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EDITORIAL

Tolerance development in non-IgE mediated food allergies: lessons from Brazil

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Allergies negatively impact quality of life, school performance and income and may be fatal.[1] Asthma affects ~10.4 % of US children.[2] Eczema/atopic dermatitis has a lifetime prevalence approaching 20 % in US children.[3] The National Academy of Medicine[4] notes that the prevalence of food allergies is rising dramatically, with the greatest increase in children.

Classification

Food allergies can be immunoglobulin E (IgE)-mediated, non-IgE mediated, or a mixture of both.[5] Non-IgE mediated food allergies include food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis (FPIAP), food protein-induced allergic enteropathy (FPE), and food protein-induced dysmotility disorders, (e.g. gastroesophageal reflux disease, colic, diarrhea and constipation). Mixed-type disease includes eosinophilic gastrointestinal disorders such as eosinophilic esophagitis (EoE).

FPIES

FPIES is a severe form of non-IgE-mediated reaction in the gastrointestinal tract to one or more specific foods that are typically presents in infants. FPIES can present as acute or chronic. In the acute form of FPIES, most patients present with repetitive projectile vomiting and /or diarrhea with dehydration, 1—4 h after the ingestion of the trigger food.

See paper by Vasconcelos et al. in pages 40—45.

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In contrast to acute FPIES, in which symptoms are more easily correlated with the culprit food, chronic FPIES presents predominantly with chronic or intermittent vomiting and/or diarrhea. In the most severe form of FPIES, nutritional deficiencies and growth faltering can be observed. The lack of a temporal relationship between the exposure to the food allergen and the onset of symptoms may influence a delay in diagnosis. Atypical FPIES describes children with FPIES who are also sensitized to the food (positive skin prick or food-specific IgE test).

FPIAP

FPIAP is a milder form of non-IgE mediated food allergy and presents mainly in infants under 1 year of age. The main characteristic is the presence of streaks or drips of blood associated with mucus in the stool in otherwise young infants with adequate growth and development. Symptoms usually start gradually between 2 and 8 weeks of age and may occur in infants who are exclusively breastfed.

FPE

FPE occurs in infants and young children and is characterized by chronic diarrhea, malabsorption with steatorrhea, and growth faltering. Diagnosis is confirmed by a small bowel biopsy in a symptomatic child, showing variable degrees of villous injury, crypt hyperplasia, and inflammation.

GERD

Gastroesophageal reflux (GER) is a physiologic phenomenon defined as the passage of any gastric contents into the

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esophagus with or without regurgitation and/or vomiting. When GER is associated with complications or troublesome symptoms, affecting the infant and family, it is referred to gastroesophageal disease (GERD). The joint European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) - North American Society for Pediatric Gastroenterology Hepatology and Nutrition guidelines on Pediatric Gastroesophageal Reflux published in 2018 suggest a trial of a cow's milk exclusion before the initiation of medication in infants < 1 year of age.[6]

EoE

EoE is a chronic type 2 (T2) immune/antigen-mediated clinicopathologic disorder characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil inflammation of the esophagus. Symptoms in infants may include food refusal, vomiting and growth faltering. The diagnosis is made by endoscopy and histological assessment demonstrating ≥ 15 eosinophils per high-power-field (eos/hpf) on esophageal biopsies.

Epidemiology

Of the ~7.5 % of children in the US with IgE-mediated food allergies, 40 % have multiple food allergies, and 42 % have experienced a severe reaction.[7] In Europe, a systematic review and meta-analysis of 93 studies concluded that the point prevalence of self-reported specific food allergies (both IgE and non-IgE mediated food allergies) were as follows: cow's milk (5.7 %, 95 % confidence interval 4.4–6.9), egg (2.4 %, 1.8–3.0), wheat (1.6 %, 0.9–2.3), soy (0.5 %, 0.3–0.7), peanut (1.5 %, 1.0–2.1), tree nuts (0.9 %, 0.6–1.2), fish (1.4 %, 0.8–2.0) and shellfish (0.4 %, 0.3–0.6). The point prevalence of specific food allergies based on oral food challenge (OFC) outcome was as follows: cow's milk (0.3 %, 0.1–0.5), egg (0.8 %, 0.5–1.2), wheat (0.1 %, 0.01–0.2), soy (0.3 %, 0.1–0.4), peanut (0.1 %, 0.0–0.2), tree nuts (0.04 %, 0.02–0.1), fish (0.02 %, 0.0–0.1) and shellfish (0.1 %, 0.0–0.2).[8]

