

Predictors for late tolerance development in food protein-induced allergic proctocolitis

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ABSTRACT

Background: Food protein-induced allergic proctocolitis (FPIAP) is a non-immunoglobulin E (IgE) mediated food allergy that typically presents with blood-mixed mucoid stool.

Objective: To identify the predictors that affect the tolerance development in infants with FPIAP and laboratory as well as clinical differences between patients with early and with late tolerance.

Methods: A total of 185 infants with FPIAP were included. The patients were grouped and analyzed based on laboratory tests and clinical characteristics.

Results: The median (interquartile range [IQR]) age of onset of symptoms was 2.0 months (1.0–3.0 months). Symptoms began in severe cases in patients ($n = 23$) at a younger median (IQR) age (1.5 months [0.7–2.0 months]) than the group with nonsevere presentation (median 2.0 months [IQR 1.5–3.0 months]) ($p < 0.001$). The frequency of neutropenia ($<1500/\text{mm}^3$) ($p = 0.045$) and eosinophilia ($450/\text{mm}^3$) ($p = 0.018$) was increased in severe cases. Concomitant IgE-related food allergy (odds ratio [OR] 3.595 [95% confidence interval {CI}, 1.096–11.788], $p = 0.035$), non-IgE-mediated multiple food allergy (OR 3.577 [95% CI, 1.595–8.018], $p = 0.002$), feeding with cow's milk-based formula (at least once during infancy) (OR 2.517 [95% CI, 1.188–5.333], $p = 0.016$), and late complementary feeding (OR 5.438 [95% CI, 2.693–10.981], $p < 0.001$) were the predictors for late tolerance development. The estimated optimal cutoff value for introduction of complementary foods for the resolution of allergy was 5.5 months, with 69.4% sensitivity, 74.4% specificity, and an area under the curve of 0.737 (95% CI, 0.626–0.812) ($p < 0.001$).

Conclusion: This study showed that the early introduction of complementary feeding accelerates tolerance development in FPIAP. A longer duration of an elimination diet has no impact on the resolution of allergy. Physicians should consider conservative avoidance measures and earlier introduction of complementary feeding in FPIAP.

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Food protein-induced allergic proctocolitis (FPIAP) is a non-immunoglobulin E (IgE) mediated food allergy that typically presents in the first 6 months of life with blood-mixed mucoid, frothy stool in healthy infants. The prevalence of FPIAP has been shown as 0.16% in a large cohort that consisted of infants with rectal bleeding.¹ Diagnosing FPIAP is based on a clinical history, exclusion of the other causes of rectal bleeding, responsiveness to restriction of causative food allergen, and rectal bleeding after reintroduction of the offending foods after a 2- to 4-week period of elimination for confirmatory challenge.^{2,3} Sixty percent of infants with FPIAP are breast-fed, and the underlying cause of the disease is mostly due to cow's milk protein,⁴ followed by soy, egg, and corn proteins.⁴ Characteristically, conducting a diet by elimination of these foods leads to

improvement in the symptoms within 72–96 hours of the allergen restriction in most of the infants.⁵

However, persistent bloody stool refractory to maternal dietary restrictions may occur in a small proportion of the patients.⁴ In these circumstances, the patients respond well to temporary interruption of breast-feeding and of feeding with extensively hydrolyzed or amino acid-based formulas.⁶ The majority of the patients may consume causative food by the age of 1 year; however, resolution of the allergy can even be delayed up to 3 years of age in a small number of patients.⁴ FPIAP is a completely benign transient condition; however, an evaluation of the risk factors for late tolerance in FPIAP may help to eliminate psychological stress of long-term exhausting elimination diets on mothers. Therefore, we aimed to determine the variables that predict early or late tolerance in infants with FPIAP.

MATERIALS AND METHODS

This prospective study was conducted between January 2014 and November 2018 at the Division of Pediatric Allergy in Hacettepe University School of Medicine, with the enrollment of infants diagnosed

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with FPIAP. The study was performed in accordance with the protocol approved by the local ethical committee (Hacettepe University, GO 15/649-07), and all parents and guardians provided written informed consent.

FPIAP was diagnosed by the presence of blood and mucus in stool after ingestion of the suspected food in a well-appearing healthy infant in the first few months of life after the exclusion of other causes of rectal bleeding and by the resolution of rectal bleeding on the elimination diet, typically within 72 hours but reoccurrence of the symptoms after oral provocation with the causative food.⁷ Infants diagnosed with FPIAP according to the international guidelines^{8,9} and only the patients with visible bloody stool were included in the study. Furthermore, questions were asked to distinguish IgE and non-IgE-mediated reactions, such as the timing of the symptoms (whether initiation of the symptoms in the first few minutes or after hours), if the infant was exclusively breast-fed and/or formula-based fed, or fed with complementary foods, age of onset of the first symptoms (whether presented in the first few months of life or later).¹⁰

