A different starting line for allergic march: food protein-induced allergic proctocolitis

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**Abstract**

**Objective:** The aim of this study is to investigate the long-term prognosis of food protein-induced allergic proctocolitis (FPIAP) patients, the risk of developing both allergic and gastrointestinal diseases, and to evaluate whether it leads to allergic march.

**Methods:** A total of 149 children who were diagnosed with FPIAP and developed tolerance at least 5 years prior to the study and 41 children (with no history of food allergy) as a control group were enrolled. Both groups were re-evaluated for allergic diseases as well as gastrointestinal disorders.

**Results:** The mean age of diagnosis for the FPIAP group was 4.2 ± 3.0 months, while the mean age of tolerance was 13.9 ± 7.7 months. The mean age of both FPIAP and control groups at the last visit was 101.6 ± 24.4 and 96.3 ± 24.1 months, respectively ($P = 0.213$). At the final evaluation of both groups, the comorbid allergic disease was significantly higher in the FPIAP group ($P < 0.001$). There was no significant difference between the two groups in terms of functional gastrointestinal disorders (FGIDs), eosinophilic gastrointestinal diseases, and inflammatory bowel disease ($P = 0.198$, 0.579, and 0.579, respectively).

In the FPIAP group, the allergic disease was significantly higher at the final visit in patients with comorbid allergic disease at diagnosis ($P < 0.001$). In the FPIAP group, FGID was significantly higher in the group that developed allergic diseases in the future, compared to the group that did not develop allergic diseases in the future ($P = 0.034$). The proportion of both FGID and allergic diseases was significantly higher in subjects that developed tolerance at >18 months, compared to subjects that developed tolerance at ≤18 months ($P < 0.001$ and <0.001, respectively).

**Conclusions:** Patients with FPIAP may develop allergic diseases as well as FGID in the long term.

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**KEYWORDS**

allergic march; food protein-induced allergic proctocolitis; functional gastrointestinal disorders; inflammatory bowel disease; prognosis

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Introduction

Allergies often begin early in life, first being expressed as eczema in infants. The progression from eczema to food allergies, allergic rhinitis, and asthma is called the allergic march. Food protein-induced allergic proctocolitis (FPIAP) may, however, be the first allergic disease to appear in infants. FPIAP is a non-immunoglobulin E (IgE)-mediated food allergy (FA) that typically occurs in infancy and affects only the gastrointestinal tract (GIT). It represents the benign side of the non-IgE-mediated spectrum.\(^5\) Its incidence is increasing in Japan, the United States, and western countries.\(^6\)

Food protein-induced allergic proctocolitis has a significant impact on the rectosigmoid region.\(^5,7\) The pathogenesis is not fully understood. Immature innate and adaptive immune system of the infant, changes related to intestinal permeability, dysbiosis, and genetic predisposition are the main risk factors.\(^5,8\) It is suggested that T-cell-mediated inflammation plays a role in pathophysiology. In patients, eosinophilic infiltrates are predominantly observed in the rectosigmoid mucosa. However, the pathogenetic mechanisms that trigger eosinophilic inflammation in the colon are still unknown.\(^5,7\)

Food protein-induced allergic proctocolitis has a good prognosis. The majority of patients develop tolerance by the age of 1 year. However, patients with delayed tolerance development of up to 3 years of age have also been reported.\(^5,9\) Although the long-term prognosis is reported to be quite good, it may be risky for both allergic diseases and gastrointestinal system (GIS) diseases. However, our knowledge of this subject is quite limited.

The purpose of this study was to look into the long-term prognosis of patients with FPIAP in terms of both allergic diseases (such as allergic rhinitis and asthma) and GIT disorders (such as functional gastrointestinal disorders [FGIDs], eosinophilic gastrointestinal diseases [EGIDs], and inflammatory bowel disease [IBD]).

