Food protein-induced enterocolitis syndrome [FPIES]

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FPIES manifests usually in infants as profuse repetitive emesis (onset 1-3 hours following ingestion), diarrhea (onset 5-10 hours) that may be accompanied by lethargy. [1]The respiratory and skin manifestations are absent in FPIES reactions. [2] FPIES is most commonly caused by cow's milk and soy. [3,4 5 6 7] Symptoms may start in the newborn period or up to one year of age. [8,9] Later onset usually results from delayed introduction of milk, soy, or solid foods to breast-fed infants. [7] In the reports from North America, Western Europe and Australia, FPIES to milk and soy in exclusively breast-fed infants is very rare, suggesting an important protective role of breast-feeding in FPIES.[10,11] However, in a cohort of Japanese 30 infants with cow milk FPIES, 10% reported symptoms during breastfeeding, indicating that FPIES phenotype may be expressed differentially in various ethnic groups.[12 13] FPIES to solid foods such as grains (rice,

oat), meats, fish, egg, vegetables have been reported. [1] FPIES to fish or shellfish usually starts in older children and adults.[7,14]

Clinical features of FPIES

The manifestations of FPIES are modified by frequency and dose of ingested food antigen. Chronic symptoms develop when food is eaten on a regular basis while acute symptoms develop when food is eaten on an intermittent basis or following a prolonged period of avoidance.

Infantile chronic FPIES

In the most severe cases, symptoms start within first days of life in infants fed with milk or soy-based formula with intermittent emesis and chronic diarrhea (may be bloody), without specific temporal association with food ingestion.[15] [12,16] Lethargy, abdominal distension, weight loss, dehydration, metabolic acidosis, anemia, elevated white blood count with eosinophilia, and hypoalbuminemia may follow. Intramural gas may be seen on abdominal radiographs, prompting a diagnosis of necrotizing enterocolitis, sepsis evaluation and treatment with antibiotics.[17] [5] Overall 75% of infants with FPIES appear acutely ill; about 15% are hypotensive and require hospitalization.[3] Transient methemoglobinemia was reported in about 1/3 of young infants with severe reactions and acidemia; some required treatment with methylene blue and bicarbonate. [18] Methemoglobinemia may be caused by an elevation of nitrites resulting from severe intestinal inflammation and reduced catalase activity. In about 24% of acute FPIES episodes, young infants manifested with hypothermia less than 36°C. [5]Among those with a recorded complete blood count, 65% had thrombocytosis >500 $x10^9$/L.[5]

Acute FPIES

Acute FPIES can be caused by cow milk soy, and solid foods in infants and young children and in adults by seafood, especially molluscs. Symptomatic infants with chronic FPIES improve

within 3-10 days with intravenous fluids or with hypoallergenic formula. [16] Food reintroduction induces acute symptoms; usually, repetitive (up to 10-20 times) projectile, emesis starts within 1-3 hours following ingestion. Infants and children appear ill, pale and lethargic. Diarrhea may follow and usually starts within 2-10 hours (mean onset, 5 hours) with blood, mucous, leukocytes, eosinophils, and increased carbohydrate content in the stool. [16] Diarrhea is more common in infants and in more severe reactions; diarrhea may be absent in less severe acute reactions (such as during the food challenge) in older children. [7] Some patients become hypotensive and may develop hypovolemic shock. [19] [14] Peripheral blood neutrophil counts are elevated in positive challenges, peaking at 6 hours, and returning to baseline within 18-24 hours. [16] In the extreme cases, severe abdominal distension may raise suspicion of ileus and results in an exploratory laparotomy. [20]

Offending foods

The majority (about 60%) of patients react to a single food. [4,7] The most common foods are cow milk and soy; up to 40% infants may react to both foods. FPIES may also be caused by other solid foods such as rice, oat, barley, chicken, turkey, egg white, green pea, and peanut. [21-28] [29] Mean age at onset of solid food FPIES tends to be higher than the mean age of onset of milk and soy-FPIES, likely reflecting the older age of usual introduction of solids into the diet.[7] Infants often present with multiple reactions and extensive evaluations for alternative etiologies (infectious, toxic, or metabolic) before the diagnosis of FPIES is considered. [5] Delayed diagnosis may be due to the low index of suspicion due to the lack of typical cutaneous and respiratory allergic symptoms. Furthermore, rice, oat, and vegetables cause IgE-mediated allergy infrequently, are considered to be of low allergenic potential, and are not suspected as culprits in severe allergic reactions. In addition, lack of definitive diagnostic tests may contribute to the

delay in diagnosis. Among infants with solid food FPIES, 65% were previously diagnosed with milk- and / or soy FPIES and fed with casein hydrolysate- or amino acid-based formula; 35% were breast-fed.[17]

