Review paper

Food protein induced enterocolitis syndrome in adults

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Abstract

Food protein induced enterocolitis syndrome (FPIES) belongs to a group of IgE-independent food allergies. It is the domain of paediatric patients, but it can also occur in adults. In this disease there is a life-threatening risk resulting from the possibility of a severe course of the disease and the development of hypovolemic shock. The disease was first defined in the mid-1970s. Knowledge about this disease is extremely low, we do not know its exact frequency, and the disease itself usually appears between 2 and 7 months of age. FPIES occurs mainly in formula-fed infants, typically 1–4 weeks after formula introduction, very rarely in breastfed infants, but may also develop in adults.

Key words: food protein induced enterocolitis syndrome, food, allergy, adults.

Introduction

Food protein induced enterocolitis syndrome (FPIES) belongs to the group of IgE-independent allergies provoked by food allergens. It is a domain of paediatric patients, however, more and more often it is diagnosed among adult patients. In this disease there is a serious life-threatening risk, which results from the possibility of a severe course of the disease, including development of shock. Unfortunately, the knowledge about this disease is very limited, which results both from its rare prevalence and the small number of epidemiological studies as well as the lack of clear diagnostic criteria [1, 2].

The condition was first defined in the mid-1970s [3]. The exact prevalence of FPIES is not known, however, it is estimated to occur with a prevalence of 0.15% (Australia) – 0.7% (Spain) [4–6].

The disease usually manifests itself between 2 and 7 months of age, whereas FPIES induced by cow's milk proteins or soybean oil usually affects infants < 6 months of age, and that induced by solid foods (rice, oats, eggs, fish, fruits and vegetables) affects infants between 6 and 12 months of age, according to the time of food introduction to the diet [3, 6]. FPIES occurs mainly in artificially fed infants, usually 1–4 weeks after the introduction of milk mixture, and very rarely in breastfed children. The disease may also develop in adults [2].

Clinical picture

FPIES is a potentially emergent condition, manifested by delayed onset vomiting or watery or bloody diarrhoea, which may cause haemodynamic instability and metabolic disturbances in about 15–20% of patients. In children, it occurs more frequently in boys than girls and the course of the disease can be mild or severe. In the mild form of the disease, recurrent vomiting, diarrhoea, pallor and slight sleepiness are typical. In the clinical picture of severe FPIES, the above-mentioned symptoms are accompanied by dehydration, hypotension, shock and metabolic disorders.

Additionally, depending on the duration of symptoms, acute and chronic forms of the disease are distinguished [1, 2, 7].

The acute form

The acute form-occurs when the triggering food is consumed at intervals or after a period of elimination. Characteristics of this form include:

- Recurrent vomiting beginning 1–4 h after food intake,
- Watery or bloody diarrhoea,
- The child's development is usually normal, and no distressing symptoms are observed between episodes of acute FPIES,

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- The delayed onset and absence of skin and respiratory symptoms initially suggest a systemic reaction, but different from anaphylaxis,
- Severe reactions can lead to hypothermia, development of metabolic acidosis, hypotension, and shock, which may initially suggest septicaemia,
- Unlike gastrointestinal infections or sepsis, where symptoms resolve slowly (within days), acute reactions to FPIES usually resolve completely within a few hours (up to 24 h),
- After the elimination diet the patient remains asymptomatic [2, 8].

The chronic form

The chronic form of PIES develops in infants fed with milk or soy formula. The chronic form is characterized by:

- Develops with regular consumption of trigger foods,
- Manifests itself by periodic vomiting, chronic diarrhoea, impaired weight gain and physical development,
- After elimination of the harmful food, symptoms disappear within 3–10 days,
- Re-ingestion of the trigger food, induces an acute reaction within 1–4 h of ingestion [2, 7].
- Chronic FPIES is rare but seems to be diagnosed more frequently in Japan and Korea than in other countries [9]. Helpful clues to differentiate FPIES from other gastroenterological diseases are hypoalbuminemia, neutrophilia, and poor weight gain [2, 7].

FPIES – epidemiology

Estimates of the prevalence of FPIES are very limited. We do not know the exact epidemiology of FPIES; however, it is estimated that it may occur at a prevalence ranging from 0.15% in Australia to 0.7% in Spain. Katz *et al.* reported the only prospective study that identified a prevalence of FPIES of 0.34% in infants fed with cow's milk [4]. In a Japanese retrospective study of the prevalence of milk allergy involving approximately 70,000 children, the prevalence of FPIES was estimated to be approximately 0.21% [10]. In an Australian study conducted among children under 2 years of age, the prevalence of FPIES was estimated to be about 0.15% [5]. A recently published American population-based study estimated the prevalence of FPIES in children to be 0.51% [11]. In a cohort of approximately 1000 infants followed for 18 months in a single hospital in Spain (PREVALE study), the prevalence of FPIES was estimated to be 0.7% compared to a prevalence of 2.37% for IgE-mediated food allergy [12].

