



Food protein–induced allergic proctocolitis may have distinct phenotypes

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ABSTRACT

Background: Food protein–induced allergic proctocolitis (FPIAP) is a non–immunoglobulin E (IgE)–mediated food allergy, which presents with bloody mucoid stool in infants. Although IgE-mediated allergy and sensitizations to offending foods have been described in other non–IgE-mediated food allergies, it has not been investigated in FPIAP.

Objective: To investigate IgE-mediated allergy and sensitization to offending foods in FPIAP.

Methods: Patients (n = 204) were retrospectively recruited and grouped as FPIAP (n = 180; FPIAP with or without the symptoms of IgE-mediated food hypersensitivity to offending and nonoffending foods at initial consultation), FPIAP–IgE sensitization to offending foods (n = 17), and FPIAP–transition to IgE-mediated allergy to offending foods (n = 7). The study was performed in accordance with the protocol approved by the local ethical committee of the Hacettepe University.

Results: The median age of onset of symptoms and the development of tolerance was 2 months (interquartile range [IQR], 1.0–3.0) and 12 months (IQR, 10.0–14.0), respectively, and of the patients with skin prick test or serum specific IgE tests (n = 196), 38 (19.4%) had evidence of IgE sensitization to offending foods at the initial consultation or during follow-up; 17 (8.6%) had IgE sensitization, 7 (3.6%) indicated a transition to IgE-mediated allergy to FPIAP-induced foods. The median age of tolerance development of the FPIAP–transition group (19 months, IQR, 18.0–29.0) was significantly later than that of the FPIAP group (11 months, IQR, 10.0–14.0; $P < .001$) and the FPIAP–IgE sensitization group (11.0 months, IQR, 9.5–12.0; $P < .001$). Tolerance was observed within the study period in almost all the patients.

Conclusion: Children with FPIAP may have sensitization or develop IgE-mediated allergy over time to offending foods. In addition, IgE sensitization in FPIAP does not have an unfavorable effect on tolerance development; however, the transition to an IgE-mediated phenotype may delay tolerance for a brief time.

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Introduction

Food protein–induced allergic proctocolitis (FPIAP) presents in the first months of life with bloody, mucoid, frothy stool in otherwise healthy and thriving infants,¹ and elimination diet leads to the improvement of symptoms within 72 to 96 hours in most of the infants. Most patients tolerate triggering foods by the age of 1 year.^{2,3}

Food protein–induced allergic proctocolitis is a non–immunoglobulin E (IgE)–mediated food allergy that typically affects the rectosigmoid colon and presents with focal infiltration of eosinophils in the lamina propria, increased intraepithelial CD8-positive T lymphocytes, focal mucosal erythema, and aphthous ulcerations.^{3–5} Although FPIAP is a non–IgE-mediated food allergy, evidence of IgE sensitization has been previously reported in a minority of patients with FPIAP.⁶ The prevalence of IgE sensitization to the offending food and concomitant IgE sensitization and allergy to other foods in FPIAP is still unknown. The transition to IgE-mediated food allergy to offending foods has not been investigated in FPIAP. This is a complementary study of our previous report in which we characterized our patients with FPIAP.⁷ This study reports our data concerning IgE sensitization and transition to IgE-mediated

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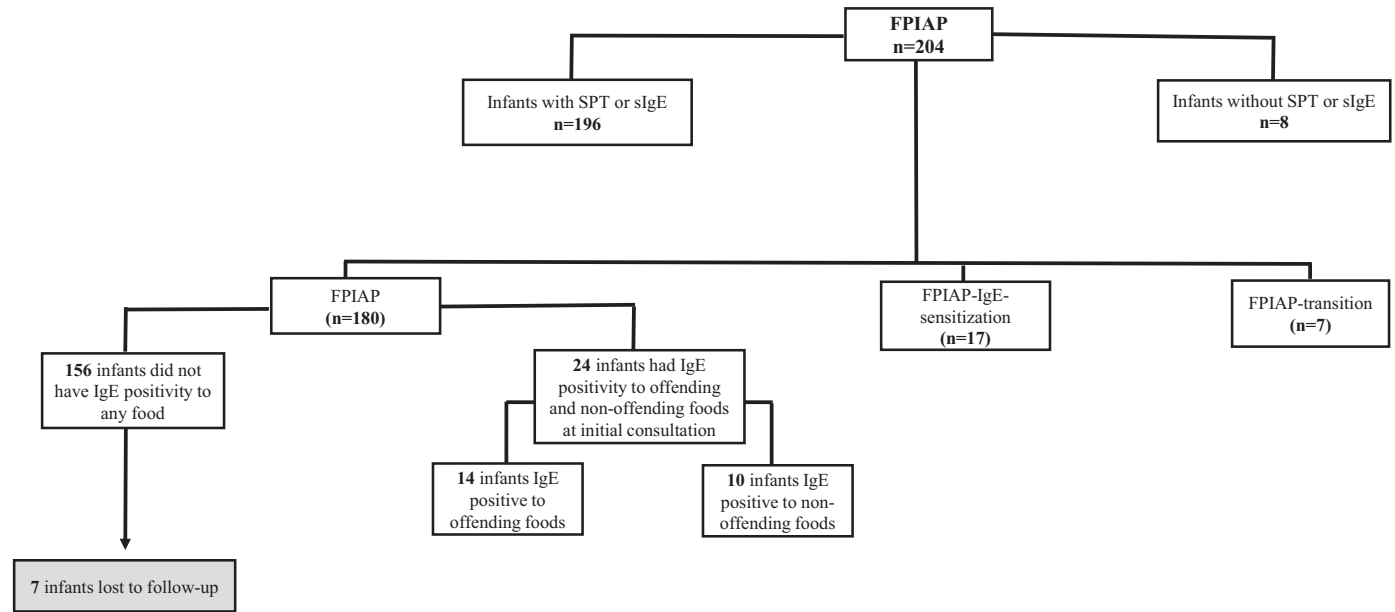


