Allergic Proctocolitis Is a Risk Factor for Functional Gastrointestinal Disorders in Children

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Objective To test the hypothesis that allergic proctocolitis, a cause of self-limiting rectal bleeding in infants, can predispose to the development of functional gastrointestinal disorders (FGIDs) later in childhood.

Study design We studied a cohort of 80 consecutive patients diagnosed with allergic proctocolitis. Their sibling or matched children presenting to the same hospital for minor trauma served as controls. Parents of the patients with allergic proctocolitis and controls participated in a telephone interview every 12 months until the child was at least 4 years old. At that time, they were asked to complete the parental Questionnaire on Pediatric Gastrointestinal Symptoms, Rome III version.

Results Sixteen of the 160 subjects (10.0%) included in the study met the Rome III criteria for FGIDs. Among the 80 patients with allergic proctocolitis, 12 (15.0%) reported FGIDs, compared with 4 of 80 (5.0%) controls ($P = .035$). After adjustment for age and sex, the OR for FGIDs in allergic proctocolitis group was 4.39 (95% CI, 1.03-18.68). FGIDs were significantly associated with iron deficiency anemia, duration of hematochezia, and younger age at presentation. In a multivariate analysis, only the duration of hematochezia was significantly associated with the development of FGIDs (OR, 3.14; 95% CI,1.72-5.74).

Conclusions We have identified allergic proctocolitis as a new risk factor for the development of FGIDs in children. Our data suggest that not only infection, but also a transient early-life allergic inflammatory trigger may induce persistent digestive symptoms, supporting the existence of "postinflammatory" FGIDs. *(J Pediatr 2017;■■:■■-■■).*

See editorial, p •••

Functional gastrointestinal disorders (FGIDs) are defined as symptoms that, after appropriate medical evaluation, cannot be attributed to another medical condition.[1] These disorders are characterized by a dysregulation of the brain-gut axis, associated with psychosocial factors, changes in intestinal motility, and visceral hypersensitivity.[1-4] In addition, several other abnormalities have been identified in subgroups of patients, including genetic factors, enteroendocrine dysfunction, neuroplastic changes, gastrointestinal infections, altered microbiota, dietary factors, mucosal and systemic immune activation, and increased mucosal permeability.[5,6] Infectious gastroenteritis is a common trigger of FGIDs, particularly irritable bowel syndrome (IBS), also in children.[7-11] A long-term, prospective, controlled, culture-proven, follow-up study examining the association between a single episode of *Salmonella* gastroenteritis and new-onset FGIDs showed that *Salmonella*-induced gastroenteritis during childhood, but not adulthood, is a risk factor for IBS.[9] These results suggest that disruption of gut homeostasis early in life by acute triggers may predispose the individual to susceptibility to the development of FGIDs later in life.[9]

Animal studies also have stressed the importance of early-life events in the development of visceral hypersensitivity.[12] Psychological or biological stressful events occurring soon after birth result in increased intestinal permeability during both the neonatal and adult period and favor the occurrence of FGIDs later in life.[13] Studies have shown that colonic inflammation during an early, vulnerable period of neural plasticity leads to long-lasting hypersensitivity that outlasts the acute inflammation.[14] This phenomenon was not seen in a similar experiment conducted in adult rats.[14] Taken together, these studies point toward a predominantly neurogenic mechanism that is more pronounced when the inflammation occurs early in life.

Although animal data are of great value in understanding the basic mechanisms underlying neuroimmune interactions in the pathogenesis of sensorimotor dysfunction, their translation to humans is not always possible. Human data

FAP	Functional abdominal pain
FGID	Functional gastrointestinal disorder
IBS	Irritable bowel syndrome

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The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.10.073

on the role of inflammation in the first weeks of life in the risk of developing subsequent FGIDs could greatly advance our knowledge on the pathogenesis of FGIDs. Saps et al[15] surveyed a large group of children with cow's milk allergy early in life several years after their initial diagnosis and found a higher frequency of FGID symptoms in children diagnosed with cow's milk allergy compared with healthy controls.

Despite marked mucosal abnormalities, allergic proctocolitis is generally a cause of self-limiting rectal bleeding.[16-23] Allergic proctocolitis may provide a human model in which to study the role of temporary colitis on the development of FGID, thus supporting a role for noninfectious causes of inflammation as an early-life predisposing factor for the development of FGIDs later in childhood.

The aim of this study was to prospectively evaluate the effect of an early-life self-limiting human model of colitis on the development of FGIDs, and the associated risk factors at least 4 years after the acute trigger.

