

Characteristics of allergic proctocolitis in early infancy; accuracy of diagnostic tools and factors related to tolerance development

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Abstract

Objectives: We aimed to overview clinical characteristics of FPIAP with the results of diagnostic tools like APT, SPT and fecal calprotectin levels and the factors associated with tolerance development.

Methods: All patients diagnosed FPIAP at the outpatient clinic between January 2015 and January 2019 were enrolled retrospectively. Data about clinical characteristics, APT or SPT results, fecal calprotectin levels, suspected triggering foods, diet and tolerance status were obtained from the hospital database program and analyzed.

Result: 169 infants with F/M ratio 78/91 were enrolled. The mean age of the study population was 3.68 months (1-35 months, mean age 3.68 ± 4.33). APT was performed 137 of the participants and 126 (92%) of them were positive to at least one food allergens, 14 (48.2%) patients had positivity to at least one of the food allergens on SPT. Specific IgE were done in 90 patients and 12 (13.3%) revealed positive results. Two groups of patients developing tolerance before and after 18 months of age were evaluated; mucoid diarrhea, family history allergic diseases, cow's milk sensitivity and multiple allergen triggers were statistically significant risk factors for delayed tolerance according to univariate logistic analysis. However, none of these factors were revealed statistical significance in multivariate logistic analysis.

Conclusion: Our study revealed that APT may be a useful tool for programming the elimination diet in breastfeeding mothers. SPT, specific IgE and fecal calprotectin are not necessary for FPIAP management. Multivariate regression analysis showed that none of the evaluated parameters had statistically significant relationship with the tolerance development.

Key words: allergic proctocolitis, atopy patch test, bloody stools, cow's milk allergy, food allergy

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Introduction

Food protein-induced allergic proctocolitis (FPIAP) is a non-IgE mediated food allergy that typically starts in early infancy with bloody and mucoid stool in well-appearing infants. FPIAP was described for the first time in 1982 in infants with rectal bleeding in the first month of life.¹ Usually, FPIAP is a benign and transient disease that affects breastfed infants commonly and resolves itself by the age of 3, with an excellent long term prognosis.

The exact prevalence of FPIAP is unknown, some studies give the rate as 0.16%,² but the estimated prevalence in infants with rectal bleeding ranges from 18% to 64%,^{3,4} and FPIAP is common in countries with a lower incidence of food allergy like Brazil or Greece.⁵

Approximately 60% of FPIAP cases occur in breastfed infants beside the ones who are formula-fed by cow's milk or soy milk. It has rarely been described in hydrolyzed formulas (4-10%).⁵ FPIAP in exclusively breast-fed infants is caused by food proteins derived from maternal diet, usually, cow's milk (CM), which the allergen protein passes into the breast milk while in some cases multiple food allergies can occur. Diagnosis of FPIAP is based on clinical features and recovery follows after the elimination of triggering foods. Usually, clinical symptoms resolve within 72-96 hours of elimination of suspected food.⁶ There are no specific diagnostic tools but atopy patch test (APT), specific IgE tests, or skin prick tests (SPT) can be used in clinical practice. SPT and specific IgE measurements are typically negative while APT can be helpful to detect non-IgE mediated sensitization to food proteins especially when multiple food allergies are suspected.

In this study, we aimed to overview the clinical characteristics of patients diagnosed with FPIAP with a diagnostic accuracy of tools like APT, SPT, and fecal calprotectin levels and the factors associated with tolerance development.

Material and Methods

Study population and diagnosis of FPIAP

The retrospective study was conducted at the outpatient clinic of the Division of Pediatric Allergy and Clinical Immunology in two centers of Northern Cyprus; Near East University-Nicosia and the University of Kyrenia-Kyrenia. All patients diagnosed with FPIAP at the outpatient clinic between January 2015 and January 2019 were enrolled. Data about demographical characteristics like age, age onset of symptoms, type of symptoms, family history, APT or SPT results, fecal calprotectin levels were obtained from the hospital database. Suspected triggering foods, diet suggestions, and tolerance status were also recorded from the database and analyzed. The study was approved by the Institutional Ethics Committee of University of Kyrenia with the approval number of 2020/01-002.

Diagnosis of FPIAP was based on the clinical features of the disease whereas all other causes like gastrointestinal infections, necrotizing enterocolitis, intussusception, or anal fissures were excluded. Symptoms of bloody or mucoid stools were resolved with the elimination diet in 72-96 hours in all patients enrolled in the current study.

