Non-IgE Food Immunological Diseases 26

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Abstract

Non-IgE food immunological diseases encompass a wide range of illnesses that can involve one of more systems in the body. The gastrointestinal track is the most commonly involved system, but cutaneous and respiratory systems can also be involved. This chapter will primarily be focused on identification, diagnosis, and treatment options for non-IgE food immunological diseases involving the gastrointestinal track directly. Current difficulties in diagnosis and pathophysiology behind non-IgE food immunological diseases will be explored.

Keywords

Non-IgE · Non-IgE food allergies · Mixed IgE food triggers · Non-IgE food immunological diseases

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26.1 Introduction

Non-IgE food immunological diseases encompass a wide range of illness. Akin to IgE-mediated food allergies, clinical history is

paramount in the diagnosis. One important difference between non-IgE and IgE-mediated immunological processes is the lack of potential confirmation in vivo, or in vitro tests for non-IgE food-related diseases. Diagnosis by personal clinical history and general common food triggers for trial avoidance remain a popular strategy for initial management. When appropriate oral challenges can be used to officially diagnose certain forms of non-IgE food immunological disease. On the occasion when there is a mixed IgE and non-IgE dietary trigger, IgE in vivo and in vitro testing have been used to help diagnosis by potential association with the non-IgE component. To date there has been no successful association of IgG or immunoglobulin subclass level testing to help elucidate the dietary trigger of non-IgE-mediated food immunological disease. Screening for them by these means is not recommended (see ▶ Chap. 33, "In Vitro Allergy Testing" for more information).

Identification of food responsible for inciting the non-IgE immunological disease is important to ensure quality of life and nutrition and prevent secondary illnesses and in certain cases life-threatening sequela. Avoidance and time often alleviate the unwanted immunological response to a specific food, and eventual reintroduction is possible. Consideration for potential confounding non-immunological food triggers is important as these tend to extend from a metabolic or pharmaceutical affect, vary in sensitivity, and remain for life.

26.2 Non-IgE Food Immunological Diseases

Food immunological disease or food allergies have been defined as: "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" (Sampson et al. 2014). This definition encompasses IgE, non-IgE, and mixed food-triggered immunological diseases. Dietary triggers can come from solid foods, drinks, chewing gum, additives, and even dietary supplements. Most non-IgE-mediated food allergies are not immediate making their diagnosis based on history more complicated for patient and practitioner alike.

One of the challenges facing practicing physicians is to help discern and educate the general public on the meaning of "specific immune response" within the definition of food allergies. Adverse reactions to one's diet can also be caused by non-immunological triggers. These sources can be from metabolic (e.g., lactose intolerance), toxic (e.g., food poisoning), and pharmacological (e.g., caffeine).

When examining more classic non-IgE-mediated food allergies, it is often divided into the system that is affected. Within the gastrointestinal track, allergic proctocolitis, food protein-induced enterocolitis syndrome, dietary protein-induced enteropathy, and celiac disease are the hallmark examples. Cutaneous manifestations can be seen in systemic contact dermatitis and dermatitis herpetiformis. In rare instances the respiratory track has also been affected with pulmonary hemosiderosis (Heiner syndrome). Other forms of mixed IgE and non-IgE food immunological disease such as systemic contact dermatitis, atopic dermatitis, and eosinophilic esophagitis will be discussed in their respective chapters. There is not one particular food that is seen in all forms of non-IgE-mediated food immunodeficiency diseases. Within a particular illness, there are often more than one possible trigger. Celiac disease is a notable exception to this generality.

26.3 Gastrointestinal Non-IgE Food Immunological Disease

26.3.1 Allergic Proctocolitis

Allergic proctocolitis, also known as food protein-induced allergic proctocolitis (FPIAP) or allergic colitis, is generally considered to be a benign condition primarily affecting infants and toddlers (Nowak-Wegrzyn et al. 2015). The exact mechanism is unknown but thought to involve T-cell-mediated pathways (Morita et al. 2013). The most prominent clinical feature is gross bloody or blood-tinged (macroscopic) stools. Diarrhea and emesis are also commonly seen but are not

essential clinical features for the diagnosis of FPIAP. On rare occasions mild anemia may result from unrecognized or untreated FPIAP, but most infants do not succumb to failure to thrive or developmental sequela.