Figure 1. Distribution of the study population according to the diagnosed groups. FPIAP, food protein–induced allergic proctocolitis; sIgE, specific IgE; SPT, skin prick test.

allergy to FPIAP-triggering foods during follow-up. Thus, this study focuses on the different phenotypes of FPIAP.

Methods

Study Population

Infants diagnosed as having FPIAP were retrospectively reviewed, and patients who consulted between January 2015 and December 2018 were included in this study. The infants in the first few months of life with blood and mucus in stool after the ingestion of the suspected food were diagnosed as having FPIAP after the exclusion of other causes of rectal bleeding, resolution of rectal bleeding after the elimination of the offending allergen within 72 hours, and reoccurrence of rectal bleeding after the ingestion of the offending allergen either by

direct consumption or through breastmilk.⁸ All infants had rectal bleeding on the reintroduction of offending foods. Patients were healthy in appearance, and weight gain in infants was as expected in line with their growth curve. Poor weight gain, failure to thrive, vomiting, or abdominal distension after exposure to offending foods were not observed. In this study, infants were grouped into the following 3 categories based on serum specific IgE (sIgE) values, skin prick test (SPT) results, and clinical features (Fig 1): (1) FPIAP (n = 180), defined as patients with FPIAP with or without the symptoms of IgE-mediated food hypersensitivity (urticaria, wheezing, vomiting, etc, typically within 2 hours after the ingestion of offending foods)⁹ to offending and nonoffending foods at initial consultation²; (2) FPIAP-IgE sensitization (n = 17), defined as patients with IgE sensitization to offending foods that were determined by SPT or serum sIgE test, either at the onset of FPIAP or during the follow-up without any

Table 1
Differences Among the Diagnosed Groups

Characteristics	FPIAP (n = 180)	FPIAP-IgE sensitization (n = 17)	FPIAP-transition (n = 7)	P value ^a
Sex (Female)	98 (54.4)	9 (53.0)	2 (28.5)	.41
Onset age of FPIAP-related symptoms (mo) ^b	2.0 (1.2–3.0)	2.0 (1.8–3.7)	2.5 (2.0–5.0)	.30
Age of the tolerance development to offending food of FPIAP (mo) ^b	12.0 (10.0–14.0)	11.0 (9.5–12.0)	19.0 (18.0–29.0)	<.001 ^a
Tolerance development ^c	170 (of 173) (98.3)	17 (100)	7 (100)	.81
More than 1 type of FPIAP-triggering foods ^c	65 (36.1)	7 (41.2)	3 (42.9)	.64
Duration between 2 SPTs to cow's milk (mo) ^b	7.0 (5.0–10.0)	4.0 (3.0–5.5)	6.3 (5.8–8.3)	<.001 ^a
Duration between 2 serum sIgE tests to cow's milk (mo) ^b	9.0 (6.0–11.4)	4.0 (3.0–5.0)	6.3 (5.8–8.3)	<.001 ^a
Duration between 2 SPTs to egg white (mo) ^b	7.0 (5.0–9.5)	4.0 (3.0–5.5)	6.5 (6.0–8.0)	<.001 ^a
Duration between 2 serum sIgE tests to egg white (mo) ^b	9.3 (7.0–13.6)	3.0 (2.0–4.5)	7.3 (6.0–8.3)	<.001 ^a
Eosinophil count (mm ³) ^b	400 (200–600)	300 (225–550)	500 (200–800)	.94
Eosinophilia (>500/mm ³) ^c	74 (41.1)	5 (29.4)	4 (57.1)	.39
Total IgE (kU/L) ^b	6.0 (2.8–15.0)	10.1 (4.3–44.5)	16.9 (2.0–39.2)	.35
AD ^c	59 (34.3)	0	0	.004 ^a
Atopy in the family ^c	61 (33.9)	4 (23.5)	2 (28.6)	.67

Abbreviations: AD, atopic dermatitis; FPIAP, food protein–induced allergic proctocolitis; IQR, interquartile range; sIgE, specific IgE; SPT, skin prick test.