FPIES in adults

In adults, molluscs (scallop), crustacean shellfish (shrimp, crab, and lobster) and fish hypersensitivity may provoke a similar syndrome with severe nausea, abdominal cramps, protracted vomiting, and diarrhea.[14]

Epidemiology of FPIES

Prevalence of FPIES in the US is not known; in general gastrointestinal immune reactions to cow's milk (CM) proteins that are mediated by T-lymphocytes with or without contribution of specific IgE antibody are estimated to account for up to 40% of milk protein hypersensitivity in infants and young children.[30] In a large unselected population-based birth cohort study in Israel, milk-FPIES was reported in 0.34%, while IgE mediated food allergy was reported in 0.5% of the infants under 12 months of age. [6]

Family history of atopy is positive in 40-80% of patients; family history is positive for food allergy in about 20% of the cases. [17]Approximately 30% of infants with FPIES develop atopic diseases such as eczema (23-57%), asthma or rhinitis (20%), or drug hypersensitivity later in life, similar to the general population. Up to 40% may have evidence of IgE- positivity to other foods. [4,7] Family history of FPIEs is reported in 6%. [7]

Diagnosis of FPIES

Diagnosis is based on the history, clinical features, exclusion of other etiologies, and food challenge.[2] The majority of patients from US, Europe, Australia, and Israel have negative skin prick tests and undetectable food-specific IgE whereas 47% of Japanese infants with milk FPIES

have detectable serum cow milk-specific IgE. [12] The data from Japan suggest that race or ethnicity may influence FPIES phenotype. [13]

Based on the presumed pathophysiology involving T cells, atopy patch test (APT) was evaluated for diagnosis of FPIES, with conflicting results. At this time, APT is not routinely recommended for diagnosis of FPIES. [4,31,32]

Oral food challenge (OFC) is the gold standard for diagnosing FPIES, however, most infants do not need to undergo confirmatory challenges for the initial diagnosis, especially if they have a classic history of severe reactions and become asymptomatic following elimination of the suspected food. [33] However, OFCs are necessary to determine whether FPIES has resolved and whether the food may be re-introduced into the diet.

Hypoalbuminemia and weight gain <10 g/day were identified as independent predictors of milk FPIES in young infants with chronic gastrointestinal symptoms.[9] Stool examination in infants with chronic FPIES and diarrhea is non-specific and shows occult blood, intact polymorphonuclear neutrophils, eosinophils, Charcot-Leyden crystals, and reducing substances.

Prior to establishment of the diagnostic criteria, endoscopy in symptomatic infants with CM and or soy-FPIES showed rectal ulceration and bleeding with friable mucosa. [15] In infants with chronic diarrhea, rectal bleeding and/or failure to thrive radiographs showed air fluid levels, non-specific narrowing and thumb-printing of the rectum and sigmoid, and thickening of the plicae circulares in the duodenum and jejunum with excess luminal fluid. [34] In the cases of ileus, in which laparotomy was performed, distention of small bowel loops and thickening of the wall of jejunum distal to Treitz's ligament with diffuse subserosal bleeding was reported. [20] Follow-up

studies performed on a restricted diet in asymptomatic patients documented resolution of radiological abnormalities.

OFCs can be used to establish diagnosis of FPIES or to determine whether FPIES has resolved. According to one conservative approach, follow-up challenges are usually recommended every 18-24 months in patients without recent reactions. Korean investigators recommended a more accelerated course as they reported that among 27 infants with milk FPIES, 64% tolerated milk at 10 months, and 92% tolerated soy at 10 months.[12] They suggested that in milk FPIES, the first milk challenge should be done after age12 months, whereas the first soy challenge could be done between 6-8 months.