The only known treatment is removal of the offending food source. In infants, elemental formula, although very effective, is reserved for cases where no trigger can be identified and partially hydrolyzed formulas have failed to resolve the blood streaking. Once the dietary antigen(s) is removed from the diet, clinical improvement is seen in as little as 48–72 h. Complete healing of the distal and sigmoid colon has been postulated, however, to take up to 4 weeks.

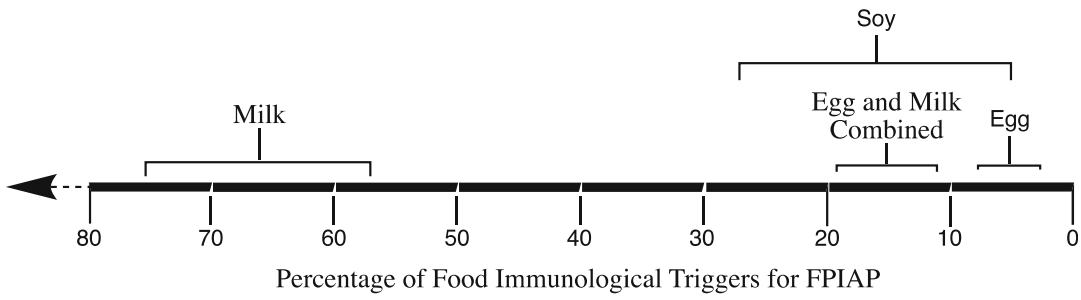
Colonoscopies have been used in studies to diagnose and monitor healing. Histological biopsies have shown the presence of eosinophil's, but not in every case, and their presence is not universally considered to be necessary for diagnosis. The number of eosinophils per high-powered field reported has been from >6 to >50 and particularly in the lamina propria (less often in muscularis mucosae) (Lake et al. 1982; Winter et al. 1990; Xanthakos et al. 2005; Yantiss 2015). Colonoscopies are not recommended in the routine clinical diagnosis or management of FPIAP (Sampson et al. 2014). In the event a trigger cannot be found and clinical symptoms persist or worsen, the use of colonoscopies has been advocated for in the literature (Erdem et al. 2017).

Maternal breast milk (MBM), unlike with IgE-mediated allergies or atopy, is not considered to help prevent FPIAP. In fact, breast milk is one of the more common dietary staples during the onset of FPIAP. Approximately 60% of babies under the age of 6 months that develop FPIAP are on MBM (Erdem et al. 2017). The first signs of FPIAP can be seen in infants that are only a few days old but more often after the age of 2 months old and under 1 year of age is typical. Children over the age of 2 and up to 14 years old have been reported to suffer from FPIAP (Ravelli et al. 2008). The true prevalence of FPIAP is not known. In adults FPIAP is poorly described, and more often eosinophilic colitis or ulcerative colitis is reported. If there is a relationship between the two latter diagnoses and FPIAP it is not well understood.

Regardless of the age of onset, the most common trigger reported is cow's milk (Sampson et al. 2014). This remains true even for infants that are exclusively breastfed. In exclusively breastfed babies, the rare recommendation that the mother ceases ingestion of dairy products is warranted and often resolves the FPIAP while still being able to breastfeed (Erdem et al. 2017). When the dietary antigens in the maternal diet cannot be identified, atopy patch testing has been reported to help identify potential triggers, but its use remains controversial (Lucarelli et al. 2011; Sampson et al. 2014). Results of atopy patch testing have shown in these severe cases of FPIAP unresponsive to maternal hypoallergenic diet which yielded up to 100% positive testing to MBM itself (Lucarelli et al. 2011).

Studies tend to differ on the exact percentage of participants with single non-IgE food immunological triggers, but cow's milk is repeatedly reported as the most common trigger followed by eggs or soy and then a mixture of other foods. Studies that include soy are far less common than those reporting on milk and eggs, with some of the original studies only containing six subjects (Lake et al. 1982). As seen in Fig. 1, the percentages for each food allergen range considerably (Erdem et al. 2017; Fiocchi et al. 2010; Lake 2000; Xanthakos et al. 2005).