NOTE: FPIAP patients were those who had FPIAP with or without symptoms of IgE-mediated food hypersensitivity symptoms to offending and nonoffending foods at initial consultation, FPIAP-IgE sensitization refers to FPIAP with IgE sensitization to offending foods, and FPIAP-transition refers to FPIAP with transition to IgE-mediated food allergy to offending foods.

^aP value should be less than .05

^bData are presented as median with IQR.

^cData are presented as number (percentage).

immediate IgE-mediated food hypersensitivity symptoms⁹ (FPIAP with IgE sensitization to offending foods)^{10,11}; and (3) FPIAP-transition ($n = 7$), or patients with IgE sensitization to offending foods that were determined by SPT and serum sIgE test results during the follow-up, but not at the time of the onset of FPIAP, and presenting with IgE-mediated food hypersensitivity symptoms⁹ (FPIAP with a transition to IgE-mediated food allergy to offending foods).¹¹

The clinical characteristics of the patients, including the age of onset of symptoms, type of the FPIAP-triggering foods, age of tolerance, serum sIgE values, SPT results, age at the time of positive SPT and serum sIgE test results, presence of atopic dermatitis, and family history of atopy, were recorded. The study was performed in accordance with the protocol approved by the local ethical committee of the Hacettepe University.

Study Measurements

SPTs with fresh cow's milk, egg white, wheat, lentil, sesame, peanut, hazelnut, walnut, soy, fish, and other suspected foods (Allergopharma, Reinbek, Germany) were performed in patients with positive (histamine) and negative (saline) controls and were interpreted 15 minutes after the application of the allergens to the skin. A positive SPT result was accepted as a wheal diameter of 3 mm or larger. Serum sIgE levels were measured (ImmunoCAP; Pharmacia and Upjohn, Uppsala, Sweden), and values above 0.35 kUA/L were considered positive.

Oral food challenges (OFCs) were performed in the infants who had negative SPT results and serum sIgE tests and without IgE-mediated food allergy symptoms (as reported by their parents) with gradual increment at home within 15 days, aiming feeding to the full extent.² Children with positive SPT or serum sIgE test results or IgE-mediated food allergy symptoms underwent OFCs in the hospital.

Statistical Analysis

Analyses were performed by using the Statistical Product and Service Solutions version 22.0 (IBM SPSS Statistics, International

Business Machines Corporation, Chicago, Illinois). A descriptive analysis was used for the characterization of the study population. The categorical values were not normally distributed; thus, the data were given as median and interquartile ranges (IQRs). The χ^2 and Fisher's exact tests were used to analyze the differences among the groups in categorical variables. The nonparametric Mann-Whitney U or Kruskal-Wallis tests were used for the statistical comparisons of the numerical variables. All analyses were 2-tailed, and a P value of less than .05 was considered statistically significant. The Spearman correlation coefficient (r) was used to determine the strength of the relationship of the age of tolerance between the mean of the SPT results and the mean of the serum sIgE measurements.

Results

The characteristics of 204 patients ($n = 109$, 53.4% of the patients were women) with FPIAP were analyzed. The median age at the onset of symptoms was 2 months (25%-75%; IQR, 1.0-3.0). In 62.7% of the patients ($n = 128$), the triggering food was only cow's milk. In 36.7% ($n = 75$), cow's milk was accompanied by other foods, and in only 0.5% ($n = 1$), the offending allergens were triggers other than cow's milk products. A total of 7 patients were lost to follow-up, and 194 patients (95.0%) tolerated FPIAP-triggering foods over time. The median age at tolerance development of the study population was 12.0 months (IQR, 10.0-14.0). Tolerance age to offending food was later in multiple food FPIAP groups (median, 13.0 months; IQR, 11.0-16.0) compared with the single food FPIAP cases (median, 11.0 months; IQR, 10.0-13.0; $P < .001$).

SPT or serum sIgE tests were performed in 196 patients (96.0%) with the most common food allergens. The study population was grouped into 3 categories according to the SPT and serum sIgE test results and clinical features (Table 1, Fig 1). A total of 48 infants (24.5% of 196) had evidence of IgE sensitization, and details are listed in Table 2.

In the FPIAP-IgE sensitization group ($n = 17$, 8.6% of 196), 15 patients had evidence of IgE sensitization in terms of positive serum sIgE, and 2 patients received positive results for both SPT and

Table 2
Number of SPT and sIgE Tests that Were Performed in Infants

	Number of SPT at initial consultation ($n = 192$)	Number of SPT during follow-up ($n = 84$)	Number of serum sIgE tests at initial consultation ($n = 155$)	Number of serum sIgE tests during follow-up ($n = 66$)
	Number of SPT at initial consultation or during follow-up ($n = 193$)		Number of sIgE tests at initial consultation or during follow-up ($n = 167$)	
Number of patients in FPIAP group who underwent testing	168		135	
Number of patients in FPIAP-IgE sensitization group who underwent testing	17		17	
Number of patients in FPIAP-transition group who underwent testing	7		7	
	Positive SPT results (≥ 3 mm) to offending foods ($n = 22$)	Positive SPT results (≥ 3 mm) to nonoffending foods ($n = 9$)	Positive sIgE test results (≥ 0.35 kU/L) to offending foods ($n = 38$)	Positive sIgE test results (≥ 0.35 kU/L) to nonoffending foods ($n = 10$)
Number of patients in FPIAP group who underwent tests	13	9	14	10
Number of patients in FPIAP-IgE sensitization group with positive test results	2	—	17	—
Number of patients in FPIAP-transition group with positive test results	7	—	7	—

Abbreviations: FPIAP, food protein–induced allergic proctocolitis; IgE, immunoglobulin E; sIgE, specific IgE; SPT, skin prick test.