Materials and Methods

Study Population

The study included patients of Behcet Uz Children’s Hospital in Izmir and Izmir Bakircay University’s Faculty of Medicine, the region’s two major reference hospitals. Between 2012 and 2017, 273 pediatric patients with FPIAP were followed up in the pediatric allergy and gastroenterology outpatient clinics of these hospitals. The records of 196 patients who were at least 5 years post-tolerance were reviewed. Of these 196 cases, 149 (76% of the 196 cases) accepted the invitation for re-evaluation and were included in the patient group (FPIAP group). Age, gender, time and type of onset of clinical manifestations, causative food(s), concomitant allergic diseases, physical examination findings, laboratory findings, treatment, tolerance time, and family history of atopy were recorded at the time of diagnosis in the FPIAP group. The control group comprised 41 children of the same age as that of the FPIAP group, with no history of FA but admitted to the hospital with minor trauma. A pediatric gastroenterologist and allergist thoroughly evaluated both FPIAP and control groups for comorbid allergic diseases (such as allergic rhinitis and asthma) and gastrointestinal system disorders (FGIDs, EGIDs, and IBD).

The study was approved by the Non-Interventional Clinical Research Ethics Committee of Izmir Bakircay University: 2022/Decision No: 664). A written informed consent was obtained from parents of all patients.

Diagnosis of FPIAP

The diagnosis of the disease was made according to the following criteria specified in the guidelines:\(^5,10-12\)

1. Mild rectal bleeding in a healthy infant.
2. Lessening in manifestations after removing the suspected food(s) (or if exclusively breast-fed, improvement after elimination of the maternal diet).
3. Recurrence of manifestations after reintroduction of suspected food(s).
4. Exclusion of other causes of rectal bleeding.

First, cow’s milk was removed from the diet (from mothers’ diet in breast-fed infants) after all other causes of rectal bleeding were ruled out. Formulas for formula-fed infants were replaced with hypoallergenic formulas. In patients with resolved manifestations, foods intended as responsible were reintroduced in the diet after 2-4 weeks. The diagnosis was confirmed by the recurrence of clinical manifestations. In patients with multiple food allergies, a similar method was used to identify the foods suspected of being responsible for allergy.

At the age of 1 year, all patients were evaluated for tolerance development, and an oral food challenge (OFC) was performed. OFC protocols were performed in accordance with the recommended protocols.\(^13,14\) Separate OFC protocols were performed with each of the causative foods in patients who had more than one FA.

Patients without tolerance development at around the age of 1 year were evaluated for tolerance development every 3 months.

Concomitant Allergic Diseases

Atopic dermatitis, allergic rhinitis, and asthma were diagnosed according to the guidelines.\(^15-17\)

Concomitant GIS Diseases

The parental questionnaire on pediatric gastrointestinal manifestations, which is the Rome IV criteria for the diagnosis of FGID, was administered to the parents of both patient and control groups by the same gastroenterologist.\(^18\)

A pediatric gastroenterologist evaluated both patient and control groups for IBD and EGID manifestations.\(^19,20\)

Diagnostic Procedures

Skin-prick tests

A series of skin prick test (SPT) was carried out by trained physicians on the volar surface of the forearm of
each patient using a commercial extract (ALK Abelló, Horsholm, Denmark). SPTs were performed with common food allergens for infants (cow’s milk, egg, wheat, peanut, fish, sesame, and soy) in addition to suspected foods reported in the clinical history and with common allergens (house dust mites [Dermatophagoides pteronyssinus and Dermatophagoides farinae], pollens [grass, tree, and weed], molds [Alternaria and Cladosporium], and animal dander [cat and dog]). The SPTs were conducted for each patient with a histamine-positive control and a saline-negative control. A positive outcome was defined as a mean wheal diameter of >3 mm after 15 min of allergen extract testing.

**Blood eosinophil counts and serum total IgE and specific IgE levels**

Mindray BC-6000 device was used to perform a complete blood count, with peripheral blood samples collected in ethylenediaminetetraacetic acid (EDTA) tubes.

Serum IgE levels were determined by the nephelometric method (Dade Behring Marburg Gmbh, Germany).

Specific IgE levels were measured with the immunoCAP system (Phadia, Uppsala, Sweden), and a specific IgE level of >0.35 kU/L was considered positive.

**Endoscopy and Histology**

Endoscopic evaluation was performed for a limited number of patients who did not have symptoms compatible with FPIAP, did not respond to treatment, or had persistent or abundant bleeding to exclude other diseases presenting with rectal bleeding. The endoscopic evaluation was performed by a pediatric gastroenterologist (Fujifilm, Japan).

