

Colon in Food Allergy

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ABSTRACT

The colon is a site of allergic reaction to food proteins. The most common manifestation is allergic proctocolitis. Although frequent in infancy, it may also affect older children. The diagnosis of allergic proctocolitis is mainly based on clinical and histological grounds, but there is a risk of overdiagnosis; challenge is strongly recommended to avoid unnecessary and expensive formula or changes in maternal diet that may discourage continuation of breast-feeding. The benign clinical course and the spontaneous resolution in most infants suggest the need for further prospective studies to validate markers that allow the identification of those children needing a dietary approach. It

remains to be assessed whether lymphoid nodular hyperplasia of the colon is a manifestation of food allergy. Finally, allergic proctitis may present clinically with refractory constipation; the true prevalence of food allergy–related constipation remains to be assessed. **JPGN 48:S89–S91, 2009. Key Words:** Allergic proctocolitis—Chronic constipation—Food allergy—Food protein–induced enterocolitis syndrome—Lymphonodular hyperplasia. © 2009 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Food allergy (FA) can be defined as an abnormal immunological response to food proteins that causes an adverse clinical reaction (1). The prevalence of FA appears to be increasing in industrialised countries, although reliable, population-based data are limited. However, it has been estimated that up to 3% to 6% of children younger than 3 years of age are affected by FA. Food allergy in children presents with a wide spectrum of clinical manifestations, including anaphylaxis, urticaria, angioedema, atopic dermatitis, and gastrointestinal symptoms (eg, vomiting, diarrhoea, failure to thrive). Food protein–induced gastrointestinal syndromes are becoming increasingly recognised in young infants and children and may affect various parts of the gastrointestinal tract, the colon being a site of allergic reaction to food proteins.

FOOD PROTEIN–INDUCED ENTEROCOLITIS SYNDROME

Food protein–induced enterocolitis syndrome (FPIES) is characterised by extensive disease of small intestine and colon (2). Food protein–induced enterocolitis syn-

drome affects young infants; it has been described especially in formula-fed but not in breast-fed infants, and is characterised by irritability, lethargy, and/or dehydration from protracted vomiting and diarrhoea. As expected in this age group, cow's milk and soy protein are the most frequently implicated proteins. Infants with this disorder appear chronically ill and continued ingestion of the protein leads to anaemia and failure to thrive. Because food challenges can cause rapid onset of symptoms and hypovolemic shock, the diagnosis is often made with a suggestive history if the symptoms remit after elimination of cow's milk or soy protein. Sensitivity resolves between 18 and 36 months of life.

ALLERGIC PROCTOCOLITIS

Food protein–induced proctocolitis is the most common cause of low-grade rectal bleeding in young infants (3). Allergic proctocolitis typically presents in the first few weeks to months of life, but its true prevalence is unknown. With the exception of possibly diarrhoea and constant blood and mucus in the stool, infants appear in good health, as they do not present growth delay or poor weight gain. Occasionally patients may have a mild anaemia, and hypoalbuminaemia is a rare manifestation. Infants with this disorder are sensitive to cow's milk or soy protein; however, the majority of infants are breast-fed and become sensitised as a result of maternally ingested proteins excreted in breast milk. Although it

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is generally thought that this condition is mostly limited to infancy, recently it has been described in childhood with features remarkably similar to those observed in infancy (4). Healthy children (2–14 years) have been reported as presenting with persistent or recurrent rectal bleeding related to a mild form of colitis characterised by a prominent eosinophilic infiltration, focal lymphoid follicle hyperplasia, and a prompt clinical and histological response to a cow's milk-free diet. None of them had a history of food-induced proctocolitis during infancy, and only 3 patients showed an IgE-mediated response to cow's milk protein. A significant proportion of patients developed tolerance to cow's milk protein after about 1 year of a strict elimination diet. Dietary protein-induced proctocolitis is then a relatively common cause of rectal bleeding also in childhood, and it shares the main clinical features with its infantile counterpart.

DIAGNOSIS

The diagnosis of FA-related gastrointestinal symptoms is a clinical exercise involving a careful history, physical examination, and diagnostic tests. Unfortunately no diagnostic test has sufficient power. If non-IgE-mediated disorder is suspected, adjunctive laboratory and endoscopic studies are often required to arrive at the correct diagnosis. Gross endoscopy findings in healthy infants with rectal bleeding are often nonspecific and not helpful for the diagnosis. It is important to remember that it is a focal disease with variability within specimens taken from different locations in the rectosigmoid colon. It is also important to consider that colonic eosinophilia does not necessarily indicate allergy (5). Peripheral blood eosinophil counts and serum IgE are higher in allergic proctocolitis as a group than in controls, but not useful discriminators in infants with normal histology. The measurement in faeces of eosinophilic cationic protein, $\alpha 1$ antitrypsin, and calprotectin has been implemented in the diagnosis of FA, but no specific data exist for allergic proctocolitis. Promising results have been obtained using atopic patch test using fresh food. However, elimination diet and challenge are required to make a definitive diagnosis.

