Food Protein-Induced Enterocolitis Syndrome: Review

Besin Proteininin Yol Açtığı Enterokolit Sendromu

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ABSTRACT Food allergy (FA) is a spectrum of diseases stemming from an abnormal immune response to food proteins, which could be mediated by either IgE or non-IgE mechanisms. One of the non-IgE-mediated reactions, though very rarely seen, is food protein-induced enterocolitis syndrome (FPIES). The disease mostly begins during early infancy and usually resolves by age 3-4 years. It occurs almost equally in both sexes. Half of FPIES patients are allergic to both milk and soy. Clinical presentation of FPIES is characterized by an allergic reaction approximately 2-4 hours after introduction of the incriminated protein and sometimes with delayed onset reactions. Symptoms commonly start with vomiting, followed by blood positive diarrhea, possibly dehydration, and lethargy and hypotensive shock. The diagnosis is based on clinical criteria and oral food challenge. All patients should undergo broad diagnostic evaluation to exclude infectious, neurological and metabolic diseases. With the limited data including a few case series and reports, it is not possible to suggest a specific course of action applicable to all situations in treatment. Certainly, no food already tolerated would be restricted. For infants, extensively hydrolyzed casein formula or breast milk is usually tolerated, but if not, an amino acid–based formula should be used. In a child who is about 1-year-old with a history of FPIES, consider challenge first to high-risk foods and wait to 18 months or more to perform challenge to a previously reactive food. Moreover, avoiding grains as first foods and delaying legumes and poultry should be taken into consideration.

Key Words: Food hypersensitivity; food

ÖZET Besin allerjisi, diyette bulunan besin proteinlerine karşı bağışıklık sisteminin sapmış bir yanıtı olarak IgE- aracılı ya da IgE-aracılı olmadan meydana gelen bir dizi hastalıktan ibarettir. Nadir olarak görülmesine rağmen, besin proteininin yol açtığı enterokolit sendromu, IgE- aracılığıyla gelişmediği düşünülen bir tür besin allerjisidir. Hastalık erken süt çocukluğu döneminde başlayıp, 3-4 yaşına kadar kaybolur. Her iki cinste eşit oranda rastlanır. Bu hastaların yarısında inek sütü ve soyaya karşı aynı zamanda allerji mevcuttur. Hastalık, sorumlu tutulan besinin alınmasından 2-4 saat sonra ve/veya gecikmiş olarak meydana gelebilen allerjik reaksiyonla karakterizedir. Semptomlar, kusma ve onu takip eden kanlı ishal ve bunların sonucunda gelişebilen dehidratasyondan letarji ve hipotansif şoka kadar uzanabilmektedir. Teşhiste, klinik kriterler ve ağız yoluyla yapılan besin provokasyon testleri esastır. Besin proteininin yol açtığı enterokolit sendromu düşünülen her hasta, enfeksiyöz, nörolojik ve metabolik nedenleri de içeren geniş bir değerlendirmeden geçirilmelidir. Çoğunluğu vaka serilerine ve olgu bildirilerine dayanan kısıtlı bir bilgi birikiminden dolayı, özgün bir tedavi şeklini tüm hastalara önermek mümkün değildir. Bu hastalığın tedavisinde daha önce tüketimi esnasında problem olmamış besinler diyetten çıkarılmaz. Süt çocukluğu döneminde tedavide anne sütü ya da yoğun şekilde hidrolize edilmiş kazein içeren hazır mamalar genel olarak iyi tolere edilmesine rağmen, gerekirse amino-asit bazlı hazır mamalar da kullanılabilir. Besin proteininin yol açtığı enterokolit sendromu bulunan bir yaşından büyük çocuklarda yüksek riskli besinlerle provokasyona öncelik verilmeli, daha önce reaksiyona yol açmış besinler için ise en az 18 aya kadar beklenmelidir. Ayrıca, ek besinlere tahıllarla başlanmamalı, bakliyat ürünleri ve kümes hayvanlarının diyete geç eklenmesine özen gösterilmelidir.

