



Food Protein-induced Enterocolitis Syndrome: A Single-center Experience

Besin Proteini İlişkili Enterokolit Sendromu: Tek Merkez Deneyimi

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ABSTRACT

Objective: Food protein-induced enterocolitis syndrome (FPIES) is an uncommon, non-IgE (immunoglobulin E) -mediated food allergy that mainly affects infants and young children. Our study aims to evaluate the etiology, clinical phenotypes, and tolerance status of our cases with FPIES.

Method: The file records of the patients who were followed up with the diagnosis of FPIES in the Departments of Pediatric Allergy and Gastroenterology of our hospital, between September 2016 and June 2022 were examined, and families who could not attend follow-up visits regularly were contacted by phone.

Results: Twelve (66.66%) of 18 cases with a mean age of admission of 33.0±27.5 (2-108) months were boy. The triggers of FPIES were fish in 66.66%, cow's milk in 16.66%, eggs in 5.55%, eggs and milk in 5.55%, and potato in 5.55% of the patients. While 94.44% of the cases had acute FPIES, and 44.4% of them had early-onset (<9 months) FPIES. The most common symptoms were vomiting (100%), diarrhea (38.88%), pallor (27.77%), lethargy (22.22%). Food-specific IgE sensitization was found in 5.55% of the patients, while tolerance developed in 33.33% of the cases during the follow-up. The mean age of tolerance development was 63±42 (19-112) months.

Conclusion: It is important to have knowledge about the symptoms of FPIES for accurate and early diagnosis. While cow's milk is the most prevalent triggers of FPIES in the literature, fish was at the forefront in our series. Despite the limited number of cases, our results are important in terms of giving us an idea about the triggers of FPIES in the western regions of Turkey.

Keywords: Food protein-induced enterocolitis syndrome, food allergy, fish allergy, children, oral food challenge

ÖZ

Amaç: Besin proteini ilişkili enterokolit sendromu, çoğunlukla bebekleri ve küçük çocukları etkileyen, immünoglobulin E (IgE) aracılı olmayan, nadir görülen bir besin alerjisidir. Çalışmamızda besin proteini ilişkili enterokolit sendromlu hastalarımızın etiyojisi, klinik fenotipleri ve tolerans durumlarının değerlendirilmesi amaçlanmıştır.

Yöntem: Hastanemiz Çocuk Alerji ve Çocuk Gastroenteroloji Bölümleri'nde Eylül 2016-Haziran 2022 tarihleri arasında besin proteini ilişkili enterokolit sendromu tanısı ile izlenen olguların dosya kayıtları incelendi ve düzenli takibe gelemeyen ailelere telefonla ulaşıldı.

Bulgular: Ortalama başvuru yaşı 33,0±27,5 (2-108) ay olan 18 olgunun 12'si (%66,66) erkek idi. Olguların %66,66'sında balık, %16,66'sında inek sütü, %5,55'inde yumurta, %5,55'inde yumurta ve süt, %5,55'inde patates tetikleyici idi. Olguların %94,44'ü akut, %44,4'ü erken başlangıçlı (<9 ay) besin proteini ilişkili enterokolit sendromu idi. En sık semptom kusma (%100), diyare (%38,88), solukluk (%27,77), letarji (%22,22) idi. Olguların %5,55'inde şüpheli gıdaya ait IgE duyarlılığı saptandı. İzlemede hastaların %33,33'ünde tolerans gelişti. Ortalama tolerans gelişme yaşı 63±42 (19-112) ay idi.

Sonuç: Semptomlar hakkında bilgi sahibi olmak doğru ve erken tanı için önemlidir. Literatürde en yaygın tetikleyiciler inek sütü ve soya iken, bizim serimizde balık ön plandadır. Olgu sayımız sınırlı olmasına rağmen sonuçlarımız Türkiye'nin batı bölgelerindeki tetikleyiciler hakkında bize fikir vermesi açısından önemlidir.