NOTE: FPIAP patients were those who had FPIAP with or without symptoms of IgE-mediated food hypersensitivity symptoms to offending and nonoffending foods at initial consultation; FPIAP-IgE sensitization refers to having FPIAP with IgE sensitization to offending foods; FPIAP-transition refers to having FPIAP with transition to IgE-mediated food allergy to offending foods.

Table 3

Characteristics of Patients With FPIAP-IgE Sensitization or FPIAP With IgE Sensitization to Offending Foods

Age at initial FPIAP symptoms (mo)	Initial serum sIgE (kUA/L)/age (mo)	Initial SPT (mm)/age (mo)	Serum sIgE during follow-up (kUA/L)/age (mo)	SPT during follow-up (mm)/age (mo)	IgE-mediated allergy symptoms (age/mo)	FPIAP to offending food	Sensitization or IgE-mediated food allergy	Age of tolerance development to FPIAP-triggering food (mo)
1	1.83/4 (cow's milk) 0.10/4 (egg white)	0/4 (cow's milk) 0/4 (egg white)	0.34/8 (cow's milk) Not done for egg white	0/8 (cow's milk) 0/8 (egg white)	—	cow's milk, egg, lentil, beef	IgE sensitization to cow's milk	Provocation: 18; cow's milk negative, 12; egg white negative, 12; beef negative, 14; lentil negative
0.5	Not done	0/4 (cow's milk) 0/4 (egg white)	0.76/8 (cow's milk) Not done for egg white	0/8 (cow's milk) 0/8 (egg white)	—	cow's milk	IgE sensitization to cow's milk	Provocation: 13; cow's milk negative
1	<0.35/4 (cow's milk) <0.35/4 (egg white)	0/4 (cow's milk) 0/4 (egg white)	0.47/8 (cow's milk) Not done for egg white	3.5/8 (cow's milk) 0/8 (egg white)	—	cow's milk	IgE sensitization to cow's milk	Provocation: 12; cow's milk negative
1	0.28/6 (cow's milk) 2.16/6 (egg white)	0/6 (cow's milk) 0/6 (egg white)	Not done for cow's milk <0.35/11 (egg white)	0/11 (cow's milk) 0/11 (egg white)	—	cow's milk, egg white	IgE sensitization to egg white	Provocation: 12; cow's milk negative, 12; egg white negative
6	1.00/10 (cow's milk) 1.41/10 (egg white)	0/10 (cow's milk) 0/10 (egg white)	<0.35/12 (cow's milk) 3.16/10 (egg white)	0/12 (cow's milk) 5.5/16 (egg white)	—	cow's milk, egg white	IgE sensitization to cow's milk and egg white	Provocation: 14; cow's milk negative 36; egg white negative
1	0.56/5 (cow's milk) 0.01/5 (egg white)	0/5 (cow's milk) 0/5 (egg white)	0.03/11 (cow's milk) Not done for egg white	0/11 (cow's milk) 0/11 (egg white)	—	cow's milk	IgE sensitization to cow's milk	Provocation: 12; cow's milk negative
3	0.43/8 (cow's milk) 0/8 (egg white)	0/8 (cow's milk) 0/8 (egg white)	Not done	0/12 (cow's milk) 0/12 (egg white)	—	cow's milk	IgE sensitization to cow's milk	Provocation: 12; cow's milk negative
2	0.39/4 (cow's milk) 0.35/4 (egg white)	0/4 (cow's milk) 0/4 (egg white)	0.01/9 (cow's milk) 0.01/9 (egg white)	Not done	—	cow's milk, egg white	IgE sensitization to cow's milk and egg white	Provocation: 12; cow's milk negative, 12; egg white negative
0.5	0.47/8 (cow's milk) 0.21/8 (egg white)	1.5/8 (cow's milk) 1.5/8 (egg white)	0.29/11 (cow's milk) 0.05/11 (egg white)	Not done	—	cow's milk	IgE sensitization to cow's milk	Provocation: 11; cow's milk negative
5	0.30/6 (cow's milk) 0.01/6 (egg white)	0/6 (cow's milk) 0/6 (egg white)	0.73/10 Not done for egg white	0/10 (cow's milk) 0/10 (egg white)	—	cow's milk	IgE sensitization to cow's milk	Provocation: 11; cow's milk negative
2	0.42/7 (cow's milk) Not done for egg white	0/7 (cow's milk) 0/7 (egg white)	0.16/10 (cow's milk) 0.13/10 (egg white)	Not done	—	cow's milk	IgE sensitization to cow's milk	Provocation: 11; cow's milk negative
3.5	<0.35/4.5 (cow's milk) 0.92/4.5 (egg white)	0/4.5 (cow's milk) 0/4.5 (egg white)	0.11/10 (cow's milk) 0.03/10 (egg white)	Not done	—	cow's milk, egg white	IgE sensitization to egg white	Provocation: 10; cow's milk negative, 12; egg white negative
2	0.67/3 (cow's milk) 0.02/3 (egg white)	0/3 (cow's milk) 0/3 (egg white)	0.12/9 (cow's milk) Not done for egg white	0/9 (cow's milk) 0/9 (egg white)	—	cow's milk	IgE sensitization to cow's milk	Provocation: 10; cow's milk negative
4	<0.35/5 (cow's milk) <0.35/5 (egg white)	0/5 (cow's milk) 0/5 (egg white)	Not done for cow's milk 2.33/7 (egg white)	0/7 (cow's milk) 0/7 (egg white)	—	cow's milk, egg white	IgE sensitization to egg white	Provocation: 9; cow's milk negative, 12; egg white negative
2	<0.35/5 (cow's milk) Not done for egg white	0/5 (cow's milk) 0/5 (egg white)	0.95/9 (cow's milk) Not done for egg white	0/9 (cow's milk) 0/9 (egg white)	—	cow's milk, egg white	IgE sensitization to cow's milk	Provocation: 9; cow's milk negative, 12; egg white negative
4	Not done	0/4 (cow's milk) 0/4 (egg white)	0.52/8 (cow's milk) 0/8 (egg white)	0/8 (cow's milk) 0/8 (egg white)	—	cow's milk	IgE sensitization to cow's milk	Provocation: 9; cow's milk negative
0.50	0.36/5 (cow's milk) 0.08/5 (egg white)	0/5 (cow's milk) 0/5 (egg white)	0.39/9 (cow's milk) 0.01/9 (egg white)	0/9 (cow's milk) 0/9 (egg white)	—	cow's milk and beef	IgE sensitization to cow's milk	Provocation: 9; cow's milk negative, 9; beef negative