**Statistical Analysis**

IBM SPSS version 24.0 (Armonk, New York, US) was used for all statistical analyses. Parametric methods were used for the analysis of variables with a normal distribution whereas nonparametric methods were used for the analysis of variables that were not normally distributed. Comparisons of continuous variables were made with independent-samples t-test and Mann-Whitney U test as appropriate. Pearson’s Chi-square and linear-by-linear association tests were used with an exact test for the comparison of categorical data. The categorical data were expressed as the percentage of the number (n) of children evaluated. The level of significance for analyses was $P < 0.05$.

**Results**

At the final visit, 149 patients in the FPIAP group and 41 patients in the control group were thoroughly evaluated by a pediatric allergy and gastroenterology specialist for both allergic diseases and gastrointestinal disorders. The mean age of the FPIAP group at the final visit was 96.3 ± 24.1 months; 39% ($n = 69$) were females and 61% ($n = 80$) were males. The mean age of the control group was 96.3 ± 24.1 months; 39% ($n = 16$) were females and 61% ($n = 25$) were males ($P = 0.213$). The mean age of the FPIAP group at the time of diagnosis was 4.2 ± 3.0 months, while the mean age of tolerance was 13.9 ± 7.7 months. Cow’s milk was the culprit food in 93.4% of the patients.

In the FPIAP group, the diagnosis was as follows: 34.9% ($n = 52$) had comorbid allergic diseases, 24.2% ($n = 36$) had atopic dermatitis, 5.4% ($n = 8$) had IgE-mediated FA, 2.7% ($n = 4$) had recurrent wheezing, 2% ($n = 3$) had urticaria and angioedema, and 0.7% ($n = 1$) had allergic rhinitis; 50% ($n = 26$) of these patients were females.

In the FPIAP group, the comorbid allergic disease rate was 30.9% ($n = 46$) at the final visit (16.1% allergic rhinitis, 9.4% asthma, 1.3% atopic dermatitis, 1.3% urticaria and angioedema, 2% IgE-mediated FA, and 0.7% drug allergy). At the time of final evaluation of both groups, the comorbid allergic disease was significantly higher in the FPIAP group, compared to the control group ($P < 0.001$). When both FPIAP and control groups were evaluated in terms of FGID ($P = 0.198$), EGID ($P = 0.579$), and IBD ($P = 0.579$), no significant difference was observed (Table 1).

In the FPIAP group, 20 patients had FGID and one patient had EGID, while in the control group, one patient had FGID and no patient had EGID. No patients with IBD manifestations was observed in both FPIAP and control groups. In the FPIAP group, in patients with concomitant allergic diseases at the time of diagnosis, probability of allergic diseases was significantly higher at the final visit ($P < 0.001$). In addition, FGID was significantly higher in the subgroup of the FPIAP group that developed allergic diseases in the future, compared to the group that did not develop allergic diseases ($P = 0.034$). In terms of EGID and IBD, no significant difference was observed between the two groups with and without allergic diseases ($P = 0.088$; Table 2).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the FPIAP and control groups at the end visit.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FPIAP Group ($n = 149$)</td>
</tr>
<tr>
<td>Gender (Female), % (n)</td>
<td>46.3 (69)</td>
</tr>
<tr>
<td>Age* (months)</td>
<td>101.6 ± 24.4</td>
</tr>
<tr>
<td>Comorbid allergic disease (%)</td>
<td>30.9</td>
</tr>
<tr>
<td>AR (%)</td>
<td>16.1</td>
</tr>
<tr>
<td>Asthma (%)</td>
<td>9.4</td>
</tr>
<tr>
<td>AD (%)</td>
<td>1.3</td>
</tr>
<tr>
<td>Urticaria &amp; angioedema (%)</td>
<td>1.3</td>
</tr>
<tr>
<td>IgE-mediated FA (%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Drug allergy (%)</td>
<td></td>
</tr>
<tr>
<td>EGID and IBD (%)</td>
<td>2.7</td>
</tr>
<tr>
<td>EGID % (n)</td>
<td>2.7</td>
</tr>
<tr>
<td>IBD, % (n)</td>
<td>0.0</td>
</tr>
<tr>
<td>FGID (%)</td>
<td>7.4</td>
</tr>
</tbody>
</table>

The risk of allergic march and GIT disorders was assessed based on the age of tolerance development. There was no significant difference in EGID and IBD between subjects with a tolerance development of ≤18 months and that of >18 months (P = 0.216). In contrast, FGID was significantly higher in the group with a tolerance age of >18 months (P < 0.001). The risk of concomitant allergic disease was significantly higher in the group with a tolerance age of >18 months (P < 0.001; Table 3).