FPIES – trigger foods

The most significant trigger foods are cow's milk, soy and cereals (mainly oats and rice – 33%) [11]. FPIES induced by soy and milk are common in the USA (25% to 50%) but rare in Australia, Italy and Israel. Fish-induced FPIES is common in Italy and Spain, which appears to be a consequence of certain dietary habits [11]. FPIES can also be induced by other foods: cereal grains (wheat, barley, corn), meats (chicken, turkey, beef), nuts (peanuts), vegetables (potatoes, green beans, tomato, pumpkin), legumes (green peas, lentils), fruits (apples, pears, bananas, peaches), fish and seafood. Rarely, however, the food that causes FPIES is a chicken egg. FPIES occurs when food is introduced into an infant's diet, usually between 2 and 7 months of age. FPIES caused by milk and soy tends to develop at a younger age (< 6 months) than that caused by solid foods (6–12 months). FPIES caused by cereal products is also thought to occur more rapidly than that caused by fish, eggs, and poultry meat [13]. In 83% of patients, FPIES is caused by one allergen, in 17% by 2 allergens and in 5–10% by 3 allergens [11].

FPIES and allergic diseases

It is widely believed that allergic diseases coexist with FPIES. This comorbidity is estimated to range from about 9% in Korea, Israel, and Italy to as high as 31–57% in the USA [14]. Familial burden of atopy is found in up to 54% of patients with FPIES [15]. About 30–50% of children with FPIES have concomitant atopic dermatitis, and 15% of patients have IgE-mediated food allergy [16]. In contrast, allergic rhinitis and bronchial asthma co-occur with FPIES in 38% and 25%, respectively [17]. In a population-based study from the USA, 19% of children with eosinophilic esophagitis (EoE) were found to have coexisting FPIES, compared to 0.48% of the general population [18]. In an older Australian case series, EoE was reported as a comorbid condition in 0.5% of patients with FPIES, with a prevalence of EoE in the general paediatric population in Australia of 0.01% [19]. However, further studies need to be conducted to confirm this association.

FPIES – recognition

The diagnosis is based primarily on the patient's history of recurrent, characteristic symptoms after ingestion of a particular food and improvement after its elimination. If the history is typical, an oral provocation test (OFC) is not necessary. If the history is uncertain, OFC is useful.

OFC in FPIES diagnosis should be performed when:

- The medical history is unclear,
- The trigger food is unidentified,
- The course of symptoms is atypical,
- Chronic FPIES is suspected [2].

FPIES in adults

Considering the time of onset and duration of symptoms, clinical signs, patient age, and presence of sIgE, FPIES is divided into 4 phenotypes:

- Acute – typical symptoms appearing 1–4 h after ingestion of the triggering food, which can lead to hemodynamic instability,
- Chronic – associated with chronic consumption of trigger foods, characterized by chronic diarrhoea and vomiting,
- Adult – occurs in older children and adults, symptoms occur faster than in children, and the most common triggers are fish, seafood, and dairy products,
- Atypical – involves the appearance of sIgE to the triggering food, and 25% of patients develop a food allergy [20].

FPIES in adults is characterized by some differences from the paediatric population:

- Reports in adults are mainly case reports and case series,
- FPIES is described more often in women than in men (3 : 1),
- Symptoms appear earlier than in children,
- Adults are considered to have only acute FPIES,
- The most common foods that trigger symptoms are fish and seafood,
- Most adults have one trigger food,
- Cross-reactions between closely related foods are not observed.

In adults, FPIES is often confused with symptoms of food poisoning, which seems to explain the underestimation of incidence [21] (Table 1).

FPIES in adults – epidemiology

FPIES, with the onset in adulthood is rare and was first described by Fernandes *et al.* in 2012 in a 53-year-old person after eating scallops [22].

The frequency of FPIES in adults is unknown. In a recent US population-based study, the frequency of FPIES was estimated to be 0.51% of the paediatric population and 0.22% of adults [11]. In a study of US adults reporting shrimp allergy, up to 20% of patients who indicated only gastrointestinal symptoms had no sIgE detected. Taking into account the criteria for diagnosis of FPIES, it can be presumed that this group of patients may be the target group of patients with FPIES. Therefore, it is supposed that FPIES in adults may occur more frequently than previously thought [23].