Clinical characteristics of the patients, including age of symptoms onset, tolerance age of the patients, concomitant IgE-related food allergy, induction of non-IgE-mediated symptoms with more than one type of food (multiple foods), temporary interruption of breast-feeding due to persistent bleeding, age at which complementary feeding was commenced, feeding with cow's milk-based formula, age of formula onset, the presence of atopic dermatitis, and a family history of atopy were recorded. Infants with FPIAP who had bleeding of more than in the form of spots in the stool, with mild-to-moderate anemia, accepted as severe FPIAP, and the remaining study population was included in the nonsevere-FPIAP group.¹¹

Study Measurements

Whole blood counts of the patients during the first visit of the patient were performed at the time of the diagnosis. Skin-prick tests (Stallergenes, SA, Antony, France) with cow's milk, egg white, wheat, sesame, peanut, and tree nuts were performed with the patients just before starting the complementary foods and the time of oral food challenges (OFC) to reveal the concomitant IgE-mediated food allergy.¹² Specific IgE (Immuno-CAP; Pharmacia and Upjohn, Uppsala, Sweden) measurements to milk and egg were done at admission to the study, and were done to other foods as needed. OFC skin-prick test results with a wheal size ≥ 3 mm than the negative control and specific IgE value > 0.35 kUA/L were considered positive.

OFC Tests in FPIAP

OFC is performed both to confirm the diagnosis and to determine the tolerance in FPIAP. All the patients underwent OFC to confirm the diagnosis of FPIAP after 2 weeks in nonsevere and 4 weeks in severe cases following the resolution of symptoms after the elimination of triggering foods from maternal diet.^{2,13} After the confirmation of the diagnosis, the elimination diet was continued, and, after 3 to 6 months of a successful elimination period, OFC tests were performed to reveal the development of tolerance.^{2,14} In the case of the recurrence of the symptoms, the patient was diagnosed as FPIAP and continued the elimination diet, and re-challenge with the suspected offending food was attempted 3–6 months after a failed OFC.¹¹ Foods were introduced at home to the children by their parents, with gradual increase from 5 g per day (approximately 1 teaspoonful) to full feeding within 15 days.⁴ However, patients with severe FPIAP and whose parents were extremely anxious underwent OFC at the hospital. In the follow-up, the parents gave information with regard to the results of the provocation *via* telephone calls or visiting our outpatient clinic.

RESULTS

A total of 185 infants (78 boys, 107 girls) with the diagnosis of FPIAP were enrolled; however, 9 of them were lost to follow-up. Characteristics of the patient population are shown in Table 1. The age of onset of FPIAP-related symptoms was median (IQR) 2.0 months (1.0–3.0 months). One hundred and seven infants (57.8%) were exclusively breast-fed, and 76 patients (41.1%) were fed cow's milk-based formula at least once before symptoms emerged. Formula-fed infants had a younger age of onset of the symptoms compared to those with exclusively breast-fed cases (median 2.0 months [IQR 1.0–2.9 months] versus median 2.0 months [IQR 1.5–3.0 months], respectively; $p = 0.014$). All mothers of the infants consumed dairy products before the initiation of the elimination diet.

Responsible Foods in FPIAP

Cow's milk was the most frequent triggering food, which was identified in 99.5% of the patients with FPIAP, and this was followed by egg white (22.2%) and beef (8.1%), respectively (Online Supplemental Fig. 1). In addition, cow's milk was determined in all patients with severe clinical manifestations ($n = 23$) as the offending food. Egg white (21.7%), beef (8.6%), lamb (4.3%), potato (4.3%), lentil (4.3%), wheat (4.3%), sesame (4.3%), and chickpea (4.3%) were the other triggers in the infants with severe FPIAP. However, cow's milk was the offending food in 99.4% of the cases in the patients with a nonsevere presentation. This was followed by egg white (22.2%), beef (8%), chicken meat

Table 1 Demographic features and laboratory tests of the study population

	Study Population (N = 185)
No. boys/girls	78/107
Onset age of FPIAP-related symptoms, median (IQR), mo	2.0 (1.0–3.0)
Time between the admission to our department and onset age of the symptoms, median (IQR), mo	2.0 (1.0–4.0)
Current age of the children, median (IQR), mo	30.6 (24.1–30.6)
Severe clinical presentation, no. (%)	23 (12.4)
Concomitant IgE-related food allergy at admission, no. (%)	21 (11.4)
Patients with non-IgE-mediated food tolerance development (<i>n</i> = 176), no. (%)	175 (99.4)
Non-IgE-mediated allergy with multiple foods, no. (%)	65 (35.1)
Tolerance age with non-IgE foods, median (IQR) mo	11.0 (10.0–13.0)
Onset age of formula, median (IQR), days	1.0 (1.0–3.0)
Onset age of the complementary foods, median (IQR), mo	5.5 (5.0–6.0)
Neutrophil level in 1 mm ³ blood, median (IQR), mm ³	2000 (1400–3100)
Eosinophil count, median (IQR), mm ³	400 (200–700)
Number of the patients with neutropenia (<1500/mm ³), no. (%)	44 (23.8)
Number of the patients with eosinophilia (>500/mm ³), no. (%)	78 (42.2)
Hemoglobin level, median (IQR), g/dL	11.3 (10.7–12.0)
Total IgE level, median (IQR), kU/L	5.7 (2.8–13.6)
Exclusively breast-fed infants, no. (%)	107 (57.8)
Temporary interruption of breast-feeding, no. (%)	9 (4.8)
First gestation, no. (%)	115 (62.2)
Caesarean section delivery, no. (%)	119 (64.3)
Birth weight, median (IQR), g	3200 (3000–3500)
Fed cow's milk-based formula (at least one time), no. (%)	76 (41.1)
Atopic dermatitis, no. (%)	48 (25.9)
Atopy in the family, no. (%)	65 (35.1)

