

LETTER TO THE EDITOR

Oral food challenge with a mixture of 'at risk' foods in children with FPIES

To the Editor,

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy (FA), characterized by repeated vomiting, pallor, lethargy, and rarely hypotension, after 1–4 h of ingestion of culprit food (1). The cornerstone of the management of FPIES is the elimination of the culprit food from the patient's diet. In addition, it has been proposed (2) to avoid also other foods, which are considered 'at risk', if the patient has never ingested them yet. For children with cow's milk (CM) FPIES in the 1st year of life, it has been suggested to avoid soy and consider the delay in introduction of solid foods. For children with solid foods FPIES, it has been suggested to introduce CM, legumes, cereals, and poultry after the completion of the first year of life (2, 3). This suggestion was based on the observation of a prevalence of about 30–60% of children with multiple foods FPIES in US case series (4, 5). However, in other countries, the prevalence of multiple foods FPIES is much lower (6–8), in our experience it is 2%. Therefore, in the geographic areas where the probability of multiple foods FPIES is low, it may not be appropriate to suggest the elimination from the diet of other foods in addition to the culprit food. More recently, Nowak-Węgrzyn et al. (9) modified Sicherer's proposal (2). They suggested for children with solid foods FPIES to avoid grains, legumes, and poultry before 6 months of age and consider, after 6 months of age, their introduction through an oral food challenge (OFC) or at home, at treating physician's discretion. For children with CM FPIES between 6 and 12 months of age, Nowak-Węgrzyn et al. (9) suggested to consider introduction of grains, legumes, and poultry, if not previously tried, through OFC or at home at treating physician's discretion. So, if the doctor was to choose to perform OFC, the child should have been admitted to hospital several times with costs for the family and the healthcare system.

We propose to perform an OFC with a mixture of foods that are considered 'at risk' (legumes, cereals, poultry) not yet introduced into the diet of children younger than 1 year. Making an OFC with a mixture saves a considerable number of hospital admissions than carrying out an OFC for each food. Of course, there is the risk that the child fails this OFC and that it is necessary to repeat an OFC for each food. This risk should be negligible in countries where the prevalence of multiple foods FPIES is low. In this study, therefore, we evaluated the probability of adverse reaction following an OFC with mixture of 'at risk' foods in a population of Italian children with acute FPIES, almost all CM FPIES.

All patients between the ages of 4 and 11 months who presented, between 01 October 2013 and 30 September 2015, at pediatric allergy unit of Agostino Gemelli hospital in Rome with a diagnosis of acute FPIES, set by an OFC or based on a

history of at least two typical episodes (1), were eligible. Exclusion criteria were as follows: (i) previous ingestion of all 'at risk' foods (legumes, cereals, poultry) without adverse reaction; (ii) chronic diseases or chronic therapies conditioning the immune response; and (iii) the lack of