RESEARCH ARTICLE

Food protein-induced enterocolitis syndrome versus necrotizing enterocolitis of the newborn, is there a relationship?

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Abstract

In recent years in neonatal units, an increase number of babies have protein allergy to cow's milk called by some FPIES (Food protein-induced enterocolitis syndrome), including term and preterm infants. Proinflammatory interleukin elevation has been reported associated to this syndrome. Hospitalized babies present in good condition but with severe abdominal distension, hematochezia, vomiting and/or diarrhea. After transient interruption of oral route and later hydrolyzed milk feedings, they become asymptomatic. Probiotics therapy has been used. On the other hand, extreme premature and some term infants develop necrotizing enterocolitis (NEC) with similar but more severe symptoms, with pneumatosis and some with porta vein gas and/or pneumoperitoneum. The incidence is higher in babies fed bovine derivate milk nutrition. NEC triggers are unknown, but probiotics are preventive. In Clínica del Country´s NICU in nine years, we treated 76 FPIES and 27 NEC. The FPIES were more mature, older and 0 mortality. NEC were very immature, younger and with 63% mortality. Three clinical scenarios are presented that illustrates the similarities and differences of these two pathologies. We speculate that proinflammatory cascade is triggered by the same antigen but acting on different populations, and so, producing either FPLIES or NEC. If this is true, hydrolyzed fortifiers could be useful.

Keywords: necrotizing enterocolitis, neonatal, food protein-induced enterocolitis syndrome, fortifiers

Introduction

In recent years, NICUs receiving outpatients have experienced an increase in patients with food protein-induced enterocolitis syndrome (FPIES).[1,2,3] Patients typically requiring hospitalization present with severe abdominal distension, hematochezia, vomiting and/or diarrhea. Apart from the abdominal symptoms, the patients are stable. This disorder is managed with the transient interruption of oral route followed by partially or fully hydrolyzed milk feedings, resulting in an asymptomatic patient.

Some authors have emphasized the presence of this pathology in small premature infants.[4] In the rare case of this condition during exclusive breastfeeding,[5] the recommendation to the mother to avoid dairy products has the same result. Probiotics have been associated with their management[6,7] and interleukin elevation has been associated in its pathophysiology.[8,9]

On the other hand, in the neonatal intensive care units (NICUs), extremely premature infants develop necrotizing enterocolitis of the newborn (NEC)[10] but not exclusively,[11] with similar symptoms of painful abdominal distention, vomiting, or presence of very large residues, hematochezia and rarely diarrhea. Abdominal radiography or sonography[12] confirms abdominal distention and is typically accompanied by pneumatosis. Severe forms show portal venous gas and pneumoperitoneum. Although some cases are progressive and persistent, others are fulminant with massive intestinal necrosis, progressive deterioration, and death despite seemingly appropriate surgery. It is not uncommon for patients to look healthy a few hours before the deterioration of the patient. It has been well documented that the frequency of enterocolitis is much lower in patients receiving exclusive breast milk[13] with human-based milk fortifiers (HB HMF),[14] followed by those receiving bovine origin fortifiers[15], with the highest incidence occuring in premature babies fed formula.[16] The clinical picture of fortifiers "intolerance" is very similar to an onset of enterocolitis.[11,16-18]

So far, it is not known what triggers NEC. It is known that there are a large number of proinflammatory cytokines,[19,20] different from those associated with FPIES, but it is not known what triggers this increase in previously healthy babies. Although the presence of bacteria plays a role in the treatment due to the risk of bacterial translocation, they have almost never been shown as a cause, and blood cultures are almost always negative. There has been

evidence of a change in the incidence of NEC with the use of prophylactic probiotics,[21,22,23] suggesting a better intestinal colonization after birth and a more adequate intestinal programming of their immune system.

Material and methods

The statistics of Clínica del Country´s NICU in the last 9 years (1/2011-12/2019) of patients with final diagnosis of suspected cow's milk protein allergy (FPIES) were reviewed (76 cases), as well as necrotizing enterocolitis of newborn (NEC) stages Bell II or more (27 cases).

Results

As expected, the average gestational age (GA) at birth for the FPIES group was 37 weeks while the NEC group was 29 weeks and the postnatal age at admission was 19 days for the first group while less than 1 day for the second. FPIES mortality was as expected 0%, while NEC was 63%. In our database there was no "intolerance to fortifiers" as a final diagnosis. However, there were several cases in which to make these premature babies grow, it was necessary to devise a form of fortification with hydrolyzed powdered milk, which although it does not contain adequate balanced nutrients as fortifiers, the final total amount of nutrition improves.