Abbreviations: FPIAP, food protein–induced allergic proctocolitis; IgE, immunoglobulin E; kUA/L, kilounits of allergen per liter; sIgE, specific IgE; SPT, skin prick test.

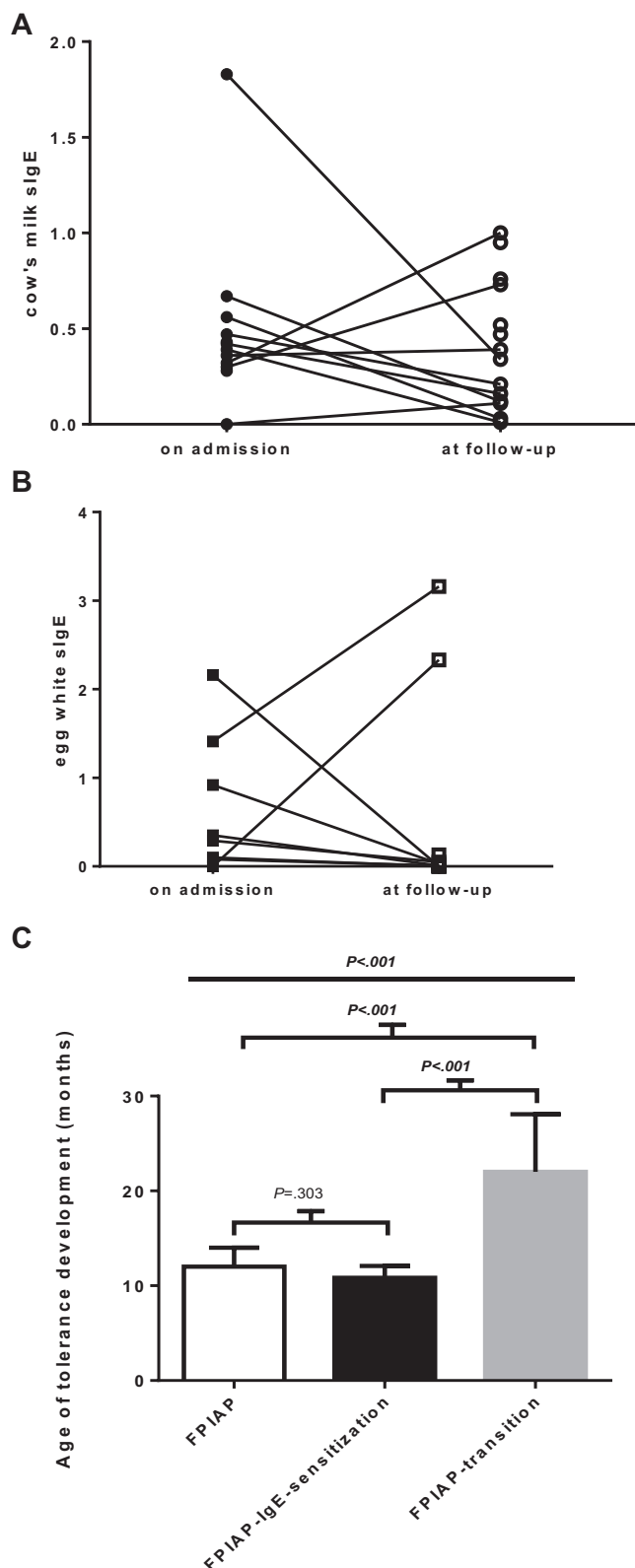


Figure 2. A, Cow's milk sIgE values on admission and follow-up of patients in FPIAP-IgE sensitization group. B, Egg white sIgE values on admission and follow-up of patients in FPIAP-IgE sensitization group. C, Differences in age of tolerance development in the diagnosed groups. FPIAP-others refers to neither development of IgE sensitization to offending foods or transition to IgE-mediated allergy to offending food, FPIAP-IgE sensitization refers to FPIAP with IgE sensitization to offending foods, and FPIAP-transition refers to FPIAP with transition to IgE-mediated food allergy to offending foods. FPIAP, food protein–induced allergic proctocolitis; sIgE, specific IgE.

serum sIgE tests to offending foods. IgE sensitization only to cow's milk was determined in 12 patients, whereas 3 children were sensitized only to egg white, and 2 patients to both cow's milk and egg white (Table 3). The median serum sIgE value in response to cow's milk was 0.5 kUA/L (IQR, 0.4–0.8) in the FPIAP-IgE sensitization group with cow's milk FPIAP ($n = 14$). The serum sIgE median value in response to egg white was 2.1 kUA/L (IQR, 0.6–2.7) in patients with egg white FPIAP ($n = 5$). The serum sIgE values in response to cow's milk ($n = 7$) and egg white ($n = 5$) were negative during follow-up (Fig 2A, Fig 2B). The FPIAP-IgE sensitization group developed tolerance to FPIAP-triggering foods at a median age of 11.0 months (IQR, 9.5–12.0).

In the FPIAP-transition group ($n = 7$, 3.6% of 196), patients developed IgE-mediated symptoms to offending foods at a median of 5 months (IQR, 5–6) of the follow-up. These patients established evidence of IgE sensitization to FPIAP-triggering foods with both positive SPT and serum sIgE test results (Table 4). A total of 4 patients had IgE transition only to cow's milk, 2 patients only to egg white, and 1 had