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CASE REPORT
ΕΝΔΙΑΦΕΡΟΥΣΑ ΠΕΡΙΠΤΩΣΗ

Food protein-induced enterocolitis syndrome (FPIES) not responding to amino acid formula

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2024, 41(1):134–137

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Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE cell mediated food allergy triggered by the ingestion of specific food proteins that may manifest in an acute or chronic form. We report a case of an infant with severe chronic FPIES presenting in the neonatal period that failed to respond to amino acid-based formulas. The patient remained on total parenteral nutrition for 4 weeks and after that he could tolerate amino acid formula. Our case suggests that bowel rest for extended periods may be necessary for severe cases of FPIES, while endoscopy may be helpful in the differential diagnosis and the therapeutic management of these cases.

Σύνδρομο εντεροκολίτιδας επαγόμενο από τροφικές πρωτεΐνες, που δεν ανταποκρίθηκε στη χορήγηση στοιχειακού γάλατος

Περίληψη στο τέλος του άρθρου

Key words

Amino acid-based formula
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Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE cell mediated food allergy triggered by the ingestion of specific food proteins that may manifest in an acute or chronic form.[1] Acute FPIES may present with profuse recurrent vomiting, diarrhea and may lead to serious dehydration, hypotension, hypothermia and lethargy. Chronic FPIES manifest as progressive intermittent vomiting and watery diarrheas (that may be bloody) leading to failure to thrive, weight loss and metabolic derangements.[1] An acute on chronic phenotype exists in patients with chronic FPIES that present features of acute FPIES when food allergen is consumed intermittently. We report a case of a term male infant that developed severe chronic FPIES in the neonatal period and did not respond initially to the management with amino acid-based formulas.

CASE PRESENTATION

The infant was conceived with *in vitro* fertilization and born by cesarean delivery after an uneventful pregnancy. The family history was negative for allergic diseases. His history begun at the 15th day of life when he presented traces of blood in the stool. He

had been fed with both breast milk and cow's milk formula since birth. The mother was instructed to withdraw milk products from her diet and to replace cow's milk formula with a partially hydrolyzed one. Ten days later, he presented profuse bloody mucous diarrhea. Consequently, partially hydrolyzed formula was replaced by extensively hydrolyzed formula.

Contrary to the expected result, on the 35th day of life the infant was admitted to a provincial hospital with sepsis symptoms and was treated with antibiotics, while blood, stool, cerebrospinal fluid, and urine cultures were sterile. The infant was hospitalized for 14 days and was fed with parenteral nutrition. Attempts to feed the infant with amino acid formula were performed (following approximately 5 days of bowel rest) that resulted to recurrence of symptoms (primary consisting of bloody diarrhea). The infant was referred to our Department at the 53rd day of life with weight loss, hypotonia, lethargy, cutis marmorata, metabolic acidosis (pH=7.33, PCO_2=14 mmHg, HCO_3=7.3 mEq/L, Lactate=4.3), methemoglobinemia, leukocytosis, increased platelet levels and anemia (Hb=8.9%). The patient's weight was below the 3rd percentile and less than birth weight. Stool samples for viruses, bacteria, *Clostridium difficile* toxins and parasites were negative. Cultures of blood, stool and urine were negative. Abdominal radiograph and ultrasound were normal. Testing for immunodeficiencies were negative as well, while total serum IgE levels were normal. After two days of hospitalization in which the infant was on total parental nutrition, he was fed with amino acid-based formula which immediately led to deterioration of symptoms (diarrhea and vomiting) with severe anemia. Thus, the infant received parenteral nutrition for the next two weeks which resulted in clinical improvement with amelioration of symptoms and adequate weight gain (25–30 g/day).

After two weeks of bowel rest, the patient was refed with amino acid formula which again resulted in clinical recurrence of diarrheas and significant increase in blood eosinophils. Specific and genetic testing was performed to rule out some of the congenital gastrointestinal entities, resulting in symptoms that overlap with FPIES, such as tufting enteropathy, microvillous inclusion disease, enterokinase deficiency, interleukin 10 deficiency, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome and very early onset inflammatory bowel disease which were negative. The patient underwent esophago-gastro-duodenoscopy and colonoscopy with normal mucosa appearance (fig. 1).

Colonic biopsy specimens demonstrated severe eosinophilic infiltration (more than 100 eosinophils per high power field) without evidence of cryptitis. Following the bioptic findings the patient remained on total parenteral nutrition for four weeks to complete regeneration of gastrointestinal epithelium. Subsequently, refeeding the patient with amino acid formula was well tolerated. The patient was discharged with significant weight gain and asymptomatic at the third month of life. At 18 months of life, we performed a follow-up oral food challenge with cow's milk during which the infant vomited profusely (positive results, according to the revised diagnostic criteria for chronic FPIES).[1] An oral food challenge with cow's milk at the age of five years had the same result with profuse vomiting.