Oral food challenge in FPIES

OFC in FPIES should be performed under physician supervision. [33] A placement of a secure peripheral venous access prior to the onset of the OFC is recommended for those patients with past severe reactions requiring emergency room visit or hospitalization. Securing a peripheral intravenous line prior to the challenge is also advisable in infants and older patients with anticipated difficult intravenous access. In the published studies, between 45-95% of the reactions during the challenge were treated with intravenous fluids and or steroids. [3,29] During an OFC, the total dose of 0.06-0.6 g/kg food protein is administered in three equal portions over 45 minutes.[3] Generally, the amount served initially during an OFC does not exceed 3-6 grams of food protein or 10-20 grams of total food weight (usually less than 100 ml of liquid food such as CM or infant formula). [1] Patient is observed for approximately 2-3 hours and if asymptomatic, a second feeding, typically an age-appropriate regular serving amount may be given followed by observation for several hours. [35] The criteria for OFC positivity have been proposed by Powell and modified by Sicherer et al. [3,16] These criteria include emesis (typically in 1-3 hours), diarrhea

(typically in 5-8 hours), fecal leukocytes, fecal eosinophils, and increase in peripheral neutrophil count > 3,500 cells/mm^3 peaking at 6 hours. The challenge is considered positive when three of five criteria positive, and equivocal when two of five criteria are met. However, in the more recent reports, diarrhea was not observed during the OFC as frequently and the magnitude of neutrophil increase was not as pronounced as reported by Powell. [6,7] Therefore the diagnostic criteria may need to be modified. The international work group has been formed by the AAAAI and the International Association for Food Protein Enterocolitis (IFPIES) to update the diagnostic guidelines for FPIES. The guidelines are expected to be published in 2016.

Management

Management relies on the avoidance of the offending food, prompt treatment of accidental reactions, anticipatory guidance regarding introduction of new foods, and periodic re-evaluations for tolerance.

Avoidance

The principles of avoidance are generally similar to that of IgE-mediated food allergy. During the ofc, the median threshold dose of cow milk was 120 mL, however, anecdotally, some infants have reacted to a tiny amount of food. [6] Extensively hydrolyzed casein formula is recommended for infants that cannot be breast-fed because concomitant milk and soy FPIES occur in up to 40% of cases. [4] The majority of patients with milk and or soy FPIES experience resolution of symptoms within 3 to 10 days of starting extensively hydrolyzed casein formula. Rarely, patients need amino acid-based formula or bowel rest and temporary intravenous fluids. [7]Infants with multiple food FPIES, especially those breast-fed are at risk to develop food refusal and may benefit from feeding therapy. [36,37]

Treatment of acute reactions

Rapid intravenous hydration (20 ml/kg boluses) is the first-line therapy for the more acute reactions at large or during a supervised oral food challenge. Intravenous corticosteroids are often used for severe reactions, based on the presumed T cell-mediated intestinal inflammation. Epinephrine should be available for potential severe cardiovascular reactions with hypotension and shock. However, prompt administration of epinephrine does not improve the symptoms of emesis and lethargy, which however resolve promptly with vigorous intravenous fluid administration. [14]

Ondansetron is a serotonin 5-HT_3 receptor antagonist used mainly to treat nausea and vomiting, often following chemotherapy but also in viral gastroenteritis. Ondansetron reduces activity of the vagus nerve both peripherally and centrally. Ondansetron is usually well tolerated and does not cause excessive drowsiness or extrapyramidal reactions, although special caution may be warranted in children with underlying heart disease, due to the potential to prolong QT interval. A small case series suggested effectiveness of intravenous ondansetron for stopping emesis induced during FPIES OFC. [38] Five children older than 3 years who developed emesis during FPIES OFC were treated with ondansetron, 0.2mg/kg/dose together with intravenous physiologic saline bolus. Three of the four children treated with intravenous ondansetron experienced resolution of emesis and lethargy within 10-15 minutes, while one required an additional ondansetron dose. Another child who was treated with oral ondansetron required an additional intravenous ondansetron dose to improve severe abdominal pain. Intramuscular ondansetron has been used in 5 young children (4 were under the age of 3 years) with rapid resolution of symptoms during the OFC. [39] Another small case series in young Italian children reported effectiveness of intramuscular ondansetron for management of acute FPIES during an oral food challenge in the physician's office. [40]

Emergency treatment plans outlining clinical features and management of acute reactions should be provided to patients with FPIES (a template can be accessed on the International Association for Food Protein Enterocolitis website, fpies.org) Mild reactions may be managed with careful oral rehydration at home. Patients with more severe reactions require resuscitation in the emergency department or inpatient unit. Emergency treatment plan outlines the emergency management for FPIES.