Tolerance Development

Tolerance can be defined as the unresponsiveness of the immune system to antigens or allergens. For non-IgE mediated allergies like FPIAP, it is recommended to re-introduce the triggered food after 6 months of diagnosis or around 1 year of age. In this study, triggered food re-introduced 6 months after diagnosis and symptom free 1 month period without and food restrictions assessed as tolerance development.

Skin Prick Test and Specific IgE Measurements

Skin prick tests were performed only on a selected number of patients. Those patients were clinically borderline cases with suspicion of any type of IgE mediated allergy-like atopic dermatitis or others. Skin prick tests (SPT) were performed with 20 or 22 common food allergens (cow's milk, casein, hens egg, cow's meat, chicken, salmon, cod, pig, shrimp, wheat, barley, oat, soy, hazelnut, peanut, walnut, almond, cinnamon, sesame, cocoa, strawberry, and banana). Histamine and saline solution were used as positive and negative controls, respectively. A drop of each allergen extract was placed on the volar surface of the left forearm or back of the patient and penetrated with a smaller point. After 15 minutes, the wheal reaction was measured as the mean of the longest diameter and the diameter perpendicular to it. Wheel diameter of at least 3 mm greater than those of the negative controls was considered positive. Food-specific IgE measurements were measured with UniCAP technology from serum (Phadia, Upsala, Sweden) and > 0.35 kU/L were based as cut off point for a positive result.

Atopy patch test

Atopy patch tests were applied on clear skin on the child's back, according to the method described by Isolauri and Turjanmaa.^{7,8} We used 8-mm diameter aluminum cups (Finn Chamber; Epitest, Helsinki, Finland). Isotonic saline solution was used as the negative control. Food allergen extracts were the commercial extracts of ALK diagnostics®. Cow's milk, casein, egg, rye, rice, wheat, barley, fish, chicken, almond, hazelnut, peanut, walnut and banana extract were used. All extracts were 1/10 v/w glycerin solution, while casein and egg extracts were 1/100. The extracts put on an 8-mm aluminum cups with adhesive tape and applied on intact skin of infants back. The occlusion was done 72 h after attaching the patch tests. The results were read for the first time 15 min after removal of the cups. If irritation and redness were found in the test area, the results were read after 30 min. Reactions were classified according to standards, as follows: 0 (negative), no-reaction, either visible or palpable; + (negative), redness, no or doubtful reaction; ++ (positive reaction), redness and palpable infiltration with papules; +++ (strong positive reaction), redness, palpable infiltration with many papules and eczema.

Fecal calprotectin measurements

The collected fecal samples of patients were analyzed within 2 hours on the day of collection. Fecal calprotectin (FC) levels were measured quantitatively using BÜHLMANN Quantum Blue® feCAL (Bühlmann Laboratories AG, Switzerland) according to the manufacturer's instructions. The test is based on quantitative lateral flow immunochromatography (LFIA). The calibration of the device was checked before use. Approximately 50~100 mg of the fecal sample was extracted and transferred into the CALEX® cap device. The stool extract was settled

for 10 minutes for obtaining the supernatant. The supernatant was then diluted in a ratio of 1:1.6 with extraction buffer in an Eppendorf tube and mixed well. The sample was left to equilibrate for at least 5 minutes to 18-28°C. Then, 60 µL of diluted stool extract was added onto the sample loading port of the test cassette and incubated for 12 minutes before reading. The suggested cut-off level of calprotectin for adults is 50 µg/g. In this study, the cut-off level for the children is based on age and gender and 95th percentile was used as upper limit.⁹

Statistical analysis

Statistical analyses were performed using the SPSS software package for Windows (release 17.0.0, SPSS Inc., Chicago, Ill, USA). Descriptive statistics were expressed as mean (SD), median, and range. Prevalence rates were expressed as percentages. Categorical data were tested using the χ² test. P < 0.05 was considered statistically significant.

Table 1. Demographical characteristics of study population.

	N = 169 (%)
Symptoms at admission *	
Group 1	134 (79.3)
Group 2	10 (5.9)
Group 3	12 (7.1)
Group 4	13 (7.7)
Gender M/F	91 (53.8)/78 (46.2)
Age of onset (mean, min-max, ± SD)	3.68, 1-35, ±4.33
Dietary status	
Extensively breast fed	82 (49.1)
Extensively formula fed	16 (9.6)
Both breast and formula fed	20 (12)
Breast fed and complementary food	18 (10.8)
Formula fed and complementary food	25 (15)
Breast fed + Formula fed + complementary food	6 (3.6)
Atopic dermatitis coexistence	56 (33.1)
Allergy Tests	
Skin prick test (n = 29)	
Positive	14 (48.2)
Negative	15 (51.8)
Atopy patch test (n = 137)	
Positive	126 (92)
Negative	11 (8)
Specific IgE positivity (n = 90)	
Positive	12 (13.3)
Negative	78 (86.7)