Anahtar Kelimeler: Gıda allerjisi; gıda

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In general, food allergy (FA) is a spectrum of diseases stemming from an abnormal immune response to food proteins mediated by either IgE or non-IgE mechanisms. In IgE-mediated FA, T-cell directed protein-specific IgE production leads to sensitization, and re-exposure to the same antigen results in the release of mediators causing allergic reaction. However, non-IgE mechanism is caused by direct T-cell response and is mediated by proinflammatory cytokines leading to a variety of chronic reactions such as food intolerance and eosinophilic esophagitis.[1-3] One of the non-IgE-mediated reactions, though very rarely seen, is FPIES.[2] This syndrome, described in 1967 by Gryboski, consists of a symptom complex of profuse vomiting and protracted diarrhea with or without microscopic blood in the stool, which is diagnosed in infancy.[3-5]

The disease mostly begins at early infancy and occurs almost equally in both sexes. FPIES usually resolves by age 3 to 4 years. Nevertheless, persistence of FPIES beyond the age of 4 years has been reported but is uncommon. Family history of atopy is positive in 75% of FPIES patients; on the other hand, family history of FA is detected in 20% of patients. Additionally, the frequency of allergic diseases such as atopic dermatitis or asthma/rhinitis in patients with FPIES is about 25%.[6]

ETIOPATHOPHYSIOLOGY

FPIES is the most severe form of non-IgE mediated gastrointestinal FA in infants. Studies on histological findings and the pathophysiology of the disease are limited. There is increasing evidence that the immune response to food protein in the gastrointestinal system may primarily involve T cells. T cells responding to the incriminated protein produce cytokines, which lead to allergic reaction with eosinophilic infiltration and increase vascular permeability.

Recent studies demonstrated that tumor necrosis factor-alpha (TNF-α) secreted by circulating milk protein-specific T cells increased intestinal permeability, thus contributing to the influx of antigen into the submucosa with further activation of antigen-specific lymphocytes.[7] Food antigen-induced secretion of TNF-α from local mononuclear cells have also been suggested to be responsible for diarrhea and hypotension. Moreover, fecal TNF-α was found to be increased after a positive milk challenge result in patients with enterocolitis.[8]

Concomitantly, another study suggested that decreased activity of transforming growth factor beta1 (TGF-β1) was implicated in the pathogenesis of FPIES in young infants. The significantly lower expression of transforming growth factor beta type I receptors (TGF-βRI) in FPIES, compared with that of transforming growth factor beta type II receptors (TGF-βRII), implies the differential contribution of each receptor to the diverse biologic activities of TGF-β in the intestinal epithelium.[9]

CLINICAL CHARACTERISTICS

Clinical presentation of FPIES is characterized by an allergic reaction approximately 2-4 hours after consumption of the protein, sometimes even with delayed onset reactions. Symptoms commonly start with vomiting (≤2 hrs), followed by blood positive diarrhea (≤5 hrs), and possibly dehydration and lethargy and hypotensive shock.[1-6] Acidemia (in ~15% of patients), methemoglobinemia and sepsis-like picture, including elevated peripheral blood polymorphonuclear (PMN) leukocyte count, can also be a part of the clinical picture. Symptoms resolve after the causal protein is removed from the diet, but recur with a characteristic symptom pattern on re-exposure.

FPIES is usually caused by cow's milk or soy protein and half of these patients are allergic to both milk and soy. Moreover, similar reaction to other solid food proteins were recently reported and were designated "solid food FPIES".[1] There is an increasing number of reports on even supposedly hypoallergenic foods as triggering factors for FPIES, such as sweet potato, barley, peas, chicken, oat, rice and fish.[10,11]

Even though Powell was the first scientist to put forward diagnostic criteria for FPIES, there have been new reports describing some patients with detectable IgE to the causal protein.[4] Consequently, later FPIES was categorized into two subgroups by Sicherer et al.[5] The patients are diagnosed with "typical FPIES" if: (1) they are ≤ 9 months of age when diagnosed; (2) repeated exposure to the incrimina-

ted food elicits diarrhea and/or repetitive vomiting within 24 hours without any other cause for the symptoms; (3) there are no symptoms other than gastrointestinal symptoms elicited by the incriminated food; (4) removal of the offending protein from the diet results in resolution of the symptoms, and/or a standardized food challenge elicits diarrhea and/or vomiting within 24 hours after administration of the food. If monitored during a challenge, an increase in the absolute neutrophil count (ANC) by over 3500/mm^3 at 5 to 8 hours after the challenge is additional presumptive evidence of a positive challenge response.[5]

Although IgE antibody to the causal food is typically not detected as mentioned before, there are recent reports of clinical FPIES in which children had detectable IgE to the causal protein either at presentation or during follow-up. These types of patients are defined as "atypical FPIES" and they are older than 9 months of age when diagnosed, even though fulfilling clinical criteria of FPIES.[5,6] These patients sometimes present with typical IgE-mediated reactions such as urticaria as well. Thus, to include screening for serum specific IgE to the suspected foods is prudent for following the course of FPIES.