FPIAP = Food protein–induced allergic proctocolitis; IQR = interquartile range; IgE = immunoglobulin E.

(2.4%), fish (2.4%), lamb (1.2%), lentil (2.4%), turkey (0.6%), walnut (1.8%), hazelnut (1.2%), sesame (1.2%), rice (0.6%), pea (1.2%), chickpea (0.6%), and mushroom (0.6%).

Moreover, single-food allergy occurred in 65% (*n* = 120), whereas multiple-food allergy was determined in 35% of the patients (*n* = 65). Tolerance developed at an earlier age in children with single-food allergy (median 11.0 months [IQR 10.0–13.0 months]) than the ones with multiple-food allergy (median 12.0 months [IQR 11.0–14.7 months]) (*p* = 0.002) (Online Supplemental Table 2). In addition, atopic dermatitis frequency was higher in the multiple-food allergy group (*p* = 0.032) (Online Supplemental Table 2).

Complementary Feeding

The complementary feeding was started at a median (IQR) age of 5.5 months (5.0–6.0 months) in the study population. Complementary foods were introduced between 4.5 and 6.0 months in 166 infants, between 6.5 and 7.5 months in 17 patients, and at 9.0 months of age only in one infant. Potatoes, carrot, apple, pear,

banana, also other types of vegetables, fruits, rice, and grains were the main introduced foods introduced to the diet of infants with increasing amounts. Twenty-one patients (11.4%) had concomitant IgE-mediated food allergy other than FPIAP-triggering foods, and 65 infants (35.1%) had non-IgE-mediated allergies with multiple foods on admission. Furthermore, 48 infants (25.9%) had atopic dermatitis.

Infants with Severe Clinical Presentation

Twenty-three patients (12.4%) presented with severe clinical manifestations at admission. The median (IQR) age of onset for FPIAP-related symptoms in this group was younger (1.5 months [0.7–2.0 months]) than in the group with a nonsevere presentation (2.0 months [1.5–3.0 months]) (*p* < 0.001) (Table 2). Breast-feeding was temporarily interrupted for 1–2 weeks in 4.8% (9/185) due to unresponsiveness to the strict elimination diets, and clinical symptoms resolved in all of these infants after the interruption of breast milk and with the introduction of amino acid–based formula. Complementary feeding could not be initiated with these infants at

Table 2 Comparison of the patients with FPIAP and with severe clinical presentation

	Severe Clinical Presentation (<i>n</i> = 23)	Nonsevere Clinical Presentation (<i>n</i> = 162)	<i>p</i>
No. boys/girls	15/8	63/99	0.017
Onset age of FPIAP related symptoms, median (IQR), mo	1.5 (0.7–2.0)	2.0 (1.5–3.0)	<0.001
Tolerance age, median (IQR), mo	12.0 (11.0–13.0)	11.0 (10.0–14.0)	0.224
Tolerance development, no. (%)	22/22 (100)	153/153 (100)	0.705
Concomitant IgE-related food allergy, no. (%)	4 (17.4)	17 (10.5)	0.330
Non-IgE-mediated allergy with multiple foods, no. (%)	8 (34.8)	57 (35.2)	0.970
Temporary interruption of breast-feeding, no. (%)	9 (39.1)	0	<0.001
Fed cow's milk-based formula (at least one time), no. (%)	8 (34.8)	68 (42.0)	0.513
Onset age of the complementary foods, median (IQR), mo	6.0 (5.5–6.0)	5.5 (5.0–6.0)	0.043
Hemoglobin level, median (IQR), g/dL	10.7 (9.8–11.2)	11.4 (10.7–12.0)	0.002
Platelet levels in 1 mm ³ blood, median (IQR), /mm ³	366,000 (320,000–456,000)	382,000 (317,250–456,000)	0.966
Neutrophil levels in 1 mm ³ blood, median (IQR), mm ³	1800 (1000–3600)	2000 (1500–3000)	0.323
Neutropenia (Blood neutrophil level) (<1500/mm ³), no. (%)	10 (43.5)	34 (21.0)	0.045
Eosinophil count, median (IQR), mm ³	1100 (500–1900)	400 (200–600)	<0.001
Eosinophilia (blood eosinophil level) (>450/mm ³), no. (%)	16 (69.6)	62 (38.3)	0.018
Severe eosinophilia (blood eosinophil level) (>1000/mm ³), no. (%)	11 (47.8)	11 (6.8)	<0.001
Total IgE, median (IQR), kU/L	5.0 (2.7–8.9)	5.8 (2.8–15.2)	0.333
Atopic dermatitis, no. (%)	7 (30.4)	41 (25.3)	0.601
Atopy in the family, no. (%)	5 (21.7)	60 (37)	0.152