Anahtar kelimeler: Besin proteini ilişkili enterokolit sendromu, besin alerjisi, balık alerjisi, çocuk, besin yüklemesi testi

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INTRODUCTION

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE (immunoglobulin E)-mediated food allergy that presents with gastrointestinal symptoms⁽¹⁾. FPIES affects the entire gastrointestinal system and presents with recurrent episodes of vomiting, diarrhea, lethargy, pallor, hypothermia, and hypovolemic shock in severe cases. In chronic FPIES, the major symptoms are intermittent vomiting, diarrhea (sometimes contaminated with mucus and/or blood), and growth retardation⁽²⁾.

The prevalence and incidence of FPIES are still unknown⁽²⁾. Its cumulative incidence in infants is estimated to be 0.015-0.7%. Its prevalence in infants in the United States (US) was reported to be 0.51%⁽³⁾. While studies from Israel, Spain, Australia reported its incidence as 0.34%, 0.35%, and 0.015%, respectively⁽⁴⁾. As has been indicated, boys are slightly more frequently affected than girls⁽¹⁾.

Its pathogenesis is still unclear, and any relevant diagnostic biomarker has not been reported up to now. Although the diagnosis of FPIES is based on clinical history, oral food challenge (OFC) test is still the gold standard for the confirmation of the diagnosis⁽²⁾. It is important to exclude other causes, and metabolic disorders while establishing the diagnosis⁽³⁾. The fact that the resulting symptoms are not specific and typical to allergy, the prolonged period of time between food intake and the onset of symptoms (1-4 hours), low levels of awareness among clinicians, and the lack of diagnostic biomarkers lead to difficulties in diagnosis. Allergy tests are usually negative. For these reasons, FPIES can usually be misdiagnosed, and/or its diagnosis may be delayed^(2,3).

Cow's milk is reported to be the most prevalent culprit food. However, triggers may differ according to geographical regions, the eating habits of a specific society, the place of a certain food in the diet, time to the onset of complementary feeding, and genetic predispositions⁽⁵⁾.

Although the prevalence of FPIES is gradually increasing with the use of currently available diagnostic criteria and the enhanced level of awareness, our knowledge of this subject is still limited. The data from Turkey are similarly limited. Our study aimed to evaluate the etiology, clinical phenotypes, and tolerance status of our cases with FPIES.

MATERIALS and METHODS

Subjects

Eighteen cases who were followed up with the diagnosis of FPIES in the Departments of Pediatric Allergy and Pediatric Gastroenterology of our hospital, between September 2016 and June 2022 were included in the study. The clinical and laboratory findings were recorded from the patients' medical files, and families who could not come to follow-up regularly were contacted by phone.

Methods

The diagnosis of the FPIES was made according to the criteria specified in the guidelines⁽³⁾. Cases with suspected metabolic disease were not included in the study.

Serum-specific IgE was studied with UniCAP 100 system fluorescence enzyme immunoassay (Phadia, Uppsala, Sweden). A result above 0.35 kUA/L was considered as positive.

The skin prick tests (SPT) were performed by physicians using a commercial food extracts (ALK Abelló, Horsholm, Denmark). Histamine was used as positive control and saline as negative control. The mean diameter of the wheal was measured after 15 minutes, with a mean diameter greater than 3 mm considered as positive.

The OFC test was used for diagnostic purposes in the presence of a single episode, in cases with a suspected clinical history or unknown food trigger in the past. In the OFC test, the responsible food was administered at a dose of 0.06-0.6 g/kg.bw (in a way not to exceed a total of 3 g of protein or a total of 10 g of food) in 3 equal doses at 30-minute intervals, and the cases were observed for 4-6 hours. OFC test was considered positive if vomiting started within 1-4 hours after food intake (usually prolonged recurrent vomiting) and in the presence of at least two minor criteria⁽³⁾.

At least 1 year after the last allergic reaction, the cases were re-evaluated for developing tolerance by the OFC test under hospital conditions.

The study was approved by the İzmir Bakırçay University Non-Invasive Clinical Research Ethics Committee (decision number: 636, date: 22.06.2022).

Statistical Analysis

IBM SPSS version 22.0 (Armonk, New York, United States) was used for all statistical analyses. Numbers

and percentages were presented for discrete variables, while means and standard deviations were presented for continuous variables.