DIAGNOSIS

The diagnosis is based on clinical criteria and oral challenge. Powell suggested specific criteria for the diagnosis of milk/soy - FPIES based on oral challenge[4]. Protein re-exposure in open challenge results in delayed profuse vomiting and late-onset diarrhea, being therefore a key diagnostic procedure. The diagnostic criteria proposed by Powell et al to define FPIES include the onset of symptoms before 2 months of age, a positive response to challenge performed during the first 9 months of age, cessation of diarrhea with elimination of the suspected protein, and recurrence of symptoms after ingestion of the protein.[4,12]

Guidelines for a challenge with milk or soy recommends a dose of 0.15 up to 0.60 g protein/kg body weight (≤3 g protein or 10 g total food weight). Diarrhea containing blood or leukocytes occurring within 24 hours of the challenge accompanied by a rise in the ANC greater than 3500/mm^3 were proposed as criteria for a positive challenge response.[4,5] These rigid criteria are expected to exclude older patients or patients with milder symptoms. Moreover, these criteria have not been systemically validated and inclusion of clinical symptoms is still controversial. However, it is also clear that a confirmatory challenge would not be needed when the typical symptoms occur after ingestion of the food (particularly more than once) and there are no alternative explanations for the symptoms. Therefore, the necessity for an oral food challenge to confirm the diagnosis must be determined on clinical grounds. Otherwise, this modality would be more typically used to observe the development of tolerance.[12] Oral challenges should be undertaken with staff and facilities prepared to manage allergic reactions, hypotension, and shock. For FPIES in particular, strong consideration must be given for insertion of an intravenous line before a challenge, because reactions may require treatment with intravenous fluids and intravenous steroids to overcome hypotension and presumed T-cell-mediated response, respectively. Depending on symptoms, vasopressors such as epinephrine may be needed.[6]

Since FPIES diagnosis is generally based on clinical presentation, there are no series in which biopsies were performed solely in patients with FPIES. However, several case series of FPIES describe varied and nonspecific histological features in the biopsies. For instance, colonic biopsies showed crypt abscesses and a diffuse inflammatory cell infiltrate with prominent plasma cells; and small bowel biopsies defined edema, acute inflammation, and mild villous injury.[3,13] In some cases, focal erosive gastritis and esophagitis was found to be associated with prominent eosinophilia and villous atrophy.

All patients should undergo broad diagnostic evaluation to exclude different infectious, neurological and metabolic diseases. Eosinophil count, total IgE, serum food-specific IgE tests, skin prick tests and hemoccult testing are required to rule out classical food allergy. Skin prick tests are characteristically negative, but if positive, the risk for a sys-

temic reaction is greater and requires a change in diagnostic approach. Most infants are noted to have low serum albumin and an elevated PMN (ANC) count and stools are positive for heme and reducing substances in the literature. Assessment of in vitro lymphocyte responses to food stimulation for diagnosis has not reached clinical utility. Hypothetically, the atopy patch test (APT) may have a role in the diagnosis of non-IgE mediated gastrointestinal allergy, but it has not been sufficiently evaluated in this disorder. In a recent study, APT was found to be a promising diagnostic tool for the diagnosis of FPIES.[14]

DIFFERENTIAL DIAGNOSIS

Many disorders of infants that could result variably experiencing vomiting, diarrhea, and poor growth, possibly progressing to dehydration, lethargy, and shock, are ruled out before a final diagnosis. Considering non-allergic causes, infection is the most likely and the most significant. Metabolic disorders and necrotizing enterocolitis, particularly for newborn preterm infants, should also be considered. Several gastrointestinal disorders may present in infancy with diarrhea that is non-bloody and possibly with growth failure, but these disorders are not associated with inflammation, and stools are typically heme-negative. For infants with bloody stools (occult or gross), considerations should include infection, Hirschsprung's disease and intussusceptions.[6]

