

Food Protein-Induced Allergic Proctocolitis: Over- or Underdiagnosed?



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Among non-IgE-mediated reactions to foods in infants, food protein-induced allergic proctocolitis (FPIAP) is considered most common. Although it generally has a benign course, FPIAP is often a cause for concern in parents and caregivers.¹ Hence, it deserves special attention.

Diagnosis is based on convincing history and resolution of symptoms with food avoidance. The gold standard confirmatory diagnostic test is a food challenge.² The mainstay of management is avoidance of the suspected inciting food, with interval challenge to assess for resolution, which usually occurs in the first years of life.²

The exact prevalence of FPIAP is not established, and studies suggest that it is often underdiagnosed³ given that clinical characteristics such as altered bowel habit, reflux, constipation, and colic often occur in otherwise healthy infants.⁴ Symptoms typically present in the first 3 months of life, but can occur later in infancy, with the main clinical manifestation of the disease being the presence of blood in the stool (hematochezia), which may appear as grossly visible blood in the stool or may be microscopic.³ Most cases of FPIAP are associated with exposure to cow's milk; however, soy, egg, and wheat are other potential culprits.⁵

Studies suggest that findings in rectal biopsy may help confirm the diagnosis of FPIAP. Histological diagnosis is based on inflammation and eosinophilic infiltration in the lamina propria (ranging from 5 to >50/high power field).³ However, in clinical practice, rectal biopsy is rarely done, and recent European guidelines recommend maternal elimination diet (usually between 2 and 4 weeks) followed by reintroduction of the allergen in order to diagnose FPIAP.³ In addition, it is important to rule out other causes of blood in the stools in infancy such as anal fissures or infectious gastroenteritis.⁶

Although studies on IgE-mediated food allergies reveal the increased prevalence of food allergies and food-induced anaphylaxis in North America over the last decades,^{7,8} there are no studies assessing the prevalence or incidence of FPIAP in North America.

In this issue, Martin et al⁹ aim to assess prospectively the incidence of FPIAP and identify factors associated with its development. The authors followed a cohort (The Gastrointestinal Microbiome and Allergic Proctocolitis) that enrolled 1003 healthy newborn infants from a single pediatrics practice in suburban Massachusetts. Diagnosis of FPIAP was made by primary care pediatricians and reviewed by study investigators to confirm inclusion by prespecified criteria, including documented gross or occult blood in the stool without other explanation. Notably, the cumulative incidence of FPIAP was 17% over 3 years. The author reported that infants fed a combination of breast milk and formula (vs infants exclusively breastfed or infants exclusively fed formula) were the least likely to develop FPIAP. Other risk factors included eczema and a first degree relative with food allergies. The authors conclude that the incidence of FPIAP is higher than published estimates and that combination feeding of formula and breast milk is associated with the lowest rate of FPIAP.

In line with other studies, the authors indicate that bloody stools during the first few months of life are the main clinical characteristic of FPIAP. However, the percentage of gross blood in stool is less than 50% in this study. Clearly, given the absence of a more rigorous diagnostic strategy, there is a high risk for misclassification bias, mainly in cases diagnosed solely due to microscopic blood in stool. Misclassification bias, also called measurement or information bias, results from improper, inadequate, or ambiguous recording of individual factors—either exposure or outcome variables.¹⁰ Indeed, studies suggest that about a third of cases with microscopic blood in stool are false positive.¹¹ Another study conducted in Israel by Elizur et al¹² on a cohort of 13,234 newborns, born between June 2004 and June 2006 at Assaf Harofeh Medical Center, Zerifin, Israel, and followed until the age of 6 years, reported that only 0.16% had FPIAP related to cow's milk consumption.¹² The difference between the estimates in these 2 studies may be attributed to numerous factors. The study conducted by Elizur et al¹² required more rigorous diagnostic criteria, mainly reliance on gross blood in the stool detected by parents rather than the presence of macro/microscopic blood and identification of cases in general pediatrics clinical practice. Indeed, in their discussion, Martin et al indicated that had their study been designed similarly, first ascertaining cases with parent-reported adverse reactions to milk, and then following up on the most likely cause of each, they would also likely find a very small number of cases of FPIAP. In addition, the authors in the Israeli study included data on symptoms occurring on subsequent reintroduction of cow milk and concluded that almost 80% reintroduced cow milk protein with no adverse effects. Although the Elizur study focused only on milk-induced FPIAP,¹² it is unlikely to account for the difference in estimates given that milk accounts for the majority of

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FPIAP cases.^{3,5} It is also possible that the difference is attributed to true differences in the 2 populations studied. Finally, it is possible that the temporal trends in FPIAP prevalence (there is a difference of more than 10 years between the 2 studies) account for the observed difference.