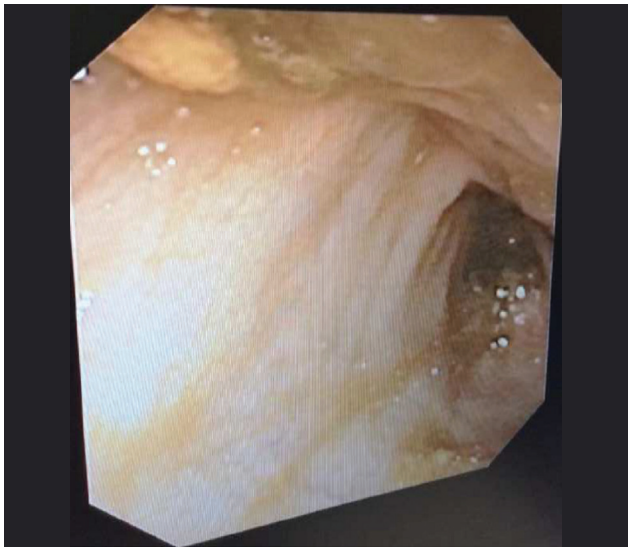

Figure 1. Macroscopic image of the colonic epithelium.

DISCUSSION

We report a case of an infant with severe chronic FPIES that developed in neonatal period and was initially unresponsive to the management with amino acid-based formulas. The most important criterion for chronic FPIES diagnosis is the absence of symptoms within days of non-exposure to the offending food and acute recurrence upon the reintroduction of food. In our patient, the symptoms led to extreme failure to thrive, dehydration and metabolic derangements that resolved with parenteral feeding, while clinical recurrence was observed when the patient fed with either extensively hydrolysate formula or amino acid formula.

Current guidelines suggest that the triggering food should completely be absent from the patients' diet. In the nursing infant, the mother should completely abstain from the offending food. In cases where breast feeding is not possible, an extensively hydrolysated formula is recommended in cows' milk FPIES. However, 10–20% of cases may require amino-acid formula.[2,3] Amino-acid formula is associated with clinical benefits in terms of symptoms and growth in patients who fail to improve with extensively hydrolysated formula.[4]

Interestingly, our patient failed to respond to both extensively hydrolysated and amino acid formula after 15 days of parenteral feeding. After four weeks of bowel rest, amino acid formula was well tolerated, and the patient improved. Intolerance to protein hydrolysate infant formulas has been reported in patients with colitis.[5] The residual antigens are usually responsible for treatment failure. Amino acid-based

infant formulas may lead to resolution of symptoms in these patients since they are considered completely non-allergenic[6] and they seem to be the optimal initial choice in severe FPIES.[7] For most patients, symptoms usually improve after 3–10 days of offending food withdrawal and challenges with amino acid-based formula are efficient for the nutrition management of FPIES. To our knowledge, this is the first case in the literature where FPIES failed to respond initially to amino acid formula and required four weeks of parenteral feeding.

Colonic biopsy specimens after 15 days of parenteral feeding revealed severe eosinophilic inflammation of the mucosa. The absence of mucosal lesions in the upper digestive tract was probably due to the 15-day parenteral nutrition. FPIES is diagnosed clinically, and endoscopy is rarely performed. In this context, data on histology of the gastrointestinal mucosa during FPIES is limited.[8] FPIES may be associated with rectal ulceration and mucosal friability, partial villous atrophy of the jejunum and inflammatory cells infiltration.[8,9] Milk avoidance diet results in normalization of the intestinal mucosa while antigen reintroduction leads to recurrence of shortening of the villi of the jejunum.

Our differential diagnosis included eosinophilic colitis due to the increased numbers of eosinophils in the colonic tract. However, according to the international literature, eosinophilic colitis is characterized by the presence of bloody diarrhea in otherwise healthy infants and is usually resolved within days following dietary avoidance of the food allergen.[10] Sepsis is not included in the clinical presentation of eosinophilic colitis. There is only one case report of a neonate with eosinophilic gastroenteritis that mimicked sepsis, which was successfully managed with a hypoallergenic formula and breastfeeding with dietary restriction by the mother for a period of six months.[11] Additionally, the positive oral food challenge in our patient further strengthens FPIES diagnosis.