FPIAP = Food protein–induced allergic proctocolitis; IQR = interquartile range; IgE = immunoglobulin E.

Bold and italic numbers represent *p* value <0.05.

median (IQR) ages as early as with the patients with nonsevere presentation (6.0 months [5.5–6.0 months] versus 5.5 months [5.0–6.0 months], *p* = 0.043) (Table 2). In addition, the median (IQR) ages of tolerance were 12.0 months (11.0–13.0 months) and 11.0 months (10.0–14.0 months) in infants with severe and nonsevere clinical manifestations (*p* = 0.224), respectively (Table 2).

Laboratory Evaluation of the Patients

Median (IQR) hemoglobin values were lower in the patients with a severe clinical presentation (10.7 g/dL [9.8–11.2 g/dL]) than the patients in whom the clinical symptoms were not severe (11.4 g/dL [10.7–12.0 g/dL]) at admission (*p* = 0.002). Most interestingly, 44 patients had neutropenia in addition to the 78 patients with eosinophilia at admission (Table 1). The frequency of

neutropenia (neutrophil level) (<1500/mm³) and eosinophilia (eosinophil level) (>450/mm³) was higher in children with severe clinical presentation (43.5% versus children with nonsevere presentation 21.0%, *p* = 0.045 for neutropenia; 69.6% versus 38.3%, *p* = 0.018 for eosinophilia). In addition, the frequency of both eosinophilia (eosinophil level) (>450/mm³) and severe eosinophilia (eosinophil level) (>1000/mm³) was significantly higher in the patients with neutropenia (*p* = 0.032 and *p* = 0.025, respectively) compared with the children with normal neutrophil counts (Fig. 1A). Furthermore, two patients with severe neutropenia (neutrophil level) (<500/mm³) underwent bone marrow aspiration to clarify any underlying reason of neutropenia but no pathological finding was found. Low neutrophil levels (neutropenia) returned to levels within the normal ranges with the improvement of symptoms.

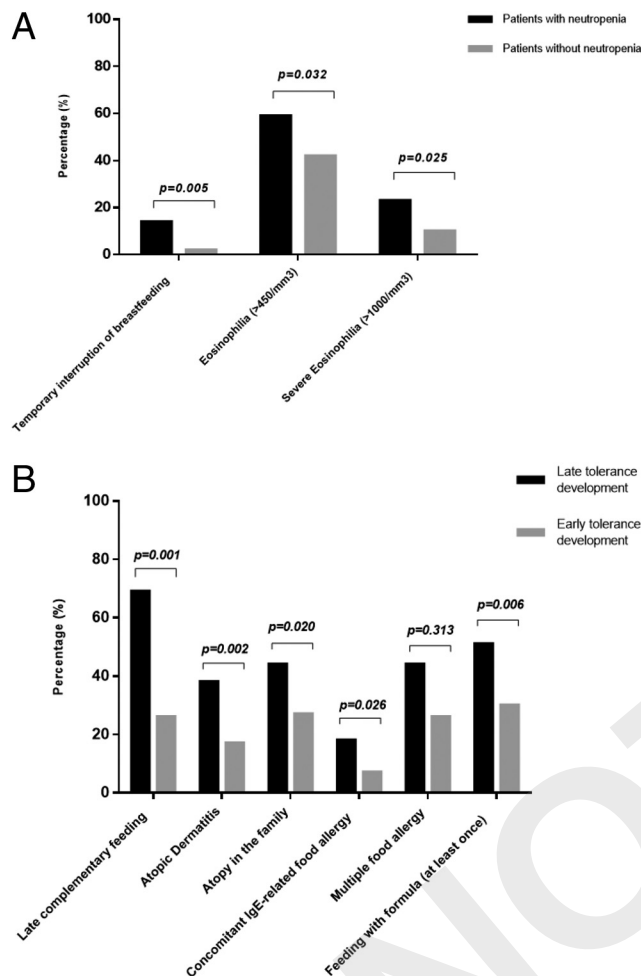


Figure 1. Differences in the patients with respect to (A) having neutropenia or not having neutropenia, and (B) late or early tolerance development.