**DISCUSSION**

Based on the assumption that the allergic march is one of the starting points, we investigated the prognosis of FPIAP at least 5 years after development of tolerance. At the final evaluation of both groups (FPIAP and control groups), we detected that allergic disease was significantly higher in the FPIAP group. This risk was especially high in those who had atopic dermatitis at the diagnosis. In terms of GIT diseases, such as FGID, EGID, and IBD, we found no significant difference between the two groups. When we compared the FPIAP group based on the age at which tolerance developed, we determined that allergic disease and FGID were significantly higher in the group that developed tolerance after 18 months versus the group that developed tolerance at ≤18 months. Furthermore, the proportion of FGID was significantly higher in the group that developed allergic disease in the future, compared to the group that did not develop allergic disease.

Very few studies have been conducted on the long-term outcome of infants with FPIAP. It has been reported in recent years that atopic comorbidities (including atopic dermatitis, asthma, and allergic rhinitis) may accompany cases of non-IgE FA, and “classical atopic march” may be observed. “New allergic march,” such as FGID, may be observed in cases without atopic comorbidities. However, to the best of our knowledge, no research has been conducted on this topic.

Our knowledge on the long-term development of allergic disease in patients with FPIAP is extremely limited. Studies have generally reported data from the period of diagnosis and the development of tolerance. In 437 children with non-IgE FA (154 with food protein-associated enterocolitis [FPIES]), 41.5% had atopic dermatitis, 32.1% had asthma, and 45.1% had allergic rhinitis. In studies involving evaluation of FPIAP cases only, the coexistence of allergic comorbidities, including atopic dermatitis, asthma, and allergic rhinitis, was also emphasized. In these studies, proportion of atopic dermatitis ranging from 8.3–34.3%, that of wheezing attacks and/or asthma ranging from 1.3–11.6%, and that of allergic rhinitis ranging from 0.4–45.1% was reported to be associated with FPIAP cases. However, the long-term prognosis in terms of allergic diseases has not been analyzed in studies. In our study, 30.9% (n = 46) of 149 patients evaluated at least 5 years after the development of tolerance had an allergic disease at the end visit. In order of frequency, 16.1% (n = 24) had allergic rhinitis, 9.4% (n = 14) had asthma, 2% (n = 3) had IgE-mediated FA, 1.3% (n = 2) had atopic dermatitis, 1.3% (n = 2) had urticaria and angioedema, and 0.7% had drug allergy (n = 1). In the control group, the proportion of allergic disease was 2.4%. These data provided information about the “classic atopic march” of FPIAP to atopic diseases, such as asthma and allergic rhinitis, in the long term and indicated that the follow-up of the cases should continue in this respect. According to our study, patients with comorbid atopic diseases and patients with concomitant atopic dermatitis at diagnosis, and those with an age of tolerance development >18 months were at a risk of atopic march.

In recent years, it has been reported that “non-IgE-mediated allergic march,” such as FGID, may be observed in non-IgE FA patients. However, we still do not have sufficient data on this course. A study published in 2018 established that FPIAP was a risk factor for FGID. The stated study emphasized that the duration of hematochezia was associated with an increased proportion of FGID, and that rapid treatment with FPIAP could provide a decreasing effect on this morbidity. Although we did not find a difference between the control group and the FPIAP group in terms of FGID development in our study, it was an important discovery that FGID was found to be significantly higher in patients who developed tolerance >18 months. The previous research has not found a link between tolerance development time and development of FGID. In addition,

Table 2  FPIAP group: evaluation of subgroups with and without allergic disease at the end visit.