IgE transition both to cow's milk and egg white. Of the patients with IgE-mediated transition to cow's milk ($n = 5$, 3.1% of 163 patients who were in the FPIAP group without atopic dermatitis [$n = 156$] and FPIAP-transition group [$n = 7$]), cow's milk sIgE indicated a median of 1.9 kUA/L (IQR, 0.5–2.7), whereas the median of cow's milk SPT was 9.0 mm (IQR, 5.3–11.0). The median age of tolerance development of the patients with IgE-mediated transition to cow's milk allergy was 18 months (IQR, 17.0–26.0). The median age of tolerance development of the FPIAP-transition group was 19 months (IQR, 18.0–29.0), which was significantly later compared with the other groups ($P < .001$) (Table 1, Fig 2C). All patients developed tolerance until the age of 33 months to IgE-mediated FPIAP-triggering food allergy (Table 4).

Of the 180 patients in the FPIAP group, 179 had cow's milk, 44 had egg white and cow's milk FPIAP, and only 1 patient had FPIAP with triggering foods other than cow's milk. Of these 180 patients, 7.7% ($n = 14$) indicated IgE sensitization with offending foods at the initial consultation. Notably, 9 of these 14 patients had IgE-mediated allergy to cow's milk and egg white at the onset of FPIAP.

The multivariate regression analysis for the risk factors to predict the transition to IgE-mediated food allergy did not indicate any risk factors.

Discussion

This study reports the transition of non-IgE food hypersensitivity to the IgE-mediated allergy and sensitization to the FPIAP-triggering foods. Among patients who underwent SPT and serum sIgE tests ($n = 196$), 38 (19.4%) had evidence of IgE sensitization to offending foods, 17 (8.6%) had IgE sensitivity, and 7 (3.6%) shifted to IgE-mediated allergy to FPIAP-triggering foods. The patients who shifted to IgE-mediated allergy to offending foods developed tolerance significantly later compared with the other groups ($P < .001$). Despite the IgE-mediated allergy or sensitization, almost all patients developed tolerance to offending foods within the time frame of the study.