Prognosis

Early tolerance (<12 months) occurred in 90, and late tolerance (≥ 12 months) was observed in 85 children. The differences with regard to parameters between patients with early tolerance and patients with late tolerance are given in Fig. 1B. In the study population, tolerance occurred in 175 children (99.4%) at a median age of 11.0 months (10.0–13.0 months); however, children with severe clinical manifestations ($n = 23$) developed tolerance by the age of 12.0 months (11.0–13.0 months). A hundred and eighteen infants (67%) could consume the triggering foods in the first year of life, whereas the rest of the patients ($n = 57$ [33%]) developed tolerance between 12 and 19 months of age. Children who were introduced complementary feeding after 5.5 months (late complementary feeding) ($n = 87$) tended to develop tolerance at an older age than did the children who were introduced complementary feeding between 4.5 and 5.5 months (early complementary feeding) ($n = 97$) (13.0 months [11.0–14.0 months] versus 10.0 months [9.0–12.0

months], respectively) ($p < 0.001$) (Table 3). In addition, there was a positive correlation between the initiation time of the complementary foods and the tolerance age ($r = 0.482$, $p < 0.001$). The patients with history of atopy in their families tolerated causative foods later (12.0 months [11.0–14.0 months]) compared with the children without atopy in their families (11.0 months [9.0–13.0 months]) ($p = 0.004$) (Online Supplemental Table 1).

DISCUSSION

The current study presented the prognosis and the risk factors for late tolerance development in infants with FPIAP. When taken together, our results revealed that concomitant IgE-related food allergy, non-IgE-mediated multiple-food hypersensitivity, feeding cow's milk-based formula (at least once) before the symptoms emerged, and delay in timing of complementary feeding were the independent predictors for late tolerance improvement. Furthermore, we assessed the optimal cutoff value and generated a probability curve for the introduction time of complementary foods that induce tolerance in FPIAP.

The median (IQR) age of symptom onset was 2.0 months (1.0–3.0 months) of the study population which was consistent with the literature data.⁷ There are reports that exhibit the relationship between the early symptom onset age and early tolerance development.¹⁵ Although a similar association could not be found in the current study, we identified that patients with severe clinical manifestation presented at a significantly younger age (median (IQR) 1.5 months (0.7–2.0 months)) than those patients with nonsevere manifestations (2.0 months [1.5–3.0 months]). There are reports of severe cases with an early onset of FPIAP.¹⁶ Nevertheless, the relationship between the severity of FPIAP symptoms and age of onset of the disease has not been well documented in a large population-based study.

In the current study, cow's milk was the most frequent triggering food, and this was followed by egg white. Similarly, cow's milk and egg were the most frequently determined triggers of FPIAP in infants according to the literature.^{14,17} Furthermore, we classified the study group as severe and nonsevere FPIAP, and compared them with regard to the type of triggering foods responsible in FPIAP symptoms. Cow's milk and egg white were the most common offending foods, and there was no difference in terms of the ratios in both groups.

The prognosis of FPIAP is favorable, with the development of tolerance in the majority of the patients by the first year of age.⁴ Similarly, allergy resolved at a median age of 11.0 months and most lately up to 19 months of age in our patient cohort. However, approximately 30% to 40% of the children with FPIAP tolerated causative foods after age 1 year,^{4,15,18,19} a further

Table 3 Comparison of the patients with FPIAP and with early complementary feeding (4.5-5.50 mo) vs late complementary feeding (>5.50 mo)

	Early Complementary Feeding (4.5-5.5 mo) (<i>n</i> = 97)	Late Complementary Feeding (>5.5 mo) (<i>n</i> = 87)	<i>p</i>
No. boys/girls	40/57	37/50	0.860
Onset age of FPIAP-related symptoms, median (IQR), mo	2.0 (1.0–3.0)	2.0 (1.5–3.0)	0.193
Severe clinical presentation, no. (%)	4 (5.9)	16 (13.8)	0.066
Tolerance age, median (IQR), mo	10.0 (9.0–12.0)	13.0 (11.0–14.0)	<0.001
Tolerance development, no./total no. (%)	93/94 (98.9)	82/82 (100)	0.350
Concomitant IgE-related food allergy, no. (%)	9 (9.3)	13 (12.8)	0.338
Non-IgE-mediated allergy with multiple foods, no. (%)	38 (39.2)	26 (29.9)	0.188
Temporary interruption of breast-feeding, no. (%)	4 (4.1)	5 (5.7)	0.611
Fed cow's milk-based formula (at least one time), no. (%)	29 (29.9)	46 (52.9)	0.002
Hemoglobin level, median (IQR), g/dL	11.5 (10.7–12.1)	11.2 (10.6–11.8)	0.205
Platelet count, median (IQR), mm ³	390,000 (316,000–450,000)	378,000 (321,000–463,000)	0.764
Total IgE, median (IQR), kU/L	4.5 (2.8–11.1)	6.13 (2.66–15.75)	0.901
Neutrophil count, median (IQR), mm ³	2000 (1400–3300)	1900 (1400–3000)	0.562
Neutropenia (Neutrophil level) (<1500/mm ³), no. (%)	21 (21.6)	23 (26.4)	0.470
Eosinophil count, median (IQR), mm ³	400 (200–600)	500 (200–800)	0.585
Eosinophilia (Eosinophil level) (>450/mm ³), no. (%)	40 (41.2)	38 (43.7)	0.785
Severe eosinophilia (Eosinophil level) (>1000/mm ³), no. (%)	11 (11.3)	11 (12.6)	0.809
Atopic dermatitis, no. (%)	21 (21.6)	27 (31)	0.149
Atopy in the family, no. (%)	29 (29.9)	36 (41.4)	0.105

