

Increased IgE-Mediated Food Allergy With Food Protein-Induced Allergic Proctocolitis

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Immunoglobulin E-mediated food allergy (IgE-FA) can be life-threatening in children, and rates are rising in the United States.¹ We now know that early introduction of allergenic foods can reduce the risk of IgE-FA.² Food protein-induced allergic proctocolitis (FPIAP) (also called cow's milk protein allergy and/or intolerance or non-IgE-mediated milk allergy) is an early, common form of food allergy presenting with bloody or mucoid stools, often together with fussiness and feeding difficulty.^{3,4} Not thought to be associated with IgE-FA, FPIAP is treated with avoidance of the trigger antigen, most commonly milk, for the first year of life.^{3,4} Guidelines recommend an oral challenge after short dietary elimination to confirm the diagnosis,⁵⁻⁷ but this is rarely done in clinical practice.^{8,9} Given that FPIAP is associated with both eczema⁸ and diet restriction, we hypothesized that children with FPIAP would be at increased risk for IgE-FA.

METHODS

In the Gastrointestinal Microbiome and Allergic Proctocolitis prospective observational healthy-infant cohort study,⁸ FPIAP was diagnosed by the primary care provider on the basis of symptoms of fussiness, diarrhea, vomiting, poor feeding, and blood and/or mucous in the stools as is commonly done in clinical practice. Our a priori FPIAP case inclusion criteria required documented blood in the stool. IgE-FA

likelihood was ranked (“confirmed,” “probable,” “possible,” or “unlikely”) by 2 allergists who independently reviewed all clinical and sensitization data from children whose parents reported suspected reactions. IgE-FA cases were defined as those ranked by both reviewers as “confirmed” or “probable.” A strong clinical reaction history with evidence of sensitization was present in 53 (95%) of the 56 with IgE-FA (Supplemental Fig 2). Eczema was based on parental report on longitudinal surveys with physician chart review for missing data. Univariable and multivariable logistic regression with significance set at $\alpha < .05$ were done by using R version 3.5.0.¹⁰ Only variables meeting significance were included in the multivariable regression. The Gastrointestinal Microbiome and Allergic Proctocolitis study was approved by the Massachusetts General Hospital Institutional Review Board.

RESULTS

Of 903 infants analyzed (median age: 42 months; range: 24–59), 153 (17%) had FPIAP, and 56 (6%) had IgE-FA (28 peanut, 28 egg, 12 tree nut, and 9 milk) (Fig 1 A and C). As expected, children with IgE-FA were less likely girls (odds ratio [OR] = 0.5; 95% confidence interval [CI]: 0.27–0.87); $P = .02$ and more likely to have eczema (OR = 7.6; 95% CI = 3.7–15.7; $P < .001$) (Fig 1B). In total, 11% of children with FPIAP developed IgE-FA (compared with 5%

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Drs Martin and Virkud conceptualized and designed the study, coordinated and supervised data collection, conducted statistical analyses, drafted the initial manuscript, and reviewed and revised the final manuscript; Drs Yuan and Shreffler conceptualized and designed the study, coordinated and supervised data collection, supervised data analysis, and critically reviewed the manuscript for important intellectual content; Dr Keet conceptualized study design, supervised statistical analyses, and critically reviewed the manuscript for important intellectual content; Dr Phadke assisted in data generation and analysis drafting of the initial manuscript and critically reviewed the manuscript for important intellectual content; Drs Atkins and Su and Ms Seay assisted in data generation and analysis and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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without FPIAP) (Fig 1A). Adjusting for eczema, children with FPIAP had twice the odds of developing IgE-FA (OR = 1.9; 95% CI = 1.0–3.6; $P = .04$) (Table 1). Although our study was not powered to detect a relationship with individual foods, FPIAP was most strongly associated with milk IgE-FA (OR = 5.4; 95% CI = 1.4–20.8; $P = .01$) (Fig 1C, Table 1).

DISCUSSION

In this large healthy-infant cohort, children with FPIAP were at increased risk for IgE-FA. We

hypothesize 2 non-mutually exclusive mechanisms to explain this important finding. The first is a shared immunopathogenic food allergic response in both FPIAP and IgE-FA that likely culminates in a specific cluster of differentiation 4 (CD4) effector T helper type 2 (Th2) cell response, predisposing children with FPIAP to also develop IgE-FA. Like eczema, FPIAP may therefore represent the first step of the atopic march for many children. The second hypothesized mechanism is that the antigen elimination diet used to treat FPIAP in the first year of life increases IgE-FA risk. The increased rate of milk

IgE-FA that we observed in the FPIAP population supports this hypothesis, given that milk is the most common antigen restricted when FPIAP is diagnosed. Both proposed mechanisms, which are not mutually exclusive, can be evaluated by in-depth immune phenotyping together with intervention in future studies. Study limitations include single-center recruitment and lack of oral challenge IgE-FA confirmation in this observational setting.