The transition of non-IgE-mediated food allergy to an IgE-mediated phenotype has not been well characterized in FPIAP and are composed mainly of unpublished data.^{12,13} The IgE-mediated sensitization rates, rather than transition rates, have been reported in a few studies of FPIAP. In a meta-analysis, sensitization to cow's milk was determined in 10 of 98 patients (10.2%) with FPIAP who underwent SPT, and in 13 of 91 patients (14.3%) with serum sIgE tests.⁶ In another study, 37 of 132 patients (28%) with FPIAP underwent SPT, and 13 (35%) of them received positive results; serum sIgE tests were also performed in 51 patients (38.6%), and 18 (35.3%) received positive results.¹⁴ Among our patients with FPIAP, 15.8% (31 of 196) had IgE sensitization at the

Table 4
Characteristics of Patients With FPIAP-Transition or FPIAP With Transition to IgE-Mediated Food Allergy to Offending Foods

Age at initial FPIAP symptoms (mo)	Initial serum sIgE (kUA/L)/age (mo)	Initial SPT (mm)/age (mo)	Serum sIgE during follow-up (kUA/L)/age (mo)	SPT during follow-up (mm)/age (mo)	IgE-mediated allergy symptoms (age, mo)	FPIAP to offending food	Sensitization or IgE-mediated food allergy	Age of tolerance development to FPIAP-triggering food (mo)
2.5	<0.35/4 (cow's milk) <0.35/4 (egg white)	0/4 (cow's milk) 0/4 (egg white)	0.49/9 (cow's milk) Not done for egg white	6/9 (cow's milk) 0/9 (egg white)	Generalized urticaria after consumption of yogurt (9)	cow's milk	IgE-mediated allergy to cow's milk	Provocation: 18; cow's milk, negative
5	<0.35/7 (cow's milk) <0.35/7 (egg white)	0/7 (cow's milk) 0/7 (egg white)	Not done for cow's milk 0.95/15 (egg)	Not done for cow's milk 5/15 (egg white)	Urticaria after consumption of egg white (12)	cow's milk, egg white	IgE-mediated allergy to egg white	Provocation: 29; egg white, negative
2	<0.35/4 (cow's milk) Not done for egg white	0/4 (cow's milk) 0/4 (egg white)	2.4/10 (cow's milk) Not done for egg white	11/10 (cow's milk) 0/10 (egg white)	Urticaria after consumption of yogurt (10)	cow's milk	IgE-mediated allergy to cow's milk	Provocation: 10; urticaria with yogurt, 16; cow's milk, negative
2	Not done/5 (lentil) <0.35/5 (egg) <0.35/5 (cow's milk)	0/5 (lentil) 0/5 (cow's milk) 0/5 (egg)	1.31/13 (lentil) 0.60/13 (cow's milk) 4.7/13 (egg)	5/13 (lentil) 11/13 (cow's milk) 5.5/13 (egg)	Dramatic development of AD at 12 mo after mother's consumption of milk, urticaria after consumption of lentil (10) at home	cow's milk, egg white, lentil	IgE-mediated allergy to cow's milk, egg white, lentil	Provocation: 30; lentil, negative 33; cow's milk, negative 33; egg white, negative
5	<0.35/5 (cow's milk) Not done for egg white	0/5 (cow's milk) 0/5 (egg white)	3.06/14 (cow's milk) 0.95/14 (casein) Not done for egg white	9/14 (cow's milk) Not done for egg white	Urticaria, coughing, hoarseness after consumption of 100 mL cow's milk (13) at home	cow's milk	IgE-mediated allergy to cow's milk	Provocation: 13; 20 mL cow's milk, generalized urticaria 19; cow's milk, negative
3	<0.35/5 (cow's milk) <0.35/5 (egg white)	0/5 (cow's milk) 0/5 (egg white)	1.88/11 (cow's milk) <0.35/11 (egg white)	4.5/11 (cow's milk) 0/11 (egg white)	Urticaria after consumption of 40 mL yogurt soup (11) at home	cow's milk	IgE-mediated allergy to cow's milk	Provocation: 18; yogurt, negative
1.5	<0.35/4 (cow's milk) < 0.35/4 (egg white)	0/4 (cow's milk) 0/4 (egg white)	<0.35/10.5 (cow's milk) 1.7/10.5 (egg white)	0/10.5 (cow's milk) 5/10.5 (egg)	Urticaria, wheezing, vomiting after consumption of egg at home (14)	cow's milk, egg white	IgE-mediated allergy to egg white	Provocation: 15; cow's milk, negative 29; egg white, negative

Abbreviations: AD, atopic dermatitis; FPIAP, food protein–induced allergic proctocolitis; IgE, immunoglobulin E; kUA/L, kilounits of allergen per liter; sIgE, specific IgE; SPT, skin prick test.

initial consultation or during follow-up, and 3.6% developed IgE-mediated allergy to offending foods over time. The underlying reason of lower sensitization ratio in our study compared with reports on FPIAP and IgE-mediated food allergy is likely to be because of the variety in the characteristics of patient populations and a higher number of tests that we performed in the study population (96.0%), which is in contrast to other studies in the literature.