RESULTS

Twelve (66.66%) of 18 cases with a mean age of admission of 33.0 ± 27.5 (2-108) months were boy, and the mean age at symptom onset was 12.3 ± 12.8 (1-60) months. The triggers of FPIES were fish in 66.66% (n=12), cow's milk in 16.66% (n=3), eggs in 5.55% (n=1), eggs and milk in 5.55% (n=1), and potato in 5.55% (n=1) of the cases. While 94.44% (n=17) of the cases had acute FPIES, and 44.4% (n=8) of them had early-onset (<9 months) FPIES. The most common symptoms were vomiting (100%), diarrhea (38.88%), pallor (27.77%), and lethargy (22.22%). During diagnostic procedure, food-specific IgE value and SPT were positive in only one case. In the case with IgE sensitization, the culprit food was cow's milk. Atopic dermatitis was present in 11.11% of the cases, and IgE-mediated food allergy in 5.55%. Tolerance developed in 33.33% of the patients during the follow-up. The mean age of tolerance development was 63 ± 42 (19-112) months. Baked-milk tolerance emerged in two patients who developed cow's milk-induced FPIES at the age of 9 and 12 months, respectively (Table 1, 2). The tolerance developed earlier in the patients with milk and egg induced FPIES [13.3 ± 5.1 (9-19) months] compared to the patients with fish-induced FPIES [78.6 ± 36.2 (43-115) months] ($p=0.037$).

DISCUSSION

As far as we know, our study is the first survey investigating the incidence of FPIES in the Aegean

Characteristic	n (%)
Number of patients, n	18
Male patients, n (%)	12 (66.66)
Family history of atopy, n (%)	6 (33.33)
Atopic disease, n (%)	3 (16.66)
Eczema, n (%)	2 (11.11)
IgE-mediated food allergy, n (%)	1 (5.55)
No. of episodes in total, n	56
No. of episodes at diagnosis, (mean \pm SD)	3.3 ± 0.9
Skin prick test positive at diagnosis, n (%)	1 (5.55)
Specific IgE positive at diagnosis, n (%)	1 (5.55)
Diagnosis based on clinical history, n (%)	15 (83.33)
Diagnosis based on positive OFC, n (%)	3 (16.66)
OFC: Oral food challenge, IgE: Immunoglobulin E, SD: Standard deviation. *Defined as asthma, eczema, IgE-Mediated food allergy, or allergic rhinitis reported in parent or sibling	

region of Turkey. In our study, the most common trigger of FPIES was fish, and a single food was responsible for FPIES in 94.44% of our cases. IgE sensitization to the trigger food was rarely found, and tolerance developed earlier in cases with milk and egg-induced FPIES.

In some countries, fish has been reported as the second most common (12-33%) food after cow's milk⁽⁶⁾. In Greece, fish (54%) was reported to be the most prevalent food⁽⁷⁾.

Cow's milk is considered to be most frequent culprit food in infancy, while solid food FPIES tends to present after infancy as the most important triggers in the etiology of FPIES. Although cow's milk is the most frequent culprit food in the literature, fish was at the forefront in our series.

In terms of solid foods, in the literature the most frequently reported trigger foods were grain, egg and fish; but fish is at the forefront of our patients, similar to the Greece cohorts.

		n (%)
Admission symptoms	Vomiting	18 (100)
	Diarrhea	7 (38.8)
	Pallor	5 (27.77)
	Lethargy	4 (22.22)
Symptom duration	Acute	17 (94.44)
	Chronic	1 (5.55)
Hospitalization for the acute FPIES episode	Yes	12 (66.66)
	No	6 (33.34)
Age of onset	Early <9 months	8 (44.4)
	Late \geq 9 months	10 (55.56)
Severity	Mild-moderate	8 (44.44)
	Severe	10 (55.55)
Trigger foods	Fish	12 (66.66)
	Cow's milk	3 (16.66)
	Egg	1 (5.55)
	Cow's milk and egg	1 (5.55)
	Potato	1 (5.55)
Tolerance	With tolerance development	6 (33.34)
	Without tolerance development	12 (66.66)
FPIES: Food protein-induced enterocolitis syndrome		

In the studies from Turkey, while Arik Yilmaz et al.⁽⁸⁾ reported cow's milk as the most prevalent trigger in the Central Anatolia Region, Ocak et al.⁽⁹⁾ reported that the most prevalent trigger in the same region was egg, followed by fish. In a multicenter study by Metbulut et al.⁽¹⁰⁾, milk, egg white, and fish were indicated as the most common trigger foods. Trigger foods may differ according to geographical regions, the eating habits of society, the place of the trigger food in the diet, time to the onset of complementary feeding, and genetic predispositions⁽⁵⁾. Differences in breastfeeding rate and duration, the formulas used, and the order and time of giving complementary foods are among the reasons for geographical differences. Other possible reasons for geographical variations are differences in gut microbiota and genetics⁽⁶⁾.