Results

Demographical and clinical characteristics of the study population:

169 infants with a female/male ratio of 78/91 were enrolled. The mean age of the study population was 3.68 months (1-35 months, mean age 3.68 ± 4.33). The demographical and clinical characteristics like age, gender, distribution of the symptoms at admission, feeding status, atopic dermatitis co-existence, atopy patch test, skin prick test, or fecal calprotectin levels and tolerance status are shown in **Table 1**.

Atopy patch test, skin prick test fecal calprotectin levels:

Atopy patch test was performed on 137 of the participants and 126 (92%) of them were positive for at least one food allergen. Cow’s milk positivity was the most common one in 98 of the patients as expected and egg positivity was following cow’s milk with a number of 63 patients.

(Continued)	
Fecal Calprotectin Levels (High/Normal) n = 58	25/33
Elimination diet types	
Food elimination in breast feeding mother’s diet	71 (43.6)
Extensively hydrolyzed formula	2 (1.2)
Amino acid based formula	8 (4.9)
Food elimination in breast feeding mother’s diet + hydrolyzed formula	1 (0.6)
Food elimination in breast feeding mother’s diet + amino acid based formula	20 (12.3)
Elimination diet for patient (after 6 months of age)	25 (15.3)
Elimination diet for patient+ amino acid based formula	16 (9.8)
Both elimination diet for patient and breast feeding mother	20 (12.3)
Family history of allergic diseases	
Mother	32 (18.9)
Father	27 (16)
Siblings	16 (9.5)
Tolerance status (Developed/Non-Developed)	108 (75.5)/35 (24.5)
Tolerance age (months) (mean/min-max)	17.5/3-42

*Distribution of Symptoms at admission. Group 1; bloody and/or mucoid stool, Group 2; food refusal and/or weight pause, Group 3: vomiting, Group 4; constipation

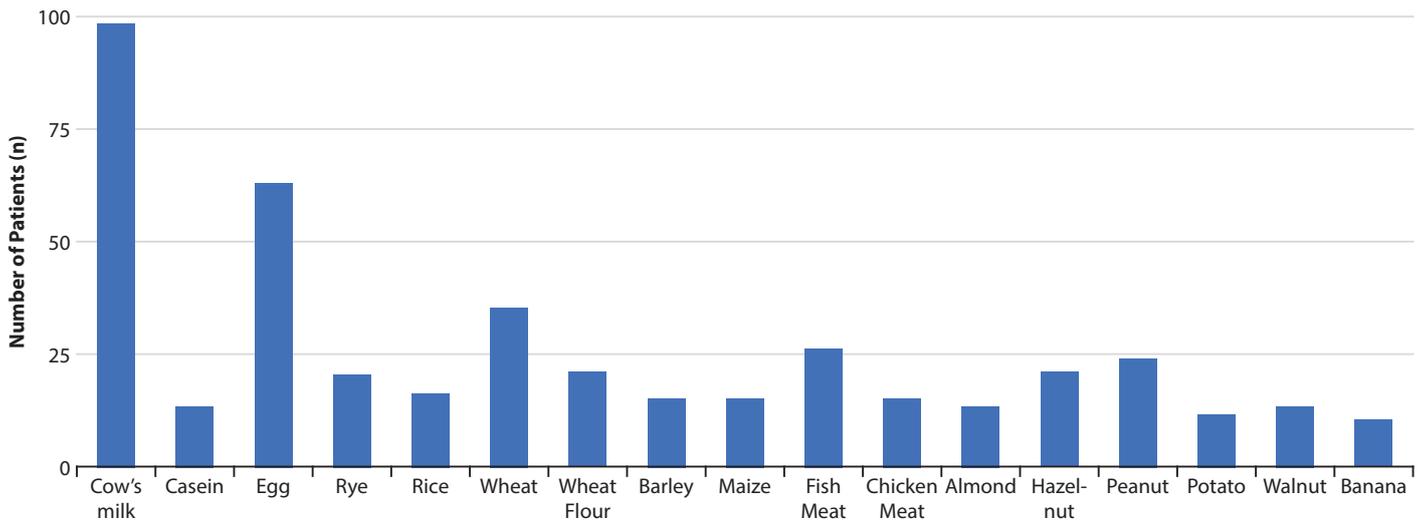


Figure 1. Distribution of food allergen sensitivities according to atopy patch test.