FPIAP = Food protein-induced allergic proctocolitis, IQR = interquartile range; IgE = immunoglobulin E.

Bold and italic all indicate *p* value <0.05. mm³ indicates the eosinophil, neutrophil, thrombocyte levels in 1 mm³ blood.

5% developed tolerance beyond the age of 3 years.¹⁵ The reason for this wide range of tolerance age may be due to a delay in the introduction of offending foods to diets of the patients because of families' anxiety. In addition, possible reasons of earlier tolerance age of our patient population was the tendency of initiation of offending foods at an early age, of median 5.5 months, even in severe cases. After the complementary feeding, we observed further improvement in the consistency of stool as well as in other presenting symptoms. Therefore, we thought that complementary feeding may induce early allergy resolution in children with FPIAP.

Overall, the clinical presentation of FPAIP is mostly mild to moderate,⁵ and only 5% to 7% of patients have severe symptoms with the requirement in which amino acid-based or extensively hydrolyzed formula should be given.⁵ In our study, 12.4% of the infants

had severe clinical manifestation, and breast-feeding was temporarily interrupted in 4.8% of the study population, similar to the data in the literature.⁵ Discontinuation of breast milk and commencement of amino acid-based or extensively hydrolyzed formulas in infants who were unresponsive or partially responsive to an elimination diet caused resolution of the symptoms, similar to the patients reported in previous studies.^{5,6,20} An underlying reason for failure of the restriction diet has been attributed to the inability to completely remove cow's milk proteins from the mother's diet.^{4,21}

The pathogenesis of FPIAP has been attributed to the marked eosinophilic infiltration in the immature gut of the infants, and these IgA binds to eosinophils that induce degranulation,²² which may disrupt the intestinal tight junction barrier, and, thus, increased permeability to food allergens directly results in FPIAP

symptoms.^{22,23} In addition to many reports that showed peripheral eosinophilia in the FPIAP,^{9,24} correlation between eosinophilia in blood and the severity of the symptoms in gastrointestinal food allergies, including FPIAP, have been well documented in a recent study.²⁵ Similarly, the patients with a severe clinical manifestation in our cohort had significantly increased peripheral eosinophilia that was presumably a direct indicator of increased eosinophilic infiltration in the gut.

In the current study, profound neutropenia in the patients, especially with severe clinical presentation, was identified, which, to our knowledge, has not been shown before. This may be because neutropenia is mostly underdiagnosed because of paying attention to eosinophilia in allergic diseases. Another possible explanation may be the formation of autoantibodies to neutrophils in FPIAP.²⁶ Because we cannot show any pathology with regard to neutrophil formation in bone marrow aspiration, we thought that autoantibodies may be another cause of neutropenia in these patients. Intriguingly, these neutrophilic autoantibodies disappeared while the patients developed tolerance or improvement of the symptoms.²⁶ These data confirmed that neutropenia may be a sign of the severity in patients with FPAIP.

According to our findings, a delay in the initiation of the complementary feeding seemed to increase the risk of late tolerance development approximately 5.4 times. All these results demonstrated that the probability of late tolerance increased by age of complementary feeding. These noteworthy results of our study emphasized the importance of the initiation of complementary foods in the “optimal window period,” including the time between 4 and 6 months of age.²⁷ Determination of the infants in this period may facilitate tolerance achievement not only in IgE-mediated but also in non-IgE-mediated food allergies. Elimination diets reduced the symptoms of the patients; however, prolongation of this process had a negative impact on tolerance according to our findings.

We introduced potato, banana, rice, and grains to the infants as the initial complementary foods, and these foods contained resistant starch, which cannot be totally digested in the gut.²⁸ The underlying mechanism of FPIAP is delayed microbiota establishment and increased mucosal inflammatory cytokines.²⁹ The introduction of foods that included resistant starch has been shown to provide epithelial integrity³⁰ and ameliorate inflammation in the intestine.³¹ However, pectin and pectic oligosaccharides in the apple, which is the other preferential complementary food, have been shown to suppress intestinal inflammation, modulate the gut microbiota,³² and even prevent diarrhea.³³ Therefore, beginning complementary feeding with these foods may

further promote tolerance in these infants who have disturbed mucosal integrity and microbiota.