In conclusion, we report a case of severe chronic FPIES that did not respond to amino acid-based formula when introduced early. Amino acid-based formula introduction following four weeks of parenteral feeding did not lead to symptoms, suggesting that in severe cases, bowel rest for a larger period may be required for the complete recovery of the intestinal epithelium. In cases with persistent symptoms, endoscopy could be helpful, not only for the differential diagnosis, but also for the documentation of the status of the intestinal mucosa, which represent an important finding for the planning of an appropriate therapeutic management avoiding long periods of parenteral nutrition and hospitalization.

ΠΕΡΙΛΗΨΗ

Σύνδρομο εντεροκολίτιδας επαγόμενο από τροφικές πρωτεΐνες, που δεν ανταποκρίθηκε στη χορήγηση στοιχειακού γάλατος

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Το σύνδρομο εντεροκολίτιδας επαγόμενο από τροφικές πρωτεΐνες (food protein induced enterocolitis syndrome, FPIES) είναι μια τροφική αλλεργία μη μεσολαβούμενη από IgE που εμφανίζεται με την πρόσληψη συγκεκριμένων πρωτεϊνών των τροφών και μπορεί να εκδηλωθεί ως οξεία ή ως χρόνια μορφή. Παρουσιάζεται μια ενδιαφέρουσα περίπτωση ενός βρέφους με σοβαρό χρόνιο FPIES, το οποίο εμφανίστηκε στη νεογνική ηλικία και δεν ανταποκρίθηκε στη χορήγηση στοιχειακού γάλατος (γάλα από αμινοξέα). Ο ασθενής παρέμεινε αποκλειστικά σε παρεντερική διατροφή για 4 εβδομάδες και στη συνέχεια έγινε ανεκτή η χορήγηση στοιχειακού γάλατος. Η περίπτωση αυτή υποδεικνύει ότι πιθανόν να απαιτηθεί «ανάπαυση» εντέρου για μακρά χρονική περίοδο σε σοβαρές περιπτώσεις FPIES, ενώ η ενδοσκόπηση μπορεί να συνδράμει στη διαφορική διάγνωση και στη διαχείριση τέτοιων περιπτώσεων.

Λέξεις ευρετηρίου: Αλλεργία στο γάλα αγελάδας, Δοκιμασία πρόκλησης, Στοιχειακό γάλα, Σύνδρομο εντεροκολίτιδας επαγόμενο από τροφικές πρωτεΐνες, Τροφική αλλεργία

References

1. NOWAK-WĘGRZYN A, CHEHADE M, GROETCH ME, SPERGEL JM, WOOD RA, ALLEN K ET AL. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary – Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2017, 139:1111–1126.e4
2. CAUBET JC, FORD LS, SICKLES L, JÄRVINEN KM, SICHERER SH, SAMPSON HA ET AL. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. *J Allergy Clin Immunol* 2014, 134:382–389
3. KATZ Y, GOLDBERG MR. Natural history of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol* 2014, 14:229–239
4. MICHELET M, SCHLUCKEBIER D, PETIT LM, CAUBET JC. Food protein-induced enterocolitis syndrome – a review of the literature with focus on clinical management. *J Asthma Allergy* 2017, 10:197–207
5. VANDERHOOF JA, MURRAY ND, KAUFMAN SS, MACK DR, ANTONSON DL, CORKINS MR ET AL. Intolerance to protein hydrolysate infant formulas: An underrecognized cause of gastrointestinal symptoms in infants. *J Pediatr* 1997, 131:741–744
6. KABUKI T, JOH K. Extensively hydrolyzed formula (MA-mi) induced exacerbation of food protein-induced enterocolitis syndrome (FPIES) in a male infant. *Allergol Int* 2007, 56:473–476
7. FIOCCHI A, BROZEK J, SCHÜNEMANN H, BAHNA SL, VON BERG A, BEYER K ET AL. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines. *Pediatr Allergy Immunol* 2010, 21(Suppl 21):1–125
8. BERIN MC. Immunopathophysiology of food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol* 2015, 135:1108–1113
9. CAUBET JC, NOWAK-WĘGRZYN A. Current understanding of the immune mechanisms of food protein-induced enterocolitis syndrome. *Expert Rev Clin Immunol* 2011, 7:317–327
10. IMPELLIZZERI G, MARASCO G, EUSEBI LH, SALFI N, BAZZOLI F, ZAGARI RM. Eosinophilic colitis: A clinical review. *Dig Liver Dis* 2019, 51:769–773
11. LEE M, CHOI SY, CHUNG ML, LEE J, SUNG M. A rare case of eosinophilic gastroenteritis in a neonate with fever. *Neonatal Med* 2019, 26:218–222

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