The only and most recent data on the population prevalence of FPIES was published by Nowak–Wegrzyn et al.[9] in 2019. The survey was conducted between October 2015 and September 2016 to a sample of 53,575 US households. Families were asked: "Have you/Has your child ever been diagnosed by a physician with foodprotein–induced enterocolitis syndrome (FPIES)?" The lifetime prevalence of physician-diagnosed FPIES was reported as 0.28 % in all ages and 0.51 % in those < 18 years. In addition, a recent study from the US estimated that up to 17 % of infants may suffer from FPIAP based on pediatrician diagnosis, though this was not confirmed by an OFC.[10] Population-based studies show that up to 25 % of children up to 5 years present with GERD for 3 or more medical visits to their pediatrician,[11] making it one of the most common complaints of early childhood. EoE used to be considered a rare disease, but a recent systematic review and meta-analysis of 40 studies (34 including children) from 15 countries across the five continents have shown that the worldwide incidence in children is estimated to be 4.95 (95 % CI, 3.91–5.98) cases per 100,000 inhabitant-years).[12] Cow's milk is the most common food allergen involved in all forms of non-IgE mediated food allergies.

Risk factors

Based on an Australian population-based study, having atopic dermatitis, a family history of allergy, and being male increase the risk of developing FPIES.[13] Premature birth, admission to neonatal intensive care unit and use of cow's milk formula without any breast milk are considered significant risk factors for the development of FPIAP.[10,14] Risk factors for GERD include being born prematurely, pulmonary disorders, neurologic disorders, hiatal hernia and surgery to correct esophageal atresia.[15] Early life factors, such as pregnancy complications, admission to a neonatal intensive care unit, and antibiotic use in infancy, are associated with the development of EoE.[16] The association of risk factors for the development of FPE is unclear.

Natural history

The natural history of FPIES varies depending on the population, trigger foods, and underlying FPIES mechanisms (acute/chronic; conventional vs. atypical), but the majority of children will outgrow FPIES in later childhood. Children with atypical FPIES may outgrow it later.

FPIAP tends to resolve by 12 months of age, though FPIAP in older children has been reported. FPE is outgrown by early childhood. The natural history of EoE indicates that it is unlikely to be outgrown. Food allergy-associated GERD is usually outgrown by 12 months of age; persistent symptoms might require further evaluation.

Guidelines

To improve the diagnosis, management, treatment, and prevention of food allergy, a number of guidelines have recently been published or updated. These include the World Allergy Organization (Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA),[17] the European Academy of Allergy and Clinical Immunology (EAACI),[18] the Global Allergy and Asthma European Network (GA^{2}LEN)[19] and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines.[20]

Diagnosis

Despite the differences and sometimes overlapping manifestations highlighted between the different forms of non-IgE-mediated food allergies, the diagnostic process is uniform. There is no test that can either confirm or exclude the diagnosis, with the exception of EoE, and in some cases FPE.

The diagnosis of non-IgE-mediated food allergies is, therefore, based on the history of clinical manifestations upon consumption of the offending food. This is then followed by a period (usually 2–4 weeks) of elimination of the suspected culprit food from the diet. If the symptoms

disappear during food exclusion, the allergenic food needs to be reintroduced by OFC or home reintroduction to confirm a diagnosis. This may need to be followed by an endoscopy in the case of EoE and FPE.