The distribution of triggering foods according to the atopy patch test is given in **Figure 1**. Fecal calprotectin levels were analyzed in 58 patients, ranged between 30-1000 µg/g, the mean value was 306.2, and SD: 281.6. According to the laboratory's range values, 89.7% of the samples were seemed high but we evaluated fecal calprotectin levels according to the study of Feng Li et al which was using the percentiles based on age and gender and only 25 (43.1%) of them were high according to their gender and age group.⁹ Skin prick test was performed only on 31 patients whose were thought to be related to IgE mediated food allergies like rapid onset of symptoms after ingestion of food or severe atopic dermatitis co-existence or history of immediate type of any kind of allergic reaction. 14 (48.2%) patients had positivity to at least one of the food allergens on SPT. Specific IgE measurements were done in 90 patients and 12 (13.3%) revealed positive results.

Factors influencing tolerance development:

In this study population, 75.5% of patients developed tolerance during their follow up period of 24-36 months. The mean age for tolerance development was 17.59 months (min-max: 3-42 months, mean 17.59, SD ±8.31). Factors that may have an impact on tolerance development like symptom type, dietary status, family history, number of triggered foods, and fecal calprotectin levels were evaluated. When we evaluated two groups of patients developing tolerance before and after 18 months of age; symptom of mucoid diarrhea ($p = 0.001$), family history of any allergic diseases ($p = 0.001$), cow's milk sensitivity on APT ($p = 0.000$), and multiple allergen triggers ($p = 0,000$) were statistically significant risk factors according to univariate logistic analysis. However, none of these factors were revealed statistical significance in the multivariate logistic analysis.

Discussion

Most of the papers studied in non-IgE mediated food allergies commonly focus on the different diseases under the same umbrella term of “Non-IgE mediated gastrointestinal food allergies”. However, this term consists of different diseases like food protein-induced enterocolitis syndrome (FPIES), Eosinophilic esophagitis (EoS), food protein-induced allergic enteropathy (FPE), and food protein-induced allergic proctocolitis (FPIAP); each of them with diversities. FPIAP is the most frequent and usually self-healing form of non-IgE mediated gastrointestinal food allergies seen in otherwise healthy infants but the prevalence, epidemiological features, and the diagnostic accuracy of laboratory tests have not been well studied specifically.

In the current study, we evaluated 169 FPIAP patients retrospectively in a single centered manner to fill in the gaps in the literature about the accuracy of diagnostic tools and factors associated with tolerance development. We could not evaluate the whole study population with same diagnostic tools is the main limitation of current study. Another limitation is that; this is not a prospective study with a well-defined method to address the factors affecting tolerance development better.

Demographical characteristics of our study population like the mean age of onset of symptoms, gender distribution, or a variety of symptoms were substantially similar to the literature. Bloody stools and mucoid diarrhea (29.6-32.5%) were the most common symptoms in our study population similar to previous reports such as Canani et al.¹⁰ who reported chronic diarrhea as 28.3% and Lucarelli et al. 42%.⁶ Dietary status at the onset of symptoms was “extensively breastfed” predominance with a ratio of 49.1%, and this finding was slightly higher than previous reports in the Turkish population; such as Yilmaz et al. reported 40.5%.²

Family history of any allergic diseases like asthma, rhinitis, eczema, or food allergy was also questioned and revealed 18.9%, 16%, 9.5% respectively for mother, father, and siblings. These results were slightly higher than another study conducted in the Turkish population, Kaya et al.¹¹ reported parental asthma and allergic rhinitis existence as 8.3% in 2015 while lower than another study; Köksal et al. reported a family history of allergy as 29.5%,¹² and Canani 53%.¹⁰ Also, atopic dermatitis co-existence was higher in our study at 33% while Kaya et al. reported 8.3%,¹¹ and Köksal et al. 7.6%.¹²

