Received: 1 February 2021 | Revised: 1 March 2021 | Accepted: 4 March 2021

DOI: 10.1111/cea.13894

RESEARCH LETTER

WILEY

Children with acute food protein-induced enterocolitis syndrome from Spain and Italy usually tolerate all other food groups

Acute food protein-induced enterocolitis syndrome ('FPIES') is a potentially severe type of non-IgE-mediated food allergy affecting mainly infants usually when foods are introduced.[1] Acute FPIES triggered by multiple unrelated foods ('multiple food FPIES') has been reported in up to two thirds of patients, particularly in the USA.[2,3] FPIES reactions are often traumatic experiences for parents, and weaning leads to significant anxiety, as there is no test to identify safe new foods. This has led to complex weaning recommendations in children with FPIES in an attempt to support parents.[4] However, evidence suggests that multiple food FPIES is rare in other regions, such as Southern Europe,[5,6] which questions the applicability of such weaning advice in this population. Studies including a detailed dietary history in children with FPIES are lacking.

We aimed to describe the prevalence of multiple food FPIES and other food allergies in a large cohort of children with acute FPIES from Spain and Italy.

Children taking part in the BIO-FPIES research project in 12 tertiary centres were screened for this study. Inclusion criteria were as follows: a) Children (0–18 years) on specialist follow-up for acute FPIES at least to one food; plus b) acute FPIES diagnosis at onset confirmed by meeting the diagnostic criteria by Lee[7] and/or Nowak-Wegrzyn[1]; plus c) no evidence of FPIES resolution to the culprit food(s) at the time of the dietary assessment. A detailed dietary history was taken at screening for all foods/food groups, which were classified as follows: cow's milk, egg, soya, grains (wheat/gluten, rice, corn), vegetables, fruits, meat and poultry, fish, shellfish, nuts, seeds, legumes. The specific food(s) causing acute FPIES within the above-mentioned food groups were also recorded. For each patient, the dietary assessment outcome for each food/food group was recorded as follows: (a) 'tolerance' if eating age-appropriate portions regularly, (b) 'no previous exposure' if food never tried, (c) 'acute FPIES' as per diagnostic criteria above, (d) 'IgE-mediated food allergy'(ie immediate typical skin, respiratory, gastrointestinal or cardiovascular symptoms within 2 h of ingestion plus positive specific IgE in serum or skin prick test to the implicated food) or e) 'non-IgE-mediated food allergy other than acute FPIES' (including chronic FPIES, allergic proctocolitis, food protein-induced enteropathy, other gastrointestinal food allergy or food protein-induced atopic dermatitis). Children with an incomplete dietary history were excluded. Descriptive data were analysed. Qualitative variables were presented as percentages, quantitative variables as mean/standard deviation when normally distributed, and median/interquartile range (IQR) when not normally distributed. Concomitant food allergies in children with FPIES to different food groups were compared using chi-square test. A p value below 0.05 was considered statistically significant. PASW Statistics 27 (SPSS Inc.) was used. Informed consent was obtained from parents and/or guardians. The study was approved by the Santiago-Lugo Research Ethics Committee, Spain (reference: BIO-FPIES, 2017/396).

We screened 196 children for the present study. We excluded seven children due to not meeting FPIES diagnostic criteria, and 10 due to an incomplete dietary history, leading to 179 children included. Mean age at onset of the index acute FPIES reaction was 9 months (IQR: 7–11), and 59% were male. Mean age when the dietary assessment took place was 42 months (IQR: 28–75). Further patients' clinical characteristics are presented in Table S1.

The culprit foods/food groups triggering acute FPIES reactions were fish (102/179, 57%), egg (35/179, 19.5%), cow's milk (28/179, 15.6%), meat/poultry (5/179, 2.8%), rice (4/179, 2.2%), shellfish (4/179, 2.2%), vegetables (4/179, 2.2%), wheat (3/179, 1.7%), fruits (2/179, 1.2%), legumes (3/179, 1.7%) and soya (1/179, 0.6%). Thirty-nine different foods (including a wide range of fish species) caused acute FPIES reactions (see supplemental text for full list).

The outcome of the full dietary assessment for each participant is shown in Figure 1. Most children (153/179, 85.5%) had FPIES to a single food/food group with no evidence of other food allergies. Most of them (95/179, 53.1%) had tried all other food groups, whilst some children (58/179, 32.4%) had not tried some, mainly shellfish, soya, nuts or seeds, generally due to family dietary habits/preference. Multiple food FPIES was detected in 11/179 children (6.1%). Only one out of 28 children with FPIES to cow's milk (3.6%) also had FPIES to soya. Children with acute FPIES to grains (7/179) reacted to a single grain and had no concomitant food allergies. All patients with acute FPIES to legumes, fruits, vegetables, meat/poultry

and grains could tolerate most other foods within their culprit food group. Out of the 102 children experiencing acute FPIES to fish, 41% had reacted to more than one fish species and 78/102 (76%) were avoiding all fish.