Abstinence of the offending food trigger is the only known treatment. The duration of avoidance required to become tolerance of the food in question ranges from a few weeks to years. The average duration of time ranges from 8 to 15 months (Erdem et al. 2017). The initial duration for avoidance is normally recommended for 12 months. This can vary and reintroduction has been suggested in as little as 4–8 weeks. Milk and/or egg has been reported to be involved in over 90% of toddlers unable to develop tolerance by the age of 2 (Erdem et al. 2017). Unlike in IgE-mediated allergies and food protein-induced enterocolitis syndrome (FPIES), trial reintroduction or challenge can be done at home and without medical supervision. There is not a universal protocol for the challenge or reintroduction (Nowak-Wegrzyn



* All Others: Idiopathic ~10%, Corn <5-6%, <5%: Wheat, Rice, Meats, Misc.

Fig. 1 Percentage spectrum of responsible food immunological triggers

et al. 2015). Some studies have modeled the challenge after protocols similar to a FPIES challenge (Erdem et al. 2017; Nowak-Wegrzyn et al. 2009; Sampson et al. 2014). The general premise however is to reintroduce the food protein back into the regular diet gradually and to observe for return of blood streaking in the stools.

26.3.2 Food Protein-Induced Enterocolitis Syndrome

Food protein-induced enterocolitis syndrome (FPIES) can be life-threatening. The onset of symptoms is 1–4 h after ingestion of the food antigen (Sampson et al. 2014). This is a delayed reaction when comparing the onset of IgE-mediated food allergies that 97% of reactions are within an hour of ingestion (with vast majority prior to 30 min). History and oral food challenges are the only known methods of diagnosis and confirmation. Although delayed, with a predictable window of 1–4 h of symptom onset after ingestion, the identification of the offending food trigger is less complicated then with FPIAP.

The exact prevalence of FPIES, much like FPIAP, is unknown. The age of onset is normally after 2 months of age but can be sooner (Manti et al. 2017). Apposed to FPIAP, FPIES is recognized to occur in adults, albeit less frequently. Cow's milk and soy are the most common triggers prior to 4 months of age. Maternal breast milk is not thought to prevent FPIES but has been reported to delay onset to when the infant starts to ingest solid foods. As an infant starts to ingest nutrition by solid foods at ages 4 months and above, the sources of possible triggers diversify to include rice, grains, eggs, vegetables, fruits, fish, and legumes. Studies have found cow's milk to be the most common causative agent (~60–70%) with conflicting data for the percentages of soy, eggs, rice, fish, and others. The discrepancies are partially thought to be due to regionally diverse diets beyond cow's milk. Most studies have favored a singular causative antigen responsible for FPIES in an individual. However with 35–80% reports of multiple food triggers, having more than one food antigen leading to FPIES in a patient is by no means rare or uncommon.

Clinical presentation of FPIES can range from mild to severe and life threatening. The onset of symptoms normally starts from 1 to 4 h after ingestion, with ~2 h being the most common. The entire reaction from start of symptom onset to clinical resolution can last 6–8 h. Although there is room for variable presentation, there does exists a prodromal sequence of events. The initial symptoms often start with abdominal cramping and nausea and closely followed by repeated and profuse emesis. The addition of diarrhea may present a few hours after onset of emesis with that average time around 5 h, but occurrence is not necessary for diagnosis. Lethargy, pallor, and hypothermia can also be seen toward the end of the attack. The most concerning and life-threatening symptoms are hypotension and shock secondary to fluid loss particularly in infants and children. It is for this reason that oral food challenges are recommended only

Table 1 Food protein-induced enterocolitis syndrome challenge dosing protocols

Protein (g)/body weight (kg)	Body weight (kg)								Maximum patient weight for 10 g protein challenge limit (kg)
	5 kg	10 kg	15 kg	20 kg	30 kg	40 kg	50 kg	60 kg	
0.6	3	6	9						16.7
0.3	1.5	3	4.5	6	9				33
0.15	0.75	1.5	2.25	3	4.5	6	7.5	9	67
0.1	0.5	1	1.5	2	3	4	5	6	100
0.06	0.3	0.6	0.9	1.2	1.8	2.4	3	3.6	167

Total protein given over 3 equal doses, with 10 g total limit

under physician supervision and often times in a hospital setting.

