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FPIES: not so rare after all!

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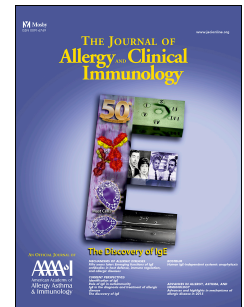
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1 Editorial re Mehr S, et al. FPIES in Australia

2 FPIES: not so rare after all!

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In the current issue of Journal of Allergy and Clinical Immunology, Mehr S et al report the results of a population-based study of food protein-induced enterocolitis syndrome (FPIES) in Australia, contributing to the knowledge on FPIES incidence and characteristics.(1)

FPIES is a non-IgE, gastrointestinal food allergic disorder that usually has an onset in infancy and is commonly triggered by cow milk, soybean and cereals (rice, oat)(2, 3) In older children and adults, FPIES to fish and shellfish has been reported. FPIES manifestations vary according to the frequency and the dose of food trigger in the diet. With intermittent exposure, acute FPIES manifests as repetitive, projectile vomiting, lethargy, and pallor within 1-4 hours following food ingestion. When the food is ingested on a regular basis (e.g. daily), chronic FPIES manifests as intermittent but progressive watery diarrhea, emesis and poor weight gain. Unlike other non-IgE gastrointestinal food allergic disorders (e.g., food protein-induced allergic proctocolitis and enteropathy), FPIES can be a medical emergency because up to 15% of the acute reactions present with hypotension and may progress to hypovolemic shock. (4) The prevalence of FPIES is unknown; while it has been traditionally considered to be a very rare food allergic disorder, the steadily increasing peer-reviewed reports and activity of the patient communities reflective of the burden of FPIES, point towards a possible increase in prevalence over the past 1-2 decades.

There is limited epidemiologic information available regarding FPIES. FPIES was only recognized and formally defined in the mid 1970's. Diagnostic code for FPIES

(K52.2) was implemented for the first time in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) in October 2015. The pathophysiology of FPIES remains obscure and no diagnostic biomarkers are available. The diagnosis of FPIES relies on the recognition of a typical symptom pattern (FIG 1) and if necessary, supervised oral food challenges which are considered to be a high-risk procedure. Potential cases may be misdiagnosed as more common pediatric illnesses, such as gastroenteritis or sepsis. For all the above reasons, FPIES does not lend itself easily to epidemiologic studies.

To date, Katz et al is the only published prospective population-based birth cohort, reporting a cumulative incidence of cow milk (CM)-FPIES of 3 per 1000 newborns born at a single hospital in Israel over 2 years (0.34%). (5) All of the cases of CM-FPIES had an onset by age 6 months and were confirmed by a physician-supervised oral food challenge. In the same cohort, there were 0.5% infants with IgE-mediated allergy to CM, suggesting that infantile CM-FPIES is much more common and may have a higher health impact than previously appreciated.

Mehr et al took an innovative approach to studying FPIES. (1) They utilized an existing national Australian Pediatric Surveillance Unit that provides monthly reports from 1400 involved pediatricians, estimated to represent at least 50% of all eligible pediatricians in Australia. They have provided the pediatricians with a standardized case definition of acute FPIES (consistent with current consensus diagnostic criteria, FIG 1) and collected monthly reports of new cases of acute FPIES in children younger than 2 years old. They identified a total of 230 infants with

FPIES, giving an estimated incidence 15.4/100,000/year. Rice has been identified as the single most common food causing acute FPIES in Australia, which differs from the US, where CM is the most common food trigger and rice is the most common solid food trigger, potentially underscoring environmental, food introduction patterns or genetic differences. The median (interquartile range) age of the first FPIES reaction to cow milk was younger, 3.0 months (2.0-5.0) vs. rice 5.5 months (5.0-6.0), in agreement with prior reports. (6, 7)

Mehr et al also identified early onset (5 months) and reactions to fruits and vegetables as risk factors for multiple food-FPIES, which helps focus attention on a select group of infants who need the most support with solid food introduction. Additional interesting observations pertain to the low incidence of acute FPIES during breastfeeding (approximately 5%) and atypical FPIES defined as IgE positivity to the FPIES trigger that was documented in overall 6% of the cases, 28% of egg-FPIES and 8% of CM-FPIES. (6, 7)