Allergic reactions to more than one food are rare. It appears that patients with cereal-induced FPIES are at higher risk of allergic reactions, especially against other types of cereals. This association was observed in the studies from Europe, Australia, and the US^(6,11-13). US studies reported allergic reactions to both cow's milk and soy in 16-29% of patients. However, this association was not common in European studies^(12,14). Metbulut et al.⁽¹⁰⁾ reported the incidence of FPIES occurring with multiple foods was 21.9%. Multiple food allergies were present in only 5.55% of our cases.

In our study, the frequency of atypical FPIES was significantly lower (Table 1). IgE sensitization to trigger foods was not found in 94.45% of the patients. This incidence rate was comparable with those reported in the studies performed in the US, Australia, and Italy (94-97%)^(6,11,14). However, the rate of IgE sensitization is higher in European countries (13-16%)^(6,7,15). In the multicenter study conducted by Metbulut et al.⁽¹⁰⁾ in Turkey, the rate of atypical FPIES was 20%. In another study examining children with FPIES in Turkey, specific IgE positivity was found in 26% of the cases⁽⁸⁾. Caubet et al.⁽¹²⁾ reported that cases with IgE sensitization to cow's milk had a more persistent course than those who did not. In our study, the only case with IgE sensitization was the case with cow's milk-induced FPIES. In this case, baked milk tolerance developed at the age of 12 months.

FPIES is mainly diagnosed based on history, typical complaints and clinical findings, exclusion of other possible diagnoses, and challenge tests. According to the diagnostic criteria for acute FPIES, vomiting within 1-4 hours suspected food intake and absence of cutaneous or respiratory symptoms and at least three of the nine

minor criteria should be present in combination. In chronic FPIES, the presence of intermittent, and not otherwise explained vomiting and/or diarrhea (with or without blood), improvement of symptoms within 3-10 days after elimination of the suspected trigger food, and the emergence of acute FPIES symptoms after re-exposure are required diagnostic criteria^(3,16). Vomiting, diarrhea, pallor were the most frequent symptoms in our cases and 66.66% of the cases were admitted to the emergency department. In a study of 462 cases, severe symptoms (such as hypotension) were reported in 5% of patients⁽¹⁴⁾. Likewise, one of our cases with metabolic acidosis and cow's milk as the culprit food was hospitalized two times and followed up.

In our study, the tolerance developed at a later stage in fish-related FPIES cases, when compared to milk and egg-induced FPIES. This finding is in line with existing literature as well⁽¹⁾.

Study Limitations

The retrospective design, the small number of subjects, and the inability to evaluate some cases in time for developing tolerance due to the pandemic can be listed among the limitations of our study.

CONCLUSION

FPIES is an uncommon, non-IgE-mediated food allergy. It is important to have knowledge about its symptoms for accurate and early diagnosis. Thus, serious reactions can be prevented by eliminating the offending food. Despite the limited number of cases, our results are important in terms of giving us an idea about the trigger foods prevalent in the western regions of Turkey.

Ethics

Ethics Committee Approval: The study was approved by the İzmir Bakırçay University Non-Invasive Clinical Research Ethics Committee (decision number: 636, date: 22.06.2022).

Informed Consent: Retrospective study.

Peer-review: Internally peer reviewed.

Author Contributions

Surgical and Medical Practices: S.B., P.K.T., Concept: S.B., P.K.T., Design: S.B., P.K.T., Data Collection or Processing: S.B., P.K.T., M.A., Analysis or Interpretation: S.B., P.K.T., M.A., Literature Search: S.B., Writing: S.B.

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