Diagnosis of FPIES is often done based on history alone provided there is reliable and repeated sequence of events related to a particular food antigen. This is of particular importance when life-threatening reactions have been described in the history. Oral food challenges (OFC) under supervision may be necessary when more than one food item is suspected or the history is not as clear. Given the potential for hypotension and shock, intravenous access is often recommended prior to initiating the OFC.

In some cases a comorbid IgE sensitization may be present. Skin prick testing and serum IgE testing can be useful in the identification of potential food triggers in up to 30% of cases. This mixed IgE and non-IgE presentation is sometimes referred to as atypical FPIES and is reported to be more common in those with atopy and prolonged or chronic FPIES. It is thought that atypical FPIES represents a more severe phenotype as the addition of classic IgE-mediated allergic responses compound potential life-threatening events.

Atopy patch testing has been studied for the potential of identifying food antigens in FPIES. Initially promising reports of high sensitivity (100%) and high negative predictive values (100%) have been challenged in recent years. Validation studies have reported markedly low sensitivity of 11.8% and positive predictive value (PPV) of 40% and negative predictive value of (54.5%). Specificity has been reported up to 85.7% in the same study. Studies on atopy patch testing have been relatively small with 19–25 participants, and further investigation has been suggested before routine use can be recommended.

Oral food challenges remain the gold standard for diagnosis and verification of food allergy resolution. Depending on the patients history, the quantity of protein ingested during the OFC varies (Table 1). Regardless of the quantity of protein given during a challenge, the total dose is divided into equal thirds and given 15 min apart over a 30-min period (or three doses for ~22 min apart over a 45-min period) (Nowak-Wegrzyn et al. 2009).

Those without a history of severe past reaction of hypotension and shock are generally challenged with the higher doses. Individuals with a severe past reaction are normally started at the lower dosing range (Nowak-Wegrzyn et al. 2009). The recommended maximum amount of food protein administered during a challenge has ranged from 3 to 10 g. If considering the total weight of the food, 10–20 g has been suggested as a reasonable cutoff (Manti et al. 2017). If a single-blind oral challenge is desired, a liquid or solid vehicle may be used depending on the protein source. The vehicle should be inert and of reasonable quantity (Nowak-Wegrzyn et al. 2009).

A positive oral food challenge to FPIES would include the clinical presentation described above along with some ancillary laboratory test. The onset of symptoms although normally start after 1 h is considered positive as they start as soon as 30 min after ingestion. Recommended laboratory tests are taken prior to starting a challenge and if clinical symptoms are observed or reported are repeated 6 h after initial ingestion. Table 2 outlines the most common laboratory indicators used during a challenge.

Table 2 FPIES Confirmation Laboratory Tests

Laboratory test	Positive result
Periphereral polymorphonuclear leukocytes (neutrophils)	>3500 cells/mm^3 or Increase by 5000–16,800 cells/mm^3
Fecal studies	Occult blood Leukocytes Eosinophils

Fecal studies are only warranted if diarrhea is present

Of note, fecal tests are only ordered if diarrhea is present during the time of the challenge. Otherwise only blood and serum serology is used. Methemoglobinemia has also been reported in more severe cases along with metabolic acidosis. Management during a positive FPIES challenge centers around aggressive hydration, prevention of hypotension, and shock. Administration of epinephrine by intramuscular means has a role if IgE-mediated symptoms are present. Otherwise standard hypotension interventions are the mainstay of treatment. For those with acute FPIES, complete resolution of clinical symptoms is normally within hours of ingestion. In individuals with chronic FPIES, clinical resolution may take up to 10 days.

With strict avoidance reintroduction after a negative oral food challenge is possible. The exact timing to challenge is not well described. It is recommended to wait till after 12 months of age to challenge to see if tolerance has been reached. Tolerance also tends to depend on the allergen in question. For cow's milk tolerance for majority of patients has been reported by ages 3–5. However, for those allergic to rice, only 50% are reported to be tolerant by age 5. Challenging 12–24 months after a positive OFC has been recommended.

The pathophysiology behind FPIES is thought to involve a T-cell-mediated process but is not universally agreed upon. Proinflammatory cytokines TNF-alpha and interferon-gamma have been detected in higher quantities in those with an acute FPIES episode. These cytokines are reported to increase intestinal permeability ultimately leading to fluid shifts. Reciprocally with elevated TNF-alpha and interferon-gamma, TGF-beta has been noted to be decreased. Upon resolution of FPIES and induction of tolerance, this imbalance of TNF-alpha and TGF-beta has been reported to be resolved.