In contrast to the paediatric population, adults with FPIES show a clear female predominance, estimated at 68.4% to even 90% of all subjects (on average about 3 : 1 in favour of women). Thus, in the study by Tan *et al.* including 31 patients, women constituted 77.4% and men 22.6% [24]. In Gleich's study, women constituted 7 out of 8 (87%) subjects [23]. Du *et al.* showed that women accounted for 90% of those diagnosed with FPIES [25]. Gonzalez-Delgado *et al.* showed an 88% female predominance in adult patients with FPIES [26]. In a Canadian study by Li *et al.*, women accounted for 68.4% in the subgroup of adults with FPIES after eating shrimps [27]. In a recent Spanish study published in 2021 by Crespo *et al.*, among 24 patients, 71% were women [28]. It seems that the predominance of females among adults may suggest some hormonal role in the pathogenesis of FPIES. Unfortunately, the mechanisms are not known and need to be thoroughly investigated.

FPIES in adults – food triggers

The first case report of FPIES in an adult was published in 2012 and involved a 53-year-old man whose OFC-verified trigger was scallops [22]. Subsequent studies have expanded the list of trigger foods. In Tan's 2014 study, the most common triggering foods for FPIES in an adult patient population were crustaceans, molluscs, and fish [24]. Similarly, in other later studies, FPIES to shellfish (mainly shrimp), molluscs, and fish were most commonly described [23]. Occasional cases of FPIES in adults after ingestion of chicken egg have also been de-

Table 1. Basic differences between FPIES in adults and children

Parameter	Adults	Children
Mean age	35 years	2–7 months
Sex	F 3 : 1	M
Symptoms	Abdominal pain > vomiting > diarrhoea	Vomiting > pallor > lethargy > diarrhoea > hypotonia
Risk of hypotension	Lack	5–15%
Metabolic acidosis	Not recorded	More common in chronic FPIES
Main foods	Shellfish, fish, cow's milk, wheat, egg	Cow's milk, rice, soybeans, oats, fish, vegetables
Natural history	Not known, no risk of anaphylaxis after re-challenge	Usually resolves by school age
Skin tests	Negative	Positive in 5–15% to cow's milk, less often to other foods
sIgE	Negative	Positive in 2–12% of unusual FPIES
Biomarker	Lack	Lack

scribed [29]. It is currently believed that fish and seafood (mainly crustaceans, molluscs) are the most common (65% in total) triggers; however, a high proportion has also been reported to develop FPIES after ingestion of dairy products (20%), wheat (20%), and eggs (5%). Cases of FPIES in adults after eating mushrooms have also been described [25]. A recent clinical case review involving 20 adults with FPIES from Canada showed that the most common provocative foods were shellfish (shrimp), fish, milk, eggs, and wheat [27].

In adults with FPIES occurring after eating seafood, 60% respond to only one food, that is, fish or seafood. It has also been observed that 55% of adults with FPIES occurring after shellfish consumption also react to shellfish and/or fish, 50% of patients with fish-induced FPIES also react to seafood (shellfish or molluscs) and 40% of patients with shellfish-induced FPIES react to molluscs [26, 28]. In the Gonzales-Delgado study, crustaceans caused FPIES symptoms in 15 of 25 patients (60%), fish in 12 (48%) patients (mainly tuna, hake, sardines, anchovies), and cephalopods and bivalves in 5 (20%) patients [26]. Ten (40%) patients had symptoms from more than one food group [26]. In a study by Crespo *et al.* published in 2021 involving 24 adults, the most common triggers were seafood (66.7%), including molluscs (58.3%), shellfish (29.2%), and fish (29.2%) [28]. Among fish, hake and salmon were the most common triggers. About 46% of patients had symptoms from more than one food group, and the most common associations were shellfish-mollusc (5 patients) and fish-shellfish [28]. In another study by Crespo *et al.* including 19 patients, the most common trigger was shellfish, while 49% of patients had triggers from more than one food [30]. In a retrospective Canadian study published in 2020, in a group of 191 patients reporting gastrointestinal symptoms after shrimp consumption, reactions consistent with FPIES were demonstrated in 19 patients. The authors of the cited study observed that 10 (41.7%) patients reacted to more than one food, and the most common association was shellfish-mollusc (5 patients – 20.8%) [27].

FPIES in adults – frequency and natural history

Infantile FPIES usually begins at 1 year of age, usually within days or weeks of introducing artificial foods into the diet. Often the infant initially tolerates feeding a small amount of food with no or minimal symptoms, but then develops acute FPIES when a larger portion of food is introduced or feeding is discontinued for several days per week and then resumed. The prognosis in paediatric patients is favourable. Unfortunately, there is no information regarding the events leading to FPIES in adults. The natural history of FPIES with onset in adulthood is unknown; limited data suggest that it persists for many years [11, 23, 26].