Methods

This prospective controlled cohort study on the long-term outcome of allergic proctocolitis on digestive functional symptoms and related risk factors comprised a cohort of consecutive patients diagnosed with allergic proctocolitis at the Pediatric Gastroenterology Unit of Sapienza, University of Rome between October 2006 and November 2011. The diagnosis of allergic proctocolitis was based on the American Gastroenterological Association's guidelines on the evaluation of food allergy in gastrointestinal disorders.[16]

Owing to their similar genetic, environmental, and socioeconomic backgrounds, which can play a role in the prevalence of FGIDs, siblings aged <6 years without a history of cow's milk allergy were selected as controls. Each index case was assigned a unique control. If a patient did not have a sibling or the sibling was aged >6 years or had a history of food allergy, another child of similar age and sex presenting to the same hospital in the emergency department for evaluation of minor trauma in the absence of previous chronic gastrointestinal symptoms was recruited as a control. Each control subject was recruited within 4 weeks of the index case. A flow chart of recruitment is provided in **Figure 1** (available at www.jpeds.com). The study was approved by the local Ethics Committee and conducted in accordance with the Declaration of Helsinki. A letter explaining the rationale of the present study was provided at all parents of the enrolled children, and written informed consent was obtained in all eligible cases.

Consecutive patients referred to our unit for suspected allergic proctocolitis underwent a screening visit including anal inspection and stool culture to exclude other causes of rectal bleeding. Blood tests, including concentrations of serum-specific IgE antibody, skin prick tests, and fecal calprotectin, were performed within 1 week before the endoscopy in all eligible cases. Rectosigmoidoscopy was performed to confirm the diagnosis and to exclude other entities. One pediatric gastroenterologist performed all endoscopic evaluation with a neonatal videogastroscope (Olympus, Tokyo, Japan), after deep sedation with midazolam (0.2 mg/kg). Endoscopic appearance of rectal and left colonic mucosa (**Figure 2**, A and B) was scored as reported previously.[24] Mucosal biopsy specimens (at least 2) were obtained from the left colon (splenic flexure to the rectosigmoid junction) and the rectum. A pathologist unaware of the clinical and laboratory data of the patients performed all histological examinations. Histological grading was assessed as described previously.[24] The scoring for eosinophil infiltration was adapted from previously described criteria (**Figure 2**, C and D).[25]

Concentrations of serum-specific IgE antibody titers to common foods (cow's milk, soy, rice, wheat, egg) were measured using the immuno-CAP system with a detection limit of 0.35 kU/L IgE.[26] Prick tests for common food proteins (eg, cow's milk, soy, rice, wheat, egg) were performed as described previously.[27] Calprotectin was detected in the fecal samples of allergic proctocolitis group by a commercially available enzyme-linked immunosorbent assay test (Calprest Eurospital, Trieste, Italy).

Therapeutic Approach and Follow-Up

Cow's milk protein maternal avoidance has been recommended for breast-feeding infants. If rectal bleeding continues for 72-96 hours, an extensively hydrolyzed formula is prescribed. Children unresponsive within 72-96 hours to the extensively hydrolyzed formula are suggested an amino acid-based formula.[23] Children with allergic proctocolitis had a clinical follow-up every month until stable remission of symptoms and tolerance acquisition were achieved, and then a telephone interview every 12 months until they reached at least 4 years of age, at which time they were mailed the validated questionnaire. Healthy controls participated in a telephone interview every 12 months until they reached at least 4 years of age. The cutoff of 4 years was fixed because FGID cannot be diagnosed according to the Rome III criteria until this age.

Participants who met the following criteria were eligible for inclusion: at least 4 years of age at the time of mailing the questionnaire, and no diagnosis of organic chronic disorder (based on self-report and review of medical records). Parents of all invited participants received a postal questionnaire and were asked to complete it and return it by mail. The questionnaire was mailed up to 3 times to nonresponders. When no reply was obtained, these individuals were contacted by telephone to encourage participation in the study. No personal interviews were performed, to avoid interference with responses and potential clinician assessment bias.

Parents were asked to review the child's history and complete the parental Questionnaire on Pediatric Gastrointestinal Symptoms, Rome III version (QPGS-RIII), a validated questionnaire for the diagnosis of FGIDs in children aged >4 years.[28]

Statistical Analyses

We estimated the sample size assuming that 2.0% of the subjects in the control group[29] and 19.2% of the subjects in the exposed group[15] would meet the criteria for FGIDs (ie, the primary endpoint of the study). With this assumption, a sample

FLA 5.5.0 DTD ■ YMPD9576_proof ■ January 15, 2018