26.3.3 Dietary Protein-Induced Enteropathy

Dietary protein-induced enteropathy, also known as food protein-induced enteropathy (FPE), and malabsorption syndrome present with protracted diarrhea as opposed to FPIES that presents with protracted emesis (Kuitunen et al. 1975; Nowak-Wegrzyn 2009; Sampson et al. 2014). Similar to FPIAP and FPIES, onset of presentation is often prior to 1 year of age. Cow's milk or cow's milk-based formula is the most common causative agent followed by soy (Nowak-Wegrzyn et al. 2015). The onset of symptoms can be as early as a few weeks after initial introduction of food allergen into a regular diet. For infants starting formula right after birth or shortly after, symptoms can be seen as soon as 4–8 weeks of life (Kuitunen et al. 1975; Saarinen et al. 1999). Mixed presentation of IgE-mediated sensitization has not been reported with FPE. The insidious nature of symptoms onset makes diagnosing FPE after starting solid foods more difficult.

Joining the FPIAP and FPIES, FPE's prevalence is also unknown. The onset of protracted diarrhea is more gradual than FPIES and does not carry the risk of acute life-threatening sequela. Diarrhea also need not start within so many hours after food ingestions like FPIES. Failure to thrive (FTT) is, however, a real concern in those with undiagnosed or poorly controlled FPE (Nowak-Wegrzyn 2009). It has been reported that 50% of infants with FPE succumb to FTT. Prognosis is however good with removal of food allergen. Breastfeeding or breast milk is thought to delay onset, but not prevent FPE's in infants. Multiple food antigens are known to coexist, but not often as in FPIES and FPIAP.

Confounders that make proper diagnosis of FPE revolve around similarities that the clinical presentation has with postinfectious gastroenteritis and lactose intolerance (Nowak-Wegrzyn et al. 2015). There are no laboratory tests to help confirm FPE. Secondary to the malabsorption,

nonspecific laboratory results of anemia, hypoalbuminemia, and hypoproteinemia are commonly seen, but not required for diagnosis (Nowak-Wegrzyn et al. 2015). It is recommended to have endoscopy with biopsy to help confirm FPE. This is in contrast to recommendations against routine endoscopy/colonoscopy for acute FPIES and FPIAP. Histological findings of lymphonodular hyperplasia in the duodenal bulb and intraepithelial lymphocytes >25/100 epithelial cells are characteristic of FPEs (Fontaine and Navarro 1975). The intestinal wall may or may not have erosions as well. Positive biopsy with clinical correlation and negative celiac disease is strongly supportive of an FPE's diagnosis. Of note, transient gluten sensitivities have been described (Walker-Smith 1970, 2005).

Management of FPEs involves removal of the suspected offending agent with close follow-up for apparent resolution. Reintroduction of food antigen into the diet can be done as soon as 4 weeks and at home gradually with monitoring for return of symptoms. The majority of cases will resolve after 2–3 years of eliminating of the food allergen from the diet. Repeat biopsies 1–2 years after clinical resolution has been suggested in the literature. This is due to the potential for subclinical pathology still present after apparent reintroduction and tolerance of the food allergy trigger (Iyngkaran et al. 1988; Shiner et al. 1975).

26.4 Conclusion

Non-IgE food immunological gastrointestinal diseases can be particularly hard to diagnose compared to IgE-mediated allergies. Historically cow's milk protein is the most common antigen source. In the case of FPIAP, this can include cow's milk peptides from maternal breast milk. In all cases dietary elimination and time are the only known effective treatments. Reintroduction can be fairly soon after complete abstaining from exposure but often takes months to years before tolerance is seen. Food protein-induced enterocolitis syndrome can be life-threatening, and medical supervision is required during challenges. Food protein-induced enteropathy and FPIES have been reported in older children and adults, unlike FPIAP. Currently mixed IgE and non-IgE-mediated food immunological mechanisms are described in FPIAP and FPIES, but not FPE. Endoscopies are only recommended routinely for FPE for both diagnosing and monitoring silent disease states.

26.5 Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Allergy Skin Testing
- ▶ Atopic Dermatitis
- ▶ Eosinophilic Esophagitis
- ▶ In Vitro Allergy Testing

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