FPIES in adults – response time

In children the time from food intake to the onset of symptoms is 1–4 h. It is believed that symptoms in adults occur earlier than in children; however, the available studies indicate that the time interval between food intake and the onset of symptoms can vary widely, from 3 min to even 720 min (mean: 60 to 212.5 min). In a study by Tan *et al*., the time from food ingestion to onset of FPIES symptoms in adult patients ranged from 52 to 120 min (mean: 60 min), symptom duration was 120 min, and symptom recurrence until diagnosis averaged 2 [24]. In a study by Gleich *et al*., symptoms after shrimp consumption occurred within 30 min to 5 h (mean: 2 h), with symptom duration up to 5 h [23]. In a Canadian study published by Li *et al*., the time between food ingestion and onset of symptoms ranged from 3 min to 6.5 h (mean: 2.8 h) and the recurrence of symptoms averaged 4.8 reactions. The authors of the cited study inferred that this may suggest that the timing of response onset is less predictable than in children and may occur earlier [27]. In the Crespo study, the latency time was 60–720 min (mean: 212.5 min), while symptom recurrence until diagnosis was 5.8 responses [28].

FPIES in adults – symptoms

The most common symptom in children is vomiting, in adults – abdominal pain. In Tan's study, the most common symptoms of FPIES in adult patients were abdominal pain (77.4%), vomiting (71.0%) and diarrhoea (58.1%) [24]. Identically in Gleich's study, the most common symptoms were abdominal pain (87.5%), vomiting (75%) and diarrhoea (62.5%) [23]. Similarly, in Du's 2018 retrospective study of 20 patients with FPIES, the most commonly reported gastrointestinal symptoms were severe crampy abdominal pain (90%), vomiting (55%) and diarrhoea (50%). In the cited study, 6 (30%) patients experienced all 3 symptoms and 6 (30%) patients reported symptoms caused by more than one food [25]. In a more recent 2019 study by Gonzalez-Delgado, the most common symptoms were abdominal cramping pain (100% of patients), vomiting (76%), and diarrhoea (64%) [26]. About 30% of patients had all 3 symptoms [26].

In 2 recently published studies of adult FPIES, pain was not the most common symptom [27, 28]. In a 2021 Spanish study, diarrhoea predominated (91.7%), followed by abdominal pain (87.5%) [28]. However, the third most common symptom was vomiting (75%) [28]. In another study involving Canadian patients, all patients reported vomiting (100%), diarrhoea (42.1%), and abdominal pain was reported by only 36.8% of patients [27]. Nevertheless, it is still believed that vomiting is not characteristic of FPIES in adults and is not the basis for its diagnosis.

FPIES in adults – co-occurrence of allergies

We have no clear data on the co-occurrence of allergic diseases with FPIES in adults. The most common allergic

diseases accompanying FPIES include allergic rhinitis, atopic dermatitis and bronchial asthma. In Tan's study, more than half of adult patients with FPIES had comorbid allergies, with 38.7% reporting ANN, 19.4% asthma, and 3.2% AD [24]. In Gleich's study, 3 (37.5%) patients had ANN and allergic conjunctivitis, while 1 (12.5%) had bronchial asthma [23]. In a Canadian study of 19 patients with FPIES, 5 (27.8%) were positive for one of the common inhalant allergens [27]. Additionally, skin tests for mites (D. pteronyssinus and D. farinae) were performed in 17 patients, with positive results in 6 (35.3%) patients. Moreover, in the cited study, 3 (15%) patients had a positive history of atopy (ANN, bronchial asthma, AD, food allergy) [27]. In a study published by Gonzalez-Delgado *et al.* in 2018, a history of atopy was reported in up to 72% of adults with FPIES (ANN in 18 patients, asthma in 4 and AD in 3) [26]. In Du's 2018 retrospective study of 20 adult patients diagnosed with FPIES, AD co-occurred in 4 patients, urticaria in 2 patients, and bronchial asthma in 1 [25].

FPIES in adults and EoE

Recently, the comorbidity of FPIES with EoE has also been raised. In a population-based study from the USA, 13% of adults with EoE were found to have FPIES coexisting, compared with 0.19% in the general population. Nevertheless, further studies need to be conducted to confirm this association [18] (Table 2).

