is important to discern FPIES from classic NEC, as treatment is vastly different. With NEC, the patient is given antibiotics, feedings are stopped, and the infant requires parenteral nutrition for periods of time. In contrast, the management of FPIES is to remove to offending antigen with dietary elimination. Typically breastfeeding can be continued with maternal dietary modifications (as breastmilk is generally an uncommon trigger), and if formula is required, it can be changed to a hypoallergenic formula, such as an extensively hydrolyzed or an amino acid-based formula. As the treatment for NEC and FPIES, as well as morbidity and mortality, are different, it is important to develop methods to accurately diagnose each entity. This study does not offer definitive diagnostic differences between NEC and FPIES but raises awareness that some cases of NEC may actually fit more closely with the diagnosis of FPIES. We recommend that, given the significant morbidity and mortality associated with NEC, routine evaluation and management should be undertaken. However, with additional studies, it is possible that we may be able to more clearly differentiate between these 2 entities and further refine our treatment regimens. ■

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Reprint requests: Josef Neu, MD, 6516 SW 93rd Ave, Gainesville, FL. E-mail: neuj@peds.ufl.edu

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