In our study, we found the prevalence of transition to IgE-mediated cow's milk allergy as 3.1% in infants during follow-up. In the literature, the prevalence of IgE-mediated cow's milk allergy was 1.4% in a cohort.¹⁵ Our patients developed tolerance to cow's milk at a median age of 18 months (IQR, 18.0–26.0), whereas in the cohort study, the children developed tolerance to cow's milk at a mean age of 20.9 plus or minus 1.1 months.¹⁶ In an unpublished study, the mean milk-specific IgE of IgE-mediated cow's milk allergic children was 7.6 (1.9–27.2) kU/L and the rate of clinical tolerance to cow's milk allergy up to 3 years of age was 43.1%, whereas the development of clinical tolerance until 5 and 6 years were 65.2% and 68.1%, respectively. The only specific risk factor for cow's milk allergy persistence was the high specific IgE level (odds ratio, 0.961; 95% confidence interval, 0.947–0.974; $P < .001$).¹⁷ In this group of patients, the mean sIgE level was rather high, and the tolerance development delayed up to 6 years of age. It is also known that the value of sIgE is inversely correlated with the probability of tolerance development.^{18,19} According to all these data, low sIgE values may be the reason for early tolerance development in our patient population.

In our study, patients who shifted to IgE-mediated food allergy (FPIAP-transition group) developed tolerance with a statistically significant delay in comparison with the patients in the FPIAP group and the FPIAP-IgE sensitization group. Despite the transition to the IgE-mediated allergy and delay in the development of tolerance, all these patients developed tolerance to the offending foods in the FPIAP-transition group during the study. This may be because of a completely benign and self-limiting disease, which are characteristic of FPIAP.¹

The exact mechanism of the shift from non-IgE-mediated allergy to IgE-mediated phenotype to offending foods is unknown.²⁰ This shift has been attributed to the extended elimination period of offending foods.²⁰ However, the elimination period is generally short in FPIAP, and tolerance development is around 1 year of age, as also indicated with our study. CD8-positive T lymphocyte-mediated process, associated with eosinophilic inflammation and causing superficial erosions or ulcerations in the colonic and rectal mucosa, has been defined in FPIAP.^{4,5} In addition, tumor necrosis factor α , which has been reported to decrease the barrier capacity of intestinal cell lines, were elevated in patients with FPIAP.^{21,22} The impaired barrier function in FPIAP²² may facilitate antigen uptake and presentation of the antigens to the immune system, which in turn may generate a tendency for the transition toward an IgE-mediated food allergy and sensitization in these patients, as indicated previously in another non-IgE-mediated disease called food protein-induced enterocolitis syndrome.²³ In contrast, in mouse models, CD86 costimulation was reported to play a role in IgE-mediated food allergy, and the expression of CD86 was higher in infants with FPIAP.^{22,24} In a study composed of patients with non-IgE-mediated food allergy, including FPIAP, skewed T_H2 immunologic response and increased T_H2 cytokine levels were documented.²⁵ Based on our study and previous reports, we suggest that shifting to an IgE-mediated allergy and sensitization against offending foods may also take place in FPIAP, and there may be different phenotypes in FPIAP, which are associated with T_H2 -mediated immunologic response. The underlying mechanism of transition to an IgE-mediated food allergy in FPIAP remains to be elucidated.

The median value of serum sIgE to cow's milk was 0.5 kUA/L in the FPIAP-IgE sensitization group, whereas it was 1.9 kUA/L in the FPIAP-transition group. In addition, whereas only 2 patients had positive SPT results in the FPIAP-IgE sensitization group, all infants had positive SPT measurements with a median of 9.0 mm in the FPIAP-transition group. Furthermore, most serum sIgE results of the patients in the FPIAP-IgE sensitization group were negative during the follow-up period. Based on these results, it can be deduced that performing SPT is more informative than serum sIgE testing for the determination of patients with an IgE-mediated transition to FPIAP-triggering foods.

In FPIAP, SPT or serum sIgE test is not recommended to be performed routinely in practice and is suggested to be performed in infants with FPIAP based on an allergy-focused history, in accordance with the guidelines.¹ Under such circumstances, deciding which patients should undergo SPT or serum sIgE test is the most critical point. Unfortunately, we did not determine any risk factors in the multivariate regression analysis to assist in deciding the recipients of the SPT or serum sIgE test. These tests may be considered for infants with symptoms associated with IgE-mediated allergies or after a long period of restriction of FPIAP-triggering food allergen before the reintroduction of the offending food to diet at home, as indicated in the literature.¹ Owing to the risk of developing anaphylaxis, as seen in 2 of our patients, families should still be given previous information regarding proper caution.

An important limitation of this study is its retrospective nature, and consequently, the follow-up SPT, serum sIgE test, and OFC were not performed systematically for each individual patient both at the initial consultation and during follow-up. Some patients have been challenged later than others, and we do not know if they became tolerant before. Nevertheless, our findings are based on a relatively large pediatric population, and the demonstration of not only the children with the evidence of IgE sensitization but also those who shifted to IgE-mediated allergies are the most important strengths of this study.

To the best of our knowledge, this is the first report that indicates the transition to IgE-mediated food allergy in FPIAP. In this study, SPT seemed to be more important and informative than serum sIgE tests in the determination of IgE-mediated transition to offending foods, especially in the case of the symptoms associated with IgE-mediated allergies or after a long period of restriction of the offending allergen before reintroduction of the food to the diet. This study strongly suggests that the evidence of IgE sensitization in FPIAP does not have an unfavorable effect on tolerance development; however, the transition to an IgE-mediated phenotype may delay the development of tolerance to the offending food for a brief time.

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