Some clinical cases are presented to emphasize the similarity and differences of the initial clinical picture between both pathologies studied:

1. The first case is of two in vitro twin girls of almost 31 weeks of gestation born due to a bleeding placenta previa. They were born by C-section in good general condition, received surfactant and evolved with minimal respiratory problems. They received probiotics by protocol and did not receive antibiotics. Parenteral and oral feeding were initiated within the first 24 hours also by protocol, with milk for premature infants as we don´t have banked milk. By the fourth day they already received 80% of breast milk from their own mother, without fortification. At the end of the 4th day suddenly one of the twins presented with vomiting, abdominal distension and in less than hours later had a pneumoperitoneum. She went into surgery and massive necrosis of the entire intestine was found with perforation of the ileum. Ileostomy was done, but the evolution was very poor and a few hours later she died. The twin sister who was receiving fortified breast

milk with bovine fortifier (we don´t have HMF HB), 4 days later developed severe abdominal distension and we believed it was NEC again. However, the general condition of the baby was very good and when the oral route was discontinued, the distention disappeared. Two days later we restarted oral feeds with breast milk from her own mother (the mother was dieting without dairy). 24 hours later, antibiotics and other forms of NEC therapy were discontinued. Her own mother´s milk was fortified with extensively hydrolyzed milk powder, but tolerance was poor. The added presence of apneas and poor reactiveness forced us to reevaluate the clinical diagnosis. Laboratory tests performed were normal and the intestinal transit only demonstrated significant delay without evidence of anatomical malformations. The oral route was continued with breast milk with slow tolerance until she was discharged home with adequate growth. The final diagnosis was FPIES.

2. A 38-day-old patient who was born less than 36 weeks GA had been hospitalized twice due to feeding problems at birth and the second time due to viral respiratory symptoms. He had a history of food intolerance with an ambulatory diagnosis of gastroesophageal reflux disease. He was admitted to another NICU due to abdominal distension and hematochezia. Radiographic findings of pneumatosis was demonstrated, enterocolitis management was initiated, and he was sent to us. During his hospital stay in our institution, the good general condition was evident, and when the oral route was suspended, the intestinal symptoms disappeared, and the abdominal radiographic finding normalized. Allergy to cow's milk protein was suspected, so he was fed during the stay and discharged with hydrolyzed milk and breast milk (mother was dieting without dairy) with very good tolerance.

3. Premature born at 30 weeks GA due to cervical incontinence of the mother who at 15 weeks GA had a cerclage. At birth due to infectious risk, he received antibiotics for 48 hours. Antibiotics were stopped due to negative blood cultures without evidence of infection. The oral route was started from birth and bovine fortifiers were started on day 7. On day 10, hematochezia and vomiting were evidenced, so NEC was suspected, and

management was initiated. On the 4th day of treatment with disappearance of blood in the stool and without evidence of abdominal distension or other signs of deterioration, he was restarted orally with breast milk (the mother was dieting without dairy) that was very well tolerated. NEC management was discontinued and diagnosis of FPIES was established. Breast milk was fortified with extensively hydrolyzed milk until discharge home.

Discussion

Although it is clear from the results that FPIES and NEC are two different pathologies, the similarity of the initial symptoms, that some evolve towards clear evidence of allergy or intolerance while others evolve to NEC when nutrition with cow's milk protein is given makes one think in a relationship between both pathologies. Would it be possible that they are related pathologies simply present in different populations with different risks?

Would it be conceivable that depending on the degree of immaturity or other unknown factors, the proinflammatory cascade that is triggered is different, producing either FPIES, intolerance or necrotizing enterocolitis?

Conclusion

If this principle is true, it would be very interesting to fortify breast milk with fortifiers made with extensively hydrolyzed milk, but with adequate protein and calcium/phosphorus content and look at the incidence of NEC.

Conflict of interest

No conflict of interest

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References

1 Mehr S, Frith K, Barnes EH, Campbell DE; FPIES Study Group. Food protein-induced enterocolitis syndrome in Australia: A population-based study, 2012-2014. J Allergy Clin Immunol. 2017 Nov;140(5):1323-30.

2 Kimura M, Shimomura M, Morishita H, Meguro T, Seto S. Serum C-reactive protein in food protein-induced enterocolitis syndrome versus food protein-induced proctocolitis in Japan. Pediatr Int. 2016 Sep;58(9):836-41.

3 Nowak-Wegrzyn A, Berin MC, Mehr S. Food Protein-Induced Enterocolitis Syndrome. J Allergy Clin Immunol Pract. 2020 Jan;8(1):24-35.

4 Lenfestey MW, de la Cruz D, Neu J. Food Protein-Induced Enterocolitis Instead of Necrotizing Enterocolitis? A Neonatal Intensive Care Unit Case Series. J Pediatr. 2018 Sep;200:270-3.