Concomitant food allergies other than acute FPIES were detected in 18/179 (10%) children (see Table S2), mainly IgE-mediated food allergy to a range of foods—mainly egg (8/179), nuts (7/179) and fruits (4/179). Only two children had other non-IgE-mediated food allergies (allergic proctocolitis to egg and food protein-induced enteropathy to soya, respectively). No cases of chronic FPIES, food protein-induced atopic dermatitis or other gastrointestinal food allergies were detected. See Figure 2 for food allergy associations in the entire cohort.

We analysed the potential association between having acute FPIES to certain food groups and having other concomitant food allergies (see Table S3). In patients with acute FPIES to the most commonly involved foods (fish, egg and cow's milk, named 'group A'), multiple food FPIES or having allergy to any other food was uncommon (9/162, 5.5% and 23/162, 14.2%, respectively). In the minority of children ('group B') with acute FPIES to fruits, vegetables, legumes (including soya), meat/poultry and shellfish, these rates were higher (8/16, 50% and 10/16, 62.5%, respectively, $p < 0.00001$ for both group A vs B comparisons, chi-square test). No differences were found between groups A and B regarding any of the clinical characteristics in Table S1 (data not shown).

To our knowledge, this is the first large cohort of children with acute FPIES providing a detailed dietary history to assess multiple food FPIES and concomitant food allergies. In our series from Spain and Italy, 85% of children have single food FPIES and they tolerate all other food groups. A minority develops multiple food FPIES (6.1%) or food allergies other than FPIES (10%)—mainly IgE-mediated food allergy with a similar rate to that seen in the general paediatric population in Europe.[8] This is in line with other European series reporting multiple food FPIES and IgE-mediated food allergy in less than 15% and 5% of children with acute FPIES, respectively.[5,6] In this context, unrestricted weaning advice seems appropriate for most children with acute FPIES in our region, and particularly those with FPIES to fish, egg and cow's milk, who account for nearly 90% in ours and other European series. This allows for faster expansion of solid food variety that increases dietary diversity, which in turn may have a positive impact on the microbiome with an associated immunomodulatory effect.[9] Most importantly, it allows for taste and texture expansion, essential for the prevention of feeding difficulties.[10] Differential pathophysiological mechanisms might explain the lack of clear association between FPIES and IgE-mediated food allergy.

Our findings contrast with US series observing multiple food FPIES is 35–69% of cases [2,3,11] and IgE-mediated food allergy in up to 39%.[11] We observed further differences regarding the coexistence of FPIES to soya and cow's milk, reported in 43%–64% of cow's milk FPIES cases in US series [2,11,12] but rare (3%) in ours. Whilst fish is rare, grains are the leading cause of FPIES in Australia and some recent US series,[2,3,7] with significant rates of multiple food FPIES. In contrast, FPIES to grains was rare in our series (4%) and involved a single grain with no other associated food allergies. These observations reinforce the geographical differences seen in FPIES phenotypes across the globe, which highlights the need to individualize weaning advice according to the regional context.

FPIES to fruits and vegetables has been associated with multiple food FPIES in two cohorts from Australia and US.[2,7] This

Key Messages

- Acute FPIES in children from Spain and Italy is vastly caused by a single food (fish/egg/cow's milk) with no associated food allergies.
- Unrestricted weaning advice seems appropriate in most patients in this context.
- Geographical particularities regarding culprit foods should be considered when developing weaning guidelines in FPIES.