With the limited value of noninvasive laboratory tests, the diagnosis is often made presumptively and that brings the risk of overdiagnosis. In a survey of North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) members, 84% indicated they would empirically change the diet of an infant with rectal bleeding to treat presumed allergic colitis (5). Also, in more severe presentations allergic colitis is first considered; in a small group of severe colitis in infancy almost half of cases underwent cow's milk protein-free diet before inflammatory bowel disease was finally diagnosed, causing an important diagnostic delay (6). Another recent study has prospectively evaluated the

clinical course of rectal bleeding and the effect of elimination diet on the duration of symptoms. The disorder proved to be benign and self-limiting, and in most cases cow's milk elimination did not affect the duration of bleeding; in fact, the number of days with rectal bleeding was identical in infants who were assigned to an elimination diet or to continue their normal diet. Real cow's milk allergy (CMA) was diagnosed in only 18% of patients. Challenge is then proposed as essential to reduce the number of false diagnoses (7).

LYMPHONODULAR HYPERPLASIA OF THE COLON

Lymphonodular hyperplasia (LNH) of the gastrointestinal mucosa is a common finding during paediatric colonoscopies, so much so that it has even been considered normal or age related. Kokkonen et al (8) demonstrated a close association between LNH of the duodenal bulb and increased densities of intraepithelial $\gamma\delta^+$ T cells in patients with untreated FA. The same group of authors later showed that LNH of the gastrointestinal tract mucosa, particularly affecting the colon, may be associated with FA (9). These findings seem to confirm that FA in children may produce patchy or diffuse LNH in any part of the gastrointestinal tract. More recently Iacono et al (10) found that LNH in colonic and terminal ileum mucosa is present in 30% of children undergoing colonoscopy, and in more than half of cases it is related to delayed-type food hypersensitivity. We have recently investigated a group of 10 consecutive children presenting with haematochezia and/or severe abdominal pain selected according to the presence of LNH when evaluated endoscopically. All of the patients underwent total and specific IgE determinations, cellobiose-mannitol sugar permeability test, and ileocolonoscopy with multiple biopsies. Cryostat sections were stained for CD3⁺ and $\gamma\delta^+$ T cells, CD25⁺ mononuclear cells, mast cell tryptase and chymase, and eosinophil major basic protein. In the study group, 4 patients had a familiar history of atopy, 7 had increased levels of total serum IgE, and intestinal permeability was abnormal in 5 patients. The ileal biopsies showed a significant increased density of intraepithelial and lamina propria $\gamma\delta^+$ T cells when compared with controls; upregulation of epithelial HLA-DR expression and increased density of mononuclear cells expressing IL-2 receptor (CD25⁺) were also noted. Eosinophil density was increased, mainly in the right colon. All of the patients were treated with a hypoallergenic diet for 4 weeks; in all clinical improvement was observed, as well as normalization of intestinal permeability. The patients underwent double-blind challenge with the main food allergens, but only 2 relapsed, both to milk proteins. At follow-up, none of them showed gastrointestinal symptoms. We concluded that children with LNH of the lower gastrointestinal tract

show immunohistochemical signs of gut inflammation, but FA seems to be implicated in a minority of patients (11).

ALLERGIC PROCTITIS AND CHRONIC CONSTIPATION

Allergic inflammation of the colon has also been advocated to explain chronic constipation as a manifestation of CMA (12). Shah et al (13) reported that 78.5% of 14 children with refractory constipation and atopy responded to dietary changes, whereas no improvement was seen in nonatopic patients after withdrawal of cow's milk. It has been reported that even in adults chronic constipation can be due to multiple food hypersensitivity (14). There are also dissenting reports: Loening-Baucke (15) reported that patients with chronic constipation and history of CMA or atopy did not improve after 2 weeks of elimination diet. To evaluate the prevalence of chronic constipation in unselected children, its association with atopy and the efficacy of a cow's milk protein elimination diet on refractory constipation, we have conducted a study in a primary care setting on a population of 5113 children (0–12 years). During a 3-month period chronic constipation prevalence in our population was 1.8% (91 children). Sixty-nine constipated children (mean age 34.9 ± 18.0 months) and 69 controls completed a questionnaire about personal and familial history of atopy and features of bowel transit. Twelve of the 69 constipated children (17.3%) and 13 of the 69 control children (18.8%) had a diagnosis of atopy. Moreover 11 of 69 (15.9%) constipated children were refractory to constipation treatment, and 3 (27.3%) of these had atopy. A trial of dietary elimination for 4 weeks did not improve constipation in any of the 11 children. In conclusion, prevalence of atopy among children with chronic constipation, in our study group, was similar to that in the general population. In this primary care setting the refractory constipation seems not to be related to CMA (16).

CONCLUSIONS

1. Allergic proctocolitis represents the most common colonic manifestation of FA in infants, but it affects also children.
2. It is a benign and self-limiting condition, and often overdiagnosed.

3. Conflicting data are reported about the association between FA and colonic LNH.
4. Refractory constipation may represent the result of food-related allergic proctitis; the true prevalence remains to be assessed.

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