In this study, the most commonly used diagnostic tool was the atopy patch test. Atopy patch tests were performed on 137 patients and 92% of them were positive for at least one allergen. Currently, the usefulness of APT is controversial while some reports demonstrate APT as a reliable, safe, and useful diagnostic tool for gastrointestinal symptoms.^{10,13} Nocerino et al. reported that APT was a valuable tool in the follow-up of non-IgE mediated CMAs and found a significant correlation with OFC outcomes.¹⁴ This study was one of the few studies determining the usefulness of APT in non-IgE mediated CMA in the first year of life. Another study focusing on the value of the atopy patch test in children with gastrointestinal symptoms, reported high sensitivity and specificity in the diagnosis of allergy to wheat in children while the sensitivity for cow's milk was low and should be verified by OFC.¹⁵ Boonyaviwat et al., reported sensitivity and positive predictive value for APT with lyophilized allergens with 85.7% and 80% respectively; while APT with commercial allergens reveals 30% and 90% and this study demonstrates the specificity and PPV of APT combined with SPT increases to 100%.¹³ Canani et al reported APT as a useful tool for children with food allergy-related gastrointestinal symptoms. This study conducted APT sensitivity with fresh food and commercial extracts come out as 64.5% and 6.45% and emphasized that diagnostic accuracy can be improved with the higher PPV and sensitivity when combined with SPT or specific IgE measurements.¹⁰

Our study is the unique one, evaluating a group of pure FPIAP with APT, without including other types of gastrointestinal allergies. In the current study, diagnostic workup was mainly focused on APT while SPT and specific IgE measurements were also added on selected cases. This study was a retrospective one with a real-life data of patients and their follow-up in allergy clinic. Most of the study population were breast fed patients which are followed up with APT guided maternal elimination diet. The symptoms resolved in expected time with this approach and tolerance developed during follow up period at the ages stated in the literature.

The most common triggering foods determined by APT were cow's milk, egg, and wheat. The elimination diet of the study population was arranged under the guidance of APT results. Specific IgE detection and SPT were performed

only on patients with co-existence of IgE mediated allergic disease or to rule out the other type of gastrointestinal allergies in some cases. SPT were performed on selected cases of 29 patients with 48.2% positivity while specific IgE detection revealed only 13.3% positivity in 90 patients. Boonyaviwat reported SPT positivity in 14.5% of 76 events,¹³ and Canani et al. reported 21.4%.¹⁰ These findings support the non-IgE mediated nature of FPIAP and IgE mediated laboratory tests can be concluded as an unnecessary approach for FPIAP.

Another diagnostic tool that we used in some of our study population were fecal calprotectin measurements. Some of our patients were evaluated in other centers before attending to our allergy clinic which is a tertiary care university hospital and they had already been investigated for inflammatory bowel diseases. Fecal calprotectin measurements are mostly had been done in this group of patients before their attendance, fecal calprotectin measurements were not a routine of our clinic's FPIAP approach.

There are a few studies are evaluating the diagnostic value of fecal calprotectin measurements for non-IgE mediated food allergies.¹⁶ International guidelines are recommending the use of fecal calprotectin measurements to rule out very early onset inflammatory bowel disease in infancy.¹⁷ In our study, 58 patients evaluated with fecal calprotectin levels in stool, and 25 of them (43.1%) were high according to the reference values based on their gender and age,⁹ not with the normal ranges defined for adults. Fecal calprotectin values were not associated with the clinical outcome or tolerance status of patients in our study population. Fecal calprotectin measurements can be useful for differential diagnosis of early-onset inflammatory diseases or only for follow up periods of FPIAP if the initial value is high and is decreasing with elimination diets.¹⁶

Tolerance development in FPIAP is common in 3 years of age. In this study, the mean age of tolerance development was 17.59 months in accordance with the literature. We evaluated several factors in our current study that were thought to be related to tolerance development. We evaluated several factors within two groups by taking 18 months of age as a cut-off point; developing tolerance before and after 18 months of age. Mucoid diarrhea, history of any allergic disease in the family, cow's milk sensitivity in APT, and having multiple triggering foods according to APT revealed statistically significant risk for delayed tolerance with univariate logistic analysis. However, all these statistical significances were lost in multivariate analysis.

As known, univariate statistics gives only the effect of one variable to a certain situation. In our study, although we have revealed some factors that may affect the development of tolerance, the strength of those factors may decrease together with the other variables, which is demonstrated by multivariate regression analysis. This is possible from a statistical point of view.

In conclusion, a specific diagnostic tool for diagnosis and follow up of FPIAP is still scarce. Our study revealed that APT may be a useful tool for programming the elimination diet in breastfeeding mothers. SPT, specific IgE measurements, and fecal calprotectin are not necessary for FPIAP management. The factors like cow's milk sensitivity, multiple triggered foods, family history of allergic diseases that are thought to be related to delayed tolerance more than 18 months of age, should be considered more carefully for delayed tolerance and follow up period of patients with these features should held longer.

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The manuscript is an original and unpublished work in which the listed authors have all made important contributions. Yuruker and Galip designed the model and the computational framework and analysed the data. Galip, Babyigit and Yuruker contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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