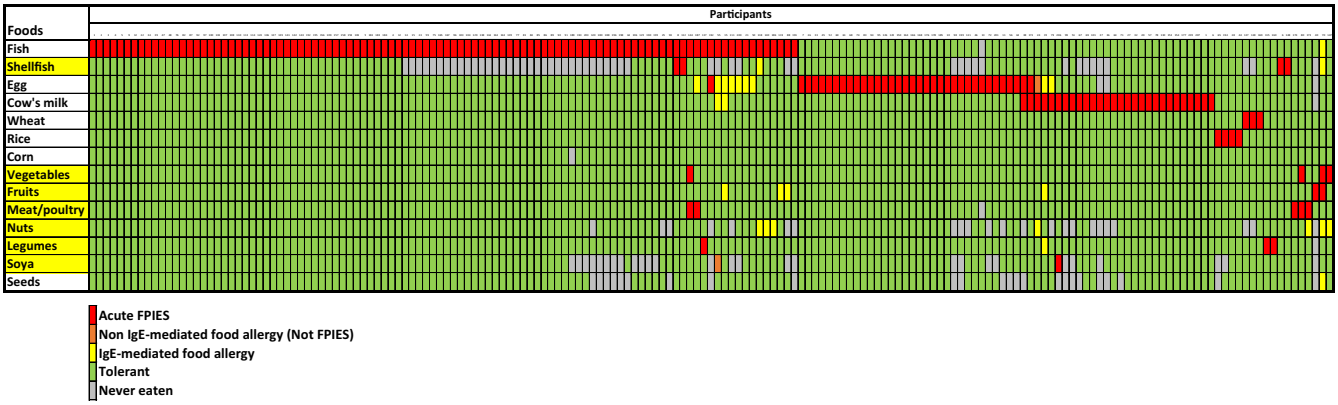

FIGURE 1 Outcome of the full dietary assessment for each individual participant in a cohort if 179 children with acute FPIES. Colour code: red (acute FPIES), orange (non-IgE-mediated food allergy other than acute FPIES), yellow (IgE-mediated food allergy) and green (tolerant), grey: never eaten. FPIES, food protein-induced enterocolitis syndrome

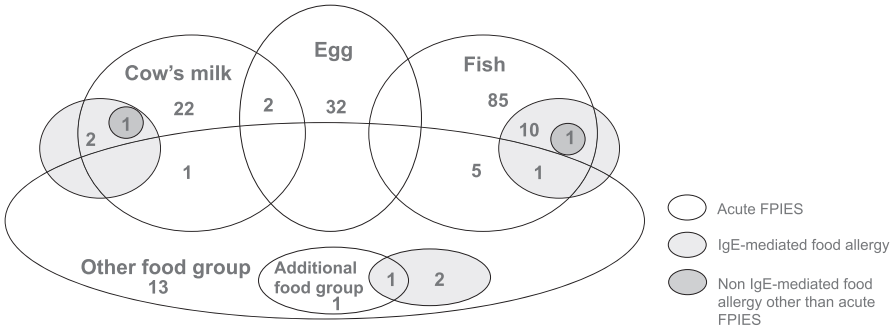

FIGURE 2 Venn diagram representing the association with acute FPIES to other food groups and other types of food allergy in children with acute FPIES to fish, egg, cow's milk and other foods (*n* = 179). White ovals indicate acute FPIES to the indicated food, light grey ovals indicate IgE-mediated food allergy, and dark grey ovals indicate non-IgE-mediated food allergy other than acute FPIES. FPIES, food protein-induced enterocolitis syndrome

seems to also apply to our series, and more careful and supported weaning would be required in these cases. Further research is needed to provide more specific evidence-based weaning advice in FPIES, given our limited sample size, the wide range of foods and mechanisms observed and the lack of a biomarker to predict tolerance.

In summary, acute FPIES in children from Spain and Italy is vastly caused by a single food (fish/egg/cow's milk) with no other associated food allergies. Unrestricted weaning advice seems appropriate in most patients in this context. Geographical particularities should be considered when developing weaning guidelines in FPIES.

ACKNOWLEDGEMENTS

We would like to thank all the clinicians, nurses, researchers and laboratory technicians within the Bio-FPIES network for their contribution to this study (J Herberg, M Kaforou, A Garcia-Moral, MV Moreno, L Mayorga, MM Fernandez-Rivas, S Quevedo, V O'Valle, N Hernandez, L De la Hoz Gil, JD Moure, A Salas-Ellacuriaga, J Gomez-Rial, C Blasco, A Figueroa, G Mangone, Laura Pisano, Silvia Boscia, G Liccioli, A Fiocchi, V Pecora, F Di Stasio). We would also like to thank Dr Nandinee Patel, Imperial College London, for her contribution to the figure in this manuscript. The BIO-FPIES study network has received research funds from the Strategic Health Action, 'Instituto de Salud Carlos III' (ref: PI19/00497), Spain, the Spanish Society of Paediatric Allergy, Asthma and Clinical Immunology (SEICAP research grant 2018), Spanish Society of Allergy and Clinical Immunology (SEAIC research grant 2018) and the FPIES Foundation, USA.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare in relation to this manuscript.

AUTHOR CONTRIBUTION

MVO and RJB designed the study. AM, TB, LE, AP, TG, LV, PGP, CGM, EG, IC, SVC, FM, SB, SA, MP and LA implemented the research and collected the data. MVO analysed the results, and MVO, LA and SI drafted the manuscript. All authors commented on the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.