Feeding with cow's milk-based formula, even only once before the symptoms emerged, was another independent risk factor for late tolerance development. In addition, formula-fed infants had a significantly younger age of onset of the disease than the infants who were breast-fed. Similar to our finding, it has been shown that infants who are breast-fed are older than the counterparts fed with formula.⁴ Presumably, this can be due to high amounts of cow's milk protein contents in cow's milk-based formulas compared with breast milk.³⁴ Exposure to high amounts of allergens of immature intestinal system may be the underlying reason of late tolerance development in infants who were formula-fed.

The majority of the infants with FPIAP have an allergy to cow's milk protein,^{6,14,24} and most of them are reactive to only one type of food,^{18,19,24} as shown in our study. However, multiple food allergy in FPIAP has been reported between 3.3%¹⁸ and 50%⁶ in previous studies, as shown as 35.1% in the current study. Moreover, we identified that patients with multiple food allergy developed tolerance significantly later compared with the infants with allergy to one type of food. One recent study, of 132 infants from Turkey, revealed the association between non-IgE-mediated allergy to multiple foods and increased peripheral eosinophil numbers in FPIAP¹⁹; however, the relation between tolerance and multiple food allergy has not been shown. Concomitant IgE-mediated food allergy was another independent predictor according to our results, in contrast to the consensus guideline on non-IgE-mediated food allergy that reported IgE-mediated sensitization to other foods was not a factor causing retardation in development of tolerance. Therefore, these conflicting results of our cohort should be clarified by further large population-based studies.

An important limitation of the current study may be the thought that these results did not reflect the general population because it was a single-center study. However, our outpatient clinic was a tertiary-referral center, and many patients from different parts of the country are referred to our hospital. However, the long-term follow-up period of these patients, well-organized study groups, homogeneous distribution of patient numbers in these groups, and inclusion of a large number of infants were the substantial strengths of our study.

CONCLUSION

FPIAP is a benign condition due to the remission by the age of one year. However, this study supported the notion that early introduction of complementary feeding accelerates tolerance in FPAIP, which indicated the

critical role of gastrointestinal exposure in development of tolerance. A longer duration of the elimination diet had no impact on the resolution of allergy, in contrast, it affected this period negatively. In the case of FPIAP, physicians should consider conservative avoidance measures and earlier introduction of complementary feeding.