The obvious limitation of the study is a lack of confirmation of FPIES by oral food challenges, the gold standard for diagnosis. However, the strict case definition is in line with currently accepted criteria for diagnosis of acute FPIES based on a constellation of symptoms and is likely to capture most relevant cases (FIG 1). (2)

The estimate of acute FPIES incidence is higher than estimates of pediatric eosinophilic esophagitis (prevalence 8.9/100,000/year) and Crohn's disease in children younger than 2 years (2.01/100,000/year) in Australia. (8, 9) However, it is possible that the incidence of FPIES is underestimated due to the methodological

limitations of the voluntary reporting system and potentially not all mild cases presenting to the pediatrician. It remains to be determined how the Australian data compare to other countries, because Australia has one of the highest rates of food allergy and eczema in the world. (8) Compared to study by Katz et al, which reported cumulative incidence of challenge-proven IgE-mediated CM-IgE- allergy as 0.5% and CM-FPIES as 0.34%, Mehr et al reported approximately 20-fold lower incidence of FPIES from any food. A recent Australian study of IgE-mediated food allergy reported that 5.6% of 12 month-old infants were sensitized to CM (no food challenges done), suggesting that IgE-mediated CM allergy may be higher than in Israel. It is certainly possible that there are major differences in the incidence and the pathophysiology of food allergy (IgE versus non-IgE, specific food triggers) among different countries reflecting dietary, genetic and other factors. However, this big difference points towards the need for further studies in various patient populations to accurately identify the incidence of FPIES.

The study also has not addressed the incidence of chronic FPIES, although it is widely accepted that acute FPIES currently represents the majority of the FPIES cases. This may be due to the wide availability of the hypoallergenic infant formulas for infants with chronic gastrointestinal manifestations, some of which might have progressed to chronic FPIES if feedings with intact CM protein have been continued. In addition, the definition of chronic FPIES is not as well established as acute FPIES and diagnosis of chronic FPIES requires confirmation by an oral food challenge.

The paper by Mehr et al represents an important step towards describing the burden of FPIES and provides a rationale for future studies. Comparable to IgE-mediated food allergy, FPIES is associated with a negative impact on the caregiver quality of life, increased financial costs to the families, and high risk of feeding difficulties, especially in infants with early-onset of multiple-food FPIES.(2, 10) While the majority of the patients have a favorable prognosis and experience resolution of FPIES usually by 3-5 years of age, a subset has persistent FPIES into adolescence and adulthood, emphasizing the need to better define the pathophysiology of FPIES and to develop immunomodulatory strategies to accelerate resolution.

Recently, an important resource for providers caring for patients with FPIES has become available. (2) The first international FPIES consensus guidelines (available as an open access) provide revised criteria for diagnosis of FPIES (FIG 1) and very practical advice regarding dietary avoidance of FPIES triggers, managing acute reactions, introducing complementary foods, and reintroducing foods that have caused FPIES reactions.

In summary, FPIES is not rare and health providers need to be familiar with its manifestations, diagnostic criteria and management principles. Additional studies are necessary to fully estimate the prevalence of acute and chronic FPIES in other populations and its impact on the patients and their families.

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Legend

Fig 1 Diagnostic criteria for acute FPIES (ICD10-K52.2)

The diagnosis of acute FPIES requires that a patient meets the major criterion and at least 3 minor criteria. (ref # 2) If only a single episode has occurred, a diagnostic oral food challenge should be strongly considered to confirm the diagnosis, especially since viral gastroenteritis is so common in this age group. Further, while not a criteria for diagnosis, it is important to recognize that acute FPIES reactions will typically completely resolve over a matter of hours, compared to the usual several day time course of gastroenteritis. The patient should be asymptomatic and growing normally when the offending food is eliminated from the diet.

1 Major criterion



>3 Minor criteria

Vomiting in 1-4 hrs
& absence of skin
and respiratory sx's

>1 episode to the same food

Repetitive emesis to another food

Lethargy

Pallor

Emergency room visit

Need for intravenous fluids

Diarrhea in 24 hours (5-10 hours)

Hypotension

Hypothermia