<table>
<thead>
<tr>
<th>Comorbid allergic disease (%)</th>
<th>Final evaluation</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Age of tolerance ≤18 months</td>
<td>Allergic disease Available, Allergic disease None</td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis at diagnosis (%)</td>
<td>39.1</td>
<td>17.5</td>
</tr>
<tr>
<td>Comorbid allergic disease at diagnosis (%)</td>
<td>58.7</td>
<td>24.3</td>
</tr>
<tr>
<td>FGID at final evaluation (%)</td>
<td>17.4</td>
<td>5.8</td>
</tr>
<tr>
<td>EGID and IBD at final evaluation (%)</td>
<td>0.7</td>
<td>0.0</td>
</tr>
</tbody>
</table>


Table 3  FPIAP group: Evaluation of EGID and IBD, FGID, and comorbid allergic disease by the age of tolerance development at the final visit.

<table>
<thead>
<tr>
<th>Comorbid allergic disease (%)</th>
<th>Age of tolerance ≤18 months</th>
<th>Age of tolerance &gt;18 months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGID and IBD (%)</td>
<td>1.3</td>
<td>0.0</td>
<td>0.216</td>
</tr>
<tr>
<td>FGID (%)</td>
<td>4.4</td>
<td>22.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comorbid allergic disease (%)</td>
<td>15.4</td>
<td>37.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

the proportion of FGID was found to be significantly higher in the group that developed allergic diseases in the final evaluation. This finding shows that the group at risk for allergic diseases in the future should also be followed up for the development of FGID. FGID in children causes a significant symptom burden, including psychological problems, poor quality of life, school nonattendance, increased healthcare expenditure, and a loss of labor force for parents. As a result, it is critical to monitor FPIAP patients for the development of FGID, particularly those who develop tolerance after 18 months and those who are at risk for atopic diseases in the future.

EGIDs are a diverse group of diseases that selectively affect different parts of the GIT and are characterized by eosinophilic inflammation in the absence of known causes of eosinophilia. It has been reported that cases of FPIAP overlapping with EGIDs have increased recently in the United States. Food allergens are known to be potential inflammation triggers, particularly in eosinophilic esophagitis (EoE). Furthermore, dietary measures are part of the treatment options for both EoE and other EGIDs. However, the relation between FPIAP and EGIDs remains undiagnosed. In our study, no significant difference was observed in EGID between the FPIAP group and the control group. In the present study, EoE was found in one patient only in the FPIAP group. In this patient, the initial clinical manifestations presented were FPIAP and asthma, and allergic rhinitis and EoE developed in the following years. The diagnosis was confirmed by an endoscopic biopsy.

In one study, no IBD was reported in patients with FPIAP followed for more than 10 years. When we evaluated our patients symptomatically for IBD, no suggestive patient of IBD was found in either the patient group or the control group.

The limitations of our study were the small cohort of patients and the short follow-up period. Cases were evaluated in terms of IBD and EGID through clinical manifestations, and no invasive intervention was performed for a definitive diagnosis in cases without manifestations. In addition, psychological factors and family dynamics, which could play a role in the pathogenesis of FGIDs, were not assessed. These can be considered among the other limitations of the present study.

Conclusions

Information on the long-term prognosis of FPIAP is limited. According to our results, FPIAP cases with concomitant atopic diseases and/or atopic dermatitis at diagnosis and those whose tolerance development is delayed for >18 months should be monitored for the development of allergic diseases, such as allergic rhinitis and asthma, in the future. In addition, it is critical to continue monitoring for the development of FGID by a pediatric gastroenterologist in case of patients whose tolerance development is delayed for more than 18 months and in patients at risk of developing atopic diseases in the future. No difference was observed in terms of other GIT diseases, such as EGID and IBD, between the FPIAP group and the control group at the time of evaluation performed at least 5 years after tolerance development. The study illuminates the long-term prognosis and allergic march of FPIAP. However, more research on FPIAP is required in this regard.

Conflict of interest

The authors declared no potential conflict of interest with respect to research, authorship, and/or publication of this article.

Author Contributions

Semih Bahceci and Pınar Kuyum Töz: literature search, study design, data collection, data analysis, manuscript preparation/editing, final manuscript approve.

Figen Celebi Celik and Demet Can: data collection and manuscript preparation/editing, final manuscript approve.

References