REFERENCES

- 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; 23:766–770.
- Venter C, Brown T, Shah N, Walsh J, Fox AT. Diagnosis and management of non-IgE-mediated cow's milk allergy in infancy – a UK primary care practical guide. *Clin Transl Allergy*. 2013; 3:23.
- Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy*. 2014; 69:1008–1025.
- Nowak-Weögrzyn A. Food protein-induced enterocolitis syndrome and allergic proctocolitis. *Allergy Asthma Proc*. 2015; 36:172–184.
- Lake AM. Food-induced eosinophilic proctocolitis. *J Pediatr Gastroenterol Nutr*. 2000; 30(Suppl):S58–S60.
- Lucarelli S, Di Nardo G, Lastrucci G, D'Alfonso Y, Marcheggiano A, Federici T, et al. Allergic proctocolitis refractory to maternal hypoallergenic diet in exclusively breast-fed infants: a clinical observation. *BMC Gastroenterol*. 2011; 11:82.
- Caubet JC, Szajewska H, Shamir R, Nowak-Weögrzyn A. Non-IgE-mediated gastrointestinal food allergies in children. *Pediatr Allergy Immunol*. 2017; 28:6–17.
- Ruffner MA, Spergel JM. Non-IgE-mediated food allergy syndromes. *Ann Allergy Asthma Immunol*. 2016; 117:452–454.
- Nowak-Weögrzyn A, Katz Y, Mehr SS, Koletzko S. Non-IgE-mediated gastrointestinal food allergy. *J Allergy Clin Immunol*. 2015; 135:1114–1124.
- Venter C, Brown T, Meyer R, Walsh J, Shah N, Nowak-Weögrzyn A, et al. Better recognition, diagnosis and management of non-IgE-mediated cow's milk allergy in infancy: iMAP-an international interpretation of the MAP (Milk Allergy in Primary Care) guideline. *Clin Transl Allergy*. 2017; 7:26.
- Academy of Breastfeeding Medicine . ABM Clinical Protocol #24: allergic proctocolitis in the exclusively breastfed infant. *Breastfeed Med*. 2011; 6:435–440.
- Caffarelli C, Dondi A, Dascola CP, Ricci G. Skin prick test to foods in childhood atopic eczema: pros and cons. *Ital J Pediatr*. 2013; 39:48.
- Koletzko S, Niggemann B, Arató A, Dias J, Heuschkel R, Husby S, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr*. 2012; 55:221–229.
- Feuille E, Nowak-Weögrzyn A. Food protein-induced enterocolitis syndrome, allergic proctocolitis, and enteropathy. *Curr Allergy Asthma Rep*. 2015; 15:50.
- Erdem SB, Nacaroglu HT, Karaman S, Erdur CB, Karkiner CU, Can D, et al. Tolerance development in food protein-induced allergic proctocolitis: single centre experience. *Allergol Immunopathol (Madr)*. 2017; 45:212–219.
- Wilson NW, Self TW, Hamburger RN. Severe cow's milk induced colitis: in an exclusively breast-fed neonate case report and clinical review of cow's milk allergy. *Clin Pediatr*. 1990; 29:77–80.
- Lake AM, Whittington PF, Hamilton SR. Dietary protein-induced colitis in breast-fed infants. *J Pediatr*. 1982; 101:906–910.
- Kaya A, Toyran M, Civelek E, Misirlioglu E, Kirsadioglu C, Kocabas CN. Characteristics and prognosis of allergic proctocolitis in infants. *J Pediatr Gastroenterol Nutr*. 2015; 61:69–73.
- Koksal BT, Baris Z, Ozcay F, Yilmaz Ozbek O. Single and multiple food allergies in infants with proctocolitis. *Allergol Immunopathol (Madr)*. 2018; 46:3–8.
- Fretzayas A, Moustaki M, Priftis KN, Attilakos A, Lapa E, Nicolaidou P. Thrombocytosis as an overt sign of cow's milk allergic proctocolitis. *Allergol Immunopathol (Madr)*. 2011; 39:381–383.
- Leonard SA, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome, food protein-induced enteropathy, proctocolitis, and infantile colic. In John M. James, Wesley Burks, and Philippe Eigenmann (Eds.). *Food Allergy E-Book: Expert Consult Basic*. 2012; 143–163.
- Atanaskovic-Markovic M. Refractory proctocolitis in the exclusively breast-fed infants. *Endocr Metab Immune Disord Drug Targets*. 2014; 14:63–66.
- Boné J, Claver A, Guallar I, Plaza AM. Allergic proctocolitis, food-induced enterocolitis: immune mechanisms, diagnosis and treatment. *Allergol Immunopathol (Madr)*. 2009; 37: 36–42.
- Arik Yilmaz E, Soyer O, Cavkaytar O, Karaatmaca B, Buyuktiryaki B, Sahiner UM, et al. Characteristics of children with food protein-induced enterocolitis and allergic proctocolitis. *Allergy Asthma Proc*. 2017; 38:54–62.
- Kimura M, Shimomura M, Morishita H, Meguro T, Seto S. Eosinophilia in infants with food protein-induced enterocolitis syndrome in Japan. *Allergol Int*. 2017; 66:310–316.
- Sekerkova A, Fuchs M, Ceardlova E, Svachova V, Kralova Lesna I, Striz I, et al. High prevalence of neutrophil cytoplasmic autoantibodies in infants with food protein-induced proctitis/proctocolitis: autoimmunity involvement?. *J Immunol Res*. 2015; 2015:902863.
- West C. Introduction of complementary foods to infants. *Ann Nutr Metab*. 2017; 70(Suppl):47–54.
- Alcázar-Alay SC, Meireles M. Physicochemical properties, modifications and applications of starches from different botanical sources. *Food Sci Technol*. 2015; 35:215–236.
- Kumagai H, Maisawa S, Tanaka M, Takahashi M, Takasago Y, Nishijima A, et al. Intestinal microbiota and secretory immunoglobulin A in feces of exclusively breast-fed infants with blood-streaked stools. *Microbiol Immunol*. 2012; 56:657–663.
- Venkataraman A, Sieber JR, Schmidt AW, Waldron C, Theis KR, Schmidt TM. Variable responses of human microbiomes to dietary supplementation with resistant starch. *Microbiome*. 2016; 4:33.
- Le Leu RK, Young GP, Hu Y, Winter J, Conlon MA. Dietary red meat aggravates dextran sulfate sodium-induced colitis in mice whereas resistant starch attenuates inflammation. *Dig Dis Sci*. 2013; 58:3475–3482.
- Jiang T, Gao X, Wu C, Tian F, Lei Q, Bi J, et al. Apple-derived pectin modulates gut microbiota, improves gut barrier function, and attenuates metabolic endotoxemia in rats with diet-induced obesity. *Nutrients*. 2016; 8:126.
- Mao X, Xiao X, Chen D, Yu B, He J, Chen H, et al. Dietary apple pectic oligosaccharide improves gut barrier function of rotavirus-challenged weaned pigs by increasing antioxidant capacity of enterocytes. *Oncotarget*. 2017; 8:92420–92430.
- Friedman NJ, Zeiger RS. The role of breast-feeding in the development of allergies and asthma. *J Allergy Clin Immunol*. 2005; 115:1238–1248.

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