5 Capitan F, Robu AC, Schiopu C, et al. β-Lactoglobulin detected in human milk forms noncovalent complexes with maltooligosaccharides as revealed by chip-nanoelectrospray high-resolution tandem mass spectrometry. Amino Acids. 2015 Nov;47(11):2399-407.

6 Guadamuro L, Diaz M, Jiménez S, et al. Fecal Changes Following Introduction of Milk in Infants With Outgrowing Non-IgE Cow's Milk Protein Allergy Are Influenced by Previous Consumption of the Probiotic LGG. Front Immunol. 2019 Aug 2;10:1819

7 Qamer S, Deshmukh M, Patole S. Probiotics for cow's milk protein allergy: a systematic review of randomized controlled trials. Eur J Pediatr. 2019 Aug;178(8):1139-49.

8 Kimura M, Ito Y, Shimomura M, Morishita H, Meguro T, Adachi Y, Seto S. Cytokine profile after oral food challenge in infants with food protein-induced enterocolitis syndrome. Allergol Int. 2017 Jul;66(3):452-7.

9 D'Apolito M, Campanozzi A, Giardino I, Pettoello-Mantovani M. Levels of inflammatory cytokines from peripheral blood mononuclear cells of children with cow's milk protein allergy. Turk Pediatri Ars. 2017 Dec 1;52(4):208-12.

10 Jones IH, Hall NJ. Contemporary Outcomes for Infants with Necrotizing Enterocolitis-A Systematic Review. J Pediatr. 2020 Jan 22. pii: S0022-3476(19)31519-7

11 Overman RE Jr, Criss CN, Gadepalli SK. Necrotizing enterocolitis in term

neonates: A different disease process? J Pediatr Surg. 2019 Jun;54(6):1143-6.

12 Tracy SA, Lazow SP, Castro-Aragon IM, et al. Is Abdominal Sonography a Useful Adjunct to Abdominal Radiography in Evaluating Neonates with Suspected Necrotizing Enterocolitis? J Am Coll Surg. 2020 Feb 17.

13 Ochoa TJ, Mendoza K, Carcamo C, Zegarra J, Bellomo S, Jacobs J, Cossey V. Is Mother's Own Milk Lactoferrin Intake Associated with Reduced Neonatal Sepsis, Necrotizing Enterocolitis, and Death? Neonatology. 2020 Feb 13:1-8.

14 Sandhu A, Fast S, Bonnar K, Baier RJ, Narvey M. Human-Based Human Milk Fortifier as Rescue Therapy in Very Low Birth Weight Infants Demonstrating Intolerance to Bovine-Based Human Milk Fortifier. Breastfeed Med. 2017 Nov;12(9):570-3.

15 Sánchez-Hidalgo VM, Flores-Huerta S, Matute-González G, Urquieta-Aguila B, Bernabe-García M, Cisneros-Silva IE. A fortifier comprising protein, vitamins, and calcium-glycerophosphate for preterm human milk. Arch Med Res. 2000 Nov-Dec;31(6):564-70.

16 Cruz D, Bazacliu C. Enteral feeding composition and necrotizing enterocolitis. Semin Fetal Neonatal Med. 2018 Dec;23(6):406-10

17 Pillai A, Albersheim S, Matheson J, Lalari V, Wei S, Innis SM, Elango R. Evaluation of A Concentrated Preterm Formula as a Liquid Human Milk Fortifier in Preterm Babies at Increased Risk of Feed Intolerance. Nutrients. 2018 Oct 4;10(10).

18 Fanaro S. Feeding intolerance in the preterm infant. Early Hum Dev. 2013 Oct;89 Suppl 2:S13-20.

19 Wisgrill L, Weinhandl A, Unterasinger L, et al. Interleukin-6 serum levels predict surgical intervention in infants with necrotizing enterocolitis. J Pediatr Surg. 2019 Mar;54(3):449-54.

20 Terrin G, Stronati L, Cucchiara S, De Curtis M. Serum Markers of Necrotizing Enterocolitis: A Systematic Review. J Pediatr Gastroenterol Nutr. 2017 Dec;65(6):e120-32.

21 Robertson C, Savva GM, Clapuci R, Jones J, Maimouni H, Brown E, Minocha A, Hall LJ, Clarke P. Incidence of necrotising enterocolitis before and after introducing routine prophylactic Lactobacillus and Bifidobacterium probiotics. Arch Dis Child Fetal Neonatal Ed. 2019 Oct 30

22 AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2014 Apr 10;(4):CD005496.

23 Chi C, Buys N, Li C, Sun J, Yin C. Effects of prebiotics on sepsis, necrotizing enterocolitis, mortality, feeding intolerance, time to full enteral feeding, length of hospital stay, and stool frequency in preterm infants: a meta-analysis. Eur J Clin Nutr. 2019 May;73(5):657-70.