Introduction of foods to children with milk or soy FPIES

The majority of children (65-80%) have FPIES to a single food, most of them react to milk. [4-7]About 5-10 % react to more than 3 foods, some to as many as 6 or more foods. [4,7] Children with milk or soy- FPIES have about 1 in 3 chances of reacting to the other food, however, the risk is higher in those who developed symptoms of FPIES in the first month of life. [7]In these infants with early onset of FPIES, it may be prudent to exclusively breast-feed or introduce a hypoallergenic formula in the first 12 months of age. In general, it is prudent to perform supervised OFC to introduce milk or soy to children with milk or soy FPIES. Children with milk or soy FPIES have about 25% chances of reacting to a solid food, the most common solid food culprits are rice and oat. [7] It is frequently recommended to empirically initiate introducing solid foods at about 6 months of age, starting from yellow fruits and vegetables, followed by others, as tolerated. In general, if an infant tolerates a variety of the early food proteins, subsequent introduction may be more liberal. Tolerance to one food from the food group is considered as a favorable prognostic indicator that other foods from the same group will be well tolerated as well. For example, tolerance of rice or oat indicates a higher likelihood of tolerance of other cereal grains, or tolerance of one legume indicates a high likelihood of tolerance of other legumes. [1,3]

Introduction of new foods to children with solid food FPIES

Approximately 50% of children with solid food FPIES report reactions to more than 1 food. [4,7] It is estimated that their risk of reacting to milk or soy is about 15-25% whereas the risk of FPIES to another solid food is about 40%. [7] In infants with cereal-induced FPIES, sensitivity to other cereal grains occurs in nearly half of the patients. [7,17] Infants with rice or oat-induced FPIES appear particularly vulnerable and may benefit from delayed introduction of grains, beyond the first year of life. It remains to be determined whether delayed introduction of other foods with high protein content such as legumes and poultry is needed. This may avoid sensitization/reactions to other foods during a possible period of developmental susceptibility. In children with fish-induced FPIES, avoidance of all fish may be unnecessary as about 37% can tolerate at least one other fish. [29] OFC is recommended to determine tolerance to other fish.

Periodic re-evaluations to assess for resolution of FPIES

Foods that have caused FPIES reactions in the past should generally be reintroduced under physician supervision during a formal OFC.

The ideal timing of OFCs to determine resolution has not been systematically investigated. In the US experience, a diagnostic OFC is usually attempted within 12-18 months following the most recent reaction.[1,30] However, a prospective study from Korea suggested that earlier re-challenging might be considered. [8] In that study, among 23 infants with milk or soy FPIES (diagnosed at a median age 36 days, range 13-58 days) who were followed until 2 years of age and underwent 3 oral food challenges, tolerance rates to milk and soy were 27% and 75% at 6 months, 42% and 91% and 8 months, and 64% and 92% at 10 months, respectively. Milk FPIES resolved in all children by age 2 years; soy FPIES resolved by age 14 months. In a prospective

cohort study from Israel, all children were diagnosed with milk-FPIES by age 6 months, and 50% of them resolved milk FPIES within first year of life, 89% by age 2 years and 90% by age 3 years. [6] In contrast, retrospective studies from the US report lower rates of resolution of FPIES to milk or soy, 35% by age 2 years, 70% by age 3 years and 85% by age 5 years. [4 7] These differences may reflect various study designs and / or selection bias towards more severe and persistent phenotype among children evaluated at the referral allergy centers compared to those identified from general population. Current data support performing oral food challenges to milk after 12 months of age, whereas soy challenges may be considered after 6 months of age. [7,8,39]

There are no data on resolution of FPIES to seafood in older children and adults. Periodic re-evaluations should be considered in these patients

IgE testing in FPIES

FPIES is classified as a non-IgE mediated disorder because in the majority of the patients, systemic IgE antibodies specific for the FPIES food cannot be detected.[17,33,41,42]. However, studies report that 4-25% of children diagnosed with FPIES initially have or develop food-specific IgE. [4,6 7] Children with milk-FPIES who develop systemic milk-specific IgE appear to have delayed resolution of FPIES. [3,30 7] Most of the children with food-specific IgE antibodies retain the FPIES phenotype, however, a subset may change to typical IgE-mediated food allergy. In one study, 35% of the children with milk-induced FPIES who developed milk-specific IgE antibodies experienced immediate allergic manifestations of milk allergy. [7] While this observation needs to be validated in prospective studies, we recommend allergy evaluations for food specific IgE prior to performing an OFC to the FPIES food, and if positive, to modify the challenge procedure to administer incrementally increasing doses of the food, as per the standard

for challenges for IgE-mediated food allergy. [33,43] The food atopy patch testing is not routinely recommended for follow up evaluation of patients with FPIES. [4,31,32]