The OFC or home reintroduction is considered the gold standard to diagnose FPIES, FPIAP, FPE, or food allergy-associated GERD after symptom resolution under dietary elimination. In FPIES, the OFC should be supervised in a medical setting due to the potential for severe reactions. In FPIAP, FPE, and GERD reintroduction of trigger food 2–4 or 2–8 weeks after elimination can safely be performed at home providing that the child is not sensitized to the food.

The diagnosis of EoE is confirmed when esophageal biopsies reveal a peak eosinophil count of $\geq$ 15 eosinophils/high power field (or $\geq$ 15 eosinophils/0.3 mm^2) or $>$ 60 eosinophils/ mm^2, in the absence of other causes of esophageal eosinophilia.

Management

Individualized food avoidance strategies and symptomatic treatment of symptoms are required for the management of non-IgE mediated food allergies. Attention to family quality of life and management strategies are also required. The role of a multidisciplinary team, including a dietitian in the approach of this group of patients, is of particular importance to ensure appropriate allergen avoidance, provide information on suitable replacement foods and support optimal growth and development. Information for the breastfeeding mother will include nutritional supplementation when required. For infants not being breastfed, or in need of a supplemental formula, a suitable hypoallergenic formula will be recommended. A plan of introduction of solid foods, while avoiding the culprit food allergen(s), will also be carefully developed by a dietitian. Parents and caregivers have an important role in planning management according to their ability to adhere to the recommendations.

Tolerance development

OFC and home reintroduction are crucial to assess tolerance development to the culprit food. An OFC can be conducted using FPIES protocols in the case of conventional FPIES or, IgE-mediated OFC protocols, in the case of atypical FPIES. For all other forms of mild non-IgE mediated allergies, foods can be safely introduced at home. If there is any suspicion of an IgE-mediated food allergy, sensitization status should be established prior to home introduction.

In this issue, Vasconcelos et al. report on outcomes and factors associated with tolerance in infants with non-IgE-mediated cow's milk allergy with gastrointestinal manifestations.

Among the 82 children included in the study, the median age of diagnosis with a non-IgE mediated gastro-intestinal cow's milk allergy was 30 days, and the median age prior to reintroduction/OFC was 8 months, i.e., the median age for tolerance assessment was around 9 months.

In this single-center, retrospective study, the authors showed that patients who were more likely to have a positive follow-up OFC were fed a cow's milk formula prior to initial diagnosis, and patients who were exclusively breastfed prior to initial diagnosis all passed their follow-up OFCs. Children with a positive OFC were more likely to have other food allergies, diarrhea, or acute FPIES. Children with blood in stool (FPIAP) were more likely to pass the OFC. These results fit with our understanding that children with multiple food allergies and FPIES may continue to suffer from food allergies longer than children with FPIAP. The findings about cow's milk consumption prior to initial diagnosis, as well as the role of diarrhea in prolonging food allergy, confirm findings from a Turkish study by Senocak et al.[14]

Vasconcelos et al.[21] give a novel insight into the natural history and risk factors associated with gastro-intestinal presentations of non-IgE mediated food allergies in a cohort from Brazil. Many questions remain, however, about the management of non-IgE-mediated food allergies. These are clear characteristics of the underlying pathology and biomarkers to assist with making the initial diagnosis and predicting prognosis.

Conflicts of interest

Dr. Fleischer has received research support from Aimmune Therapeutics, ARS Pharmaceuticals and DBV Technologies; serves on the advisory boards for FA & Anaphylaxis Connection Team and the National Peanut Board; has received royalties from UpToDate;, serves as a consultant to Aquestive, DBV Technologies, Genentech, and Nasus outside of the submitted work. Dr. Venter reports grants from Reckitt Benckiser, personal fees from Reckitt Benckiser, Nestle Nutrition Institute, Danone, personal fees Abbott Nutrition, and Else Nutrition, outside the submitted work. Dr. Vieira has received consultant and/or speaker fees from Danone Nutricia, Nestle Nutrition Institute, Sanofi and Aché Laboratories.

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