Many children diagnosed with FPIAP clinically do not have allergic colitis

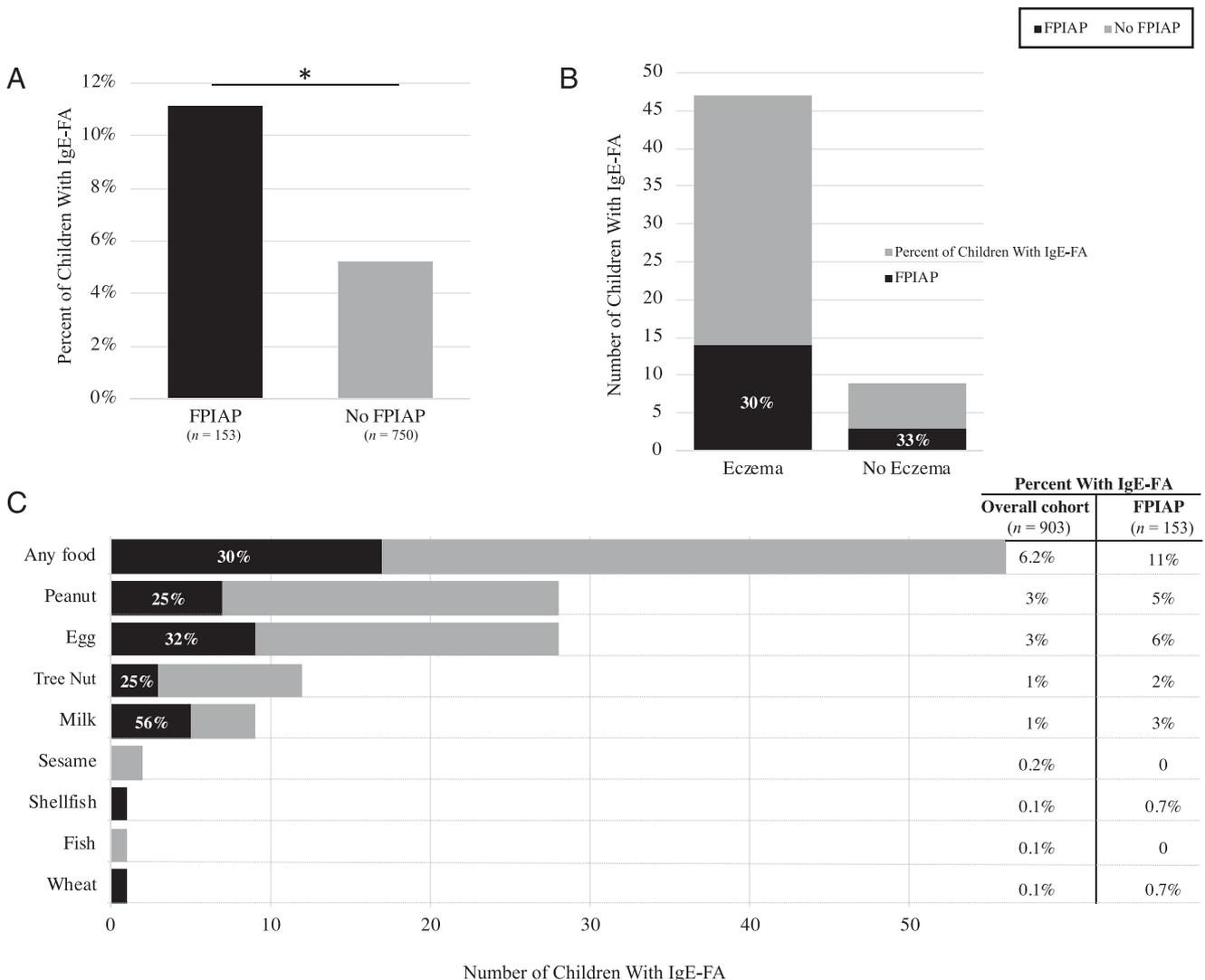


FIGURE 1

A, Increased rate of IgE-FA in children with FPIAP. B, Children with IgE-FA were more likely to have eczema, but the increased rate of FPIAP was independent of that association. C, Increased rate of IgE-FA in children with FPIAP, most strongly associated with milk. Percentages within the black bars show the percent of children with IgE-FA to that food who also had FPIAP. * $P < .05$.

TABLE 1 Prospective Association Between FPIAP and IgE-FA

	Unadjusted OR (95% CI)	P	Adjusted ^a OR (95% CI)	P
Any IgE-FA (n = 56)	2.3 (1.3–4.2)	.007	1.9 (1.0–3.6)	.04
Milk (n = 9)	6.3 (1.7–23.7)	.007	5.4 (1.4–20.8)	.01
Egg (n = 28)	2.4 (1.1–5.4)	.03	2.0 (0.9–4.5)	.11
Peanut (n = 28)	1.7 (0.7–4.0)	.25	1.4 (0.6–3.4)	.44

^a Adjusted for eczema by multivariable logistic regression.

on rectal biopsy⁹ or do not react with acute symptoms to a milk challenge.⁴ Treating FPIAP with empirical dietary elimination was previously thought to be a low-risk intervention, but it is suggested in our findings that this may have lasting consequences in the form of

IgE-FA. Given the high rates of clinically diagnosed FPIAP, it may be an important target for allergy prevention. We hence encourage the use of the international interpretation of the Milk Allergy in Primary Care guidelines,⁵ which uses oral challenges to restrict prolonged

milk elimination to only those infants with FPIAP who react to a postelimination challenge. We also recommend earlier attempts at milk reintroduction and consideration of early peanut and egg introduction for infants with FPIAP.^{2,11}

ABBREVIATIONS

CI: confidence interval
 FPIAP: food protein-induced allergic proctocolitis
 IgE-FA: immunoglobulin E-mediated food allergy
 OR: odds ratio

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