It is crucial to appropriately diagnose FPIAP as well as its resolution in order to decrease the use of unnecessary elimination diets. There are clear risks associated with elimination diets including lack of indispensable macro- and micronutrients and effect on growth.¹³ Indeed, children with food allergies are reported to have lower growth parameters than the general population, and studies reveal that children on an elimination diet (of various foods) have a lower intake of some key micronutrients, including vitamin D, folic acid, calcium, zinc, iron and B vitamins, and a detrimental effect on bone mass density.¹³ In addition, elimination of cow's milk due to food allergy in early childhood is reported to have a long-lasting effect on feeding difficulties.¹⁴ Moreover, studies suggest that elimination diets may be associated with increased risk to develop life-threatening IgE-mediated allergy.^{15,16}

In conclusion, this is the first North American study to prospectively assess the prevalence of FPIAP. The prevalence is spectacularly high and probably would not have been, had different criteria been applied (especially food challenge). However, as the authors point out, although gross blood is a prerequisite for the diagnosis of FPIAP by some practice guidelines, there is literature supporting testing for occult blood in suspected cases. The study reveals that the latter is a common diagnostic strategy among pediatricians suspecting FPIAP. The key findings of this paper spur numerous new questions related to the classification, pathogenesis, natural history, and management of 1 or more conditions that are diagnosed as FPIAP by pediatricians. This highlights the need to investigate, refine, and develop consensus definitions regarding the diagnosis, management, and differential diagnosis of infants with suspected FPIAP.

REFERENCES

1. Husby S. Food allergy as seen by a paediatric gastroenterologist. *J Pediatr Gastroenterol Nutr* 2008;47(Suppl 2):S49-52.
2. Feuille E, Nowak-Węgrzyn A. Food protein-induced enterocolitis syndrome, allergic proctocolitis, and enteropathy. *Curr Allergy Asthma Rep* 2015;15:50.
3. Meyer R, Chebar Lozinsky A, Fleischer DM, Vieira MC, Du Toit G, Vandenplas Y, et al. Diagnosis and management of non-IgE gastrointestinal allergies in breastfed infants—an EAACI position paper. *Allergy* 2020;75:14-32.
4. Iacono G, Merolla R, D'Amico D, Bonci E, Cavataio F, Di Prima L, et al. Gastrointestinal symptoms in infancy: a population-based prospective study. *Dig Liver Dis* 2005;37:432-8.
5. Atanaskovic-Markovic M. Refractory proctocolitis in the exclusively breast-fed infants. *Endocr Metab Immune Disord Targets* 2014;14:63-6.
6. Thompson EC, Brown MF, Bowen EC, Smith LM, vander Griten D. Causes of gastrointestinal hemorrhage in neonates and children. *South Med J* 1996;89:370-4.
7. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol* 2010;125:1322-6.
8. Hochstatter E, Clarke A, De SS, LaVieille S, Alizadehfah R, Joseph L, et al. Increasing visits for anaphylaxis and the benefits of early epinephrine administration: a 4-year study at a pediatric emergency department in Montreal, Canada. *J Allergy Clin Immunol* 2016;137:1888-1890.e4.
9. Martin JS, Virkud YV, Seay H, Hickey M, Ndahayo R, Roscow R, et al. A prospective assessment of food protein-induced allergic proctocolitis from the GMAP healthy infant cohort. *J Allergy Clin Immunol Pract* 2019;143:AB136.
10. Lambert J. Statistics in brief: how to assess bias in clinical studies? *Clin Orthop Relat Res* 2011;469:1794-6.
11. Concha S, Cabalin C, Iturriaga C, Perez-Mateluna G, Gomez C, Cifuentes L, et al. Diagnostic validity of fecal occult blood test in infants with food protein-induced allergic proctocolitis [in Spanish]. *Rev Chil Pediatr* 2018;89:630-7.
12. Elizur A, Cohen M, Goldberg MR, Rajuan N, Cohen A, Leshno M, et al. Cow's milk associated rectal bleeding: a population based prospective study. *Pediatr Allergy Immunol* 2012;23:766-70.
13. Meyer R. Nutritional disorders resulting from food allergy in children. *Pediatr Allergy Immunol* 2018;29:689-704.
14. Maslin K, Grundy J, Glasbey G, Dean T, Arshad SH, Grimshaw K, et al. Cows' milk exclusion diet during infancy: is there a long-term effect on children's eating behaviour and food preferences? *Pediatr Allergy Immunol* 2016;27:141-6.
15. Kessel A, Dalal I. The pendulum between food protein-induced enterocolitis syndrome and IgE-mediated milk allergy. *Acta Paediatr* 2011;100:e183-5.
16. Flinterman AE, Knulst AC, Meijer Y, Bruijnzeel-Koomen CA, Pasmans SG. Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets. *Allergy* 2006;61:370-4.