FPIES in adults – diagnosis

The diagnosis of FPIES is usually made on the basis of a detailed history; however, the gold standard for diagnosis is a provocation test, which, however, is often not performed due to significant patient discomfort [31]. Similar to FPIES in children, there are no reliable diagnostic tests; nevertheless, in many cases, significant neutrophilia or thrombocytosis measured at 4–6 h from the onset of symptoms is observed [31]. Skin tests and sIgE in patients with FPIES are usually negative. It is important to rule out other diseases (such as celiac disease, lactose intolerance, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and IgE-mediated allergies) which may mimic PIES as the presenting symptoms are generally nonspecific.

Currently, therapeutic management of adults with FPIES is based on identification of the trigger food(s) and its/their avoidance through elimination diets [25, 31].

Chronic FPIES in adults

Until recently, only the acute form of FPIES was thought to occur in adults; however, two case reports have emerged in recent years that may change this view [29, 32].

The first description is of a 41-year-old woman with a 12-year history of repeated vomiting and fatigue after eating boiled eggs or scrambled eggs [29]. The symptoms usually lasted for 3 days. Egg skin tests were negative. The sIgE values for egg, ovalbumin and ovomucoid were < 0.35 kU/l. The patient underwent SBPCFC on the egg. After ingestion of 1/4 egg, vomiting and fatigue occurred but without diarrhoea, which was consistent with her usual response [29]. Tryptase levels were normal. The patient required oral rehydration and 3 days of ondansetron to reduce symptoms. The patient was advised to avoid cooked

Table 2. Summary of major studies on FPIES in adults

Author (year)	*N*	Age	Number of episodes	Time	Female	Cause	Symptoms	Co-allergy
Tan (2014)	31	47	3	52.5–120 min	77.4%	Crustaceans Molluscs Fish	Abdominal pain Vomiting Diarrhoea	Allergic rhinitis Asthma Atopic dermatitis
Du (2015)	20	38.5	2	60 min	90%	Crustaceans Molluscs Dairy	Abdominal pain Vomiting Diarrhoea	Atopic dermatitis Urticaria Asthma
Gleich (2015)	8	48	4	30–300 min	87%	Shrimp Crabs Clams Scallops	Abdominal pain Vomiting Diarrhoea	Allergic rhinitis Allergic conjunctivitis Asthma
Gonzales-Delgado (2018)	25	25	8	60–120 min	88%	Crustaceans Fish Octopuses Clams	Abdominal pain Vomiting Diarrhoea	Allergic rhinitis Asthma Atopic dermatitis
Li (2020)	19	34.3	4.8	3–720 min	68.4%	Shrimp Lobsters Crabs	Vomiting Diarrhoea Abdominal pain	Allergic rhinitis Asthma Atopic dermatitis
Crespo (2021)	24	37	5.8	60–720 min	71%	Molluscs Crustaceans Fish	Diarrhoea Abdominal pain Vomiting	Allergic rhinitis Asthma Atopic dermatitis

eggs and the conclusion was made that this case suggests that atypical FPIES can occur in adults [29].

A case of a 20-year-old man who was admitted to hospital after several days of significant weakness, dizziness, feeling of swirling surroundings and blurred vision was also reported in 2020 [32]. Additionally, he reported chronic abdominal pain, diarrhoea and vomiting for several months. For this reason, he followed a restrictive diet during which he lost 7 kg of weight. Due to lactose intolerance he had avoided milk since the age of 15. His allergic history was negative. The patient suspected that eggs were the factor causing his complaints, and he consumed 3–4 eggs a day, but after their elimination, the symptoms only partially subsided [32]. After the elimination of meat and fish, the symptoms disappeared completely and reappeared only occasionally after their accidental ingestion. Skin and sIgE tests were negative. Neurological and toxic causes were excluded. Laboratory tests showed mild anaemia. Endoscopic examinations performed showed no abnormalities. After several months of diet he underwent provocation tests with egg, salmon and beef, which were positive (abdominal pain, repeated vomiting, pallor, hypothermia, lethargy and hypotension (77/50 mm Hg, which resolved after about 5 h of fluid therapy)). Other species of fish and poultry did not cause the patient's complaints. The patient was diagnosed with chronic FPIES caused by eggs, beef and salmon. Therefore, the patient was advised to continue to strictly avoid these foods and follow-up visits while following the recommended diet did not show any recurrence [32].

FPIES in adults – conclusions

FPIES in adults seems to occur more frequently than previously thought. It should be taken into account in patients who react with gastrointestinal symptoms to food when allergic tests are negative. Since the clinical profile of FPIES with onset in adulthood seems to differ from FPIES in children, it is reasonable to develop appropriate diagnostic criteria for the adult population. Unfortunately, further studies are needed to understand the natural course of this disorder in adult patients.

Conflict of interest

The authors declare no conflict of interest.

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