Natural history

In general, FPIES is a self-limiting food allergy of infancy and childhood that resolves with age and has no long-lasting sequelae. [44] The data on the resolution of FPIES vary widely, depending on the food and the population studied. [45] In the only population based cohort study from Israel, 90% of milk-FPIES resolved by age 3 years.[6] In a small prospective study from Korea, among 23 infants with milk or soy FPIES (diagnosed at a median age 36 days, range 13-58 days) who were followed until 2 years of age and underwent 3 oral food challenges, tolerance rates to milk and soy were 27% and 75% at 6 months, 42% and 91% and 8 months, and 64% and 92% at 10 months, respectively. Milk FPIES resolved in all children by age 2 years; soy FPIES resolved by age 14 months. [8] In a retrospective study from the US, significantly lower rates of resolution of FPIES to milk or soy were found, 35% by age 2 years, 70% by age 3 years and 85% by age 5 years. [4] In a mixed design study from the US, overall median age at resolution of milk-FPIES was 13 years, while the median age for patients with undetectable milk-IgE antibodies was 5 years. [7] These differences may reflect differences in study designs and / or selection bias towards more severe and persistent phenotype among children evaluated at the referral allergy centers compared to those identified from general population. The age of resolution of solid FPIES is older, about 50% of children outgrow rice or oat FPIES by age 4-5 years. [4,7,45] Children with milk FPIES who develop cow milk specific IgE antibody positivity have a more protracted course. In one study from the US, among children who developed specific IgE to cow's milk, age when milk-tolerance was established for subjects with undetectable milk-IgE was 5.1 years, whereas none of the subjects with detectable milk-specific IgE became tolerant to milk during

the study, P=0.003. [7] There are no data on resolution of FPIES to seafood in older children and adults.

Milk-FPIES resolves in 60% and soy-FPIES resolves in 25% of patients by age 3 years.[5, 13] Resolution of solid food FPIES by age 3 years occurred in 67% for vegetables, 66% for oat, and 40% for rice. FPIES rarely develops to foods upon initial feeding beyond 1 year of age, although onset of FPIES to fish and shellfish has been reported in older children and adults. For example, wheat allergy has not been reported in infants with oat- or rice-induced FPIES, but introduction of wheat was significantly delayed, presumably avoiding the "window of physiologic susceptibility" for FPIES development.[2, 5] Patients presenting initially or developing food-specific IgE antibodies after the diagnosis of FPIES have a more protracted course.[5, 13] It may be prudent to include prick skin testing and / or measurement of serum food-specific IgE level in the initial as well as follow-up evaluations, to identify patients at risk for persistent FPIES.

Pathophysiology of FPIES

The mechanisms underlying FPIES remain poorly characterized. FPIES is often considered to be a T-cell-mediated disorder, however, few studies have investigated T cells in FPIES. There is some evidence of T cell proliferation upon stimulation with food antigens, however, the stimulation index is not consistently different from control, non-allergic subjects. T-cell activation by food allergens may mediate local intestinal inflammation through release of pro-inflammatory cytokines, e.g., TNF-α and IFN-γ, causing increased intestinal permeability and fluid shift. [44] Local inflammation may be mediated by activated peripheral mononuclear cells, increased TNF-α and decreased expression of TGF-β receptors in the intestinal mucosa. [46] Leukocytosis and thrombocytosis are frequently observed in FPIES reactions and are thought to reflect an inflammatory response. The potential active contribution of neutrophils and platelets in

FPIES pathophysiology requires further investigation. Humoral responses are poorly characterized in FPIES but IgE, IgA and IgG4 antibody responses to casein are generally suppressed. A recent case series of children with FPIES successfully treated with intravenous ondansetron during the supervised oral food challenge raised questions about the role of serotonin signaling in FPIES.[38] Ondansetron is a serotonin 5-HT_3 receptor antagonist used mainly to treat nausea and vomiting, following chemotherapy and in viral gastroenteritis. It reduces peripheral and central activity of the vagus nerve. The effectiveness of ondansetron suggests the potential role of an impaired neuroendocrinologic pathomechanism in FPIES.

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