Dietary protein proctitis, dietary protein enteropathy and eosinophilic gastroenteropathies are conditions, which essentially should be ruled out as allergic causes. Key features of dietary protein proctitis are typical blood-streaked stools seen in breast-fed infants; this condition differs from FPIES with the absence of constitutional symptoms. Dietary protein enteropathy is characterized with nonbloody diarrhea, vomiting, edema, failure to thrive despite vomiting and food protein induced reaction is less prominent and not acute. Eosinophilic gastroenteropathies may present with vomiting, obstruction, gastric or colonic bleeding based on sites of inflammation. However, onset of systemic and gastrointestinal symptoms is not immediate and serum specific IgE tests for multiple foods are detected to be positive.[6,15] Before an allergy consultation, many of the abovementioned disorders should have been considered.

In summary, the characteristic clinical pattern of reactions in FPIES patients can aid the allergist in verifying a diagnosis and partnership with a gastroenterologist can be sometimes helpful in ruling out other entities.

MANAGEMENT

With the limited data including a few case series and reports, it is not possible to suggest a specific course of action applicable to all situations. However, an approach to diet must take into consideration of the reaction history, age of the child, number of foods involved, results of specific IgE antibody tests, and results of oral food challenges. Certainly, no food already tolerated would be limited. The clinician must determine a reasonable sequence, timing, and modality of administration from possible options such as an oral food challenge or routine addition to the diet at home.[6,12]

For infants diagnosed with milk or solid food -FPIES at first year, extensively hydrolyzed casein formula is usually tolerated, but if not, an amino acid-based formula should be given.[6] Since there has been a new case report on FPIES induced by accidental ingestion of an extensively hydrolyzed casein/whey formula, hydrolyzed formulas should be used cautiously and hydrolyzed casein formula should be preferred.[16] Although infants are known to react to maternally ingested proteins passed into breast milk, this problem has generally not been noted in FPIES and breastfeeding could be continued. With a 1-year-old child with a history of FPIES, consider challenge first with high-risk foods and wait to 18 months or more to challenge with a previously reactive food. Moreover, avoiding grains as first foods and delaying legumes and poultry should be considered. However, most fruits and vegetables are not implicated in FPIES and might not be restricted.[6,12]

Reactions to accidental exposures can be severe, so instructions on emergency management should be given. Prescription of self-injectable

epinephrine may be considered. Furthermore, if ingestion is known to have occurred, the patient should be instructed to seek medical attention to be monitored. Intravenous fluid resuscitation may be needed. For patients with a history of severe reaction and onset of any symptoms, consideration should be given for administration of corticosteroids to suppress a presumed T-cell-mediated reaction and steroid treatment could be considered for any patient with more than minimal symptoms. The reaction may include symptoms of hypotensive shock that presumably responds to epinephrine, but intravenous hydration and steroids are the only medications typically required. The role for and efficacy of antihistamines are unknown.[6,12]

CONCLUSION

Previous clinical data were discussed in this review to assist the clinician in making decisions regarding diagnosis and management. However, further research is needed to determine the best course of dietary management, to develop laboratory tests to avoid the need for oral food challenges and to address prevention modalities. Pediatricians and other primary care physicians are at the front line for diagnosis and initial management of FPIES, and efforts to educate them are necessary.

QUESTION	
A.	One of the non-IgE-mediated FA reactions, though very rarely seen, is FPIES.
B.	Specific IgE antibody to foods is never detected even in atypical FPIES cases.
C.	Although FPIES is frequently accompanied by anaphylactic reactions as seen in IgE-mediated food hypersensitivity, ingestion of the incriminated food usually results in profuse vomiting and diarrhea with dehydration.
D.	FPIES is an infrequent allergic reaction whose symptoms may be quite misleading, suggesting a life-threatening disease such as sepsis or metabolic syndrome rather than a food-induced reaction.
E.	Although cow's milk and soy proteins are most often responsible for FPIES, typical symptoms could also been induced by wheat, rice, chicken, and fish.

Answers to the Questions

A. Correct.
B. Wrong.
C. Wrong.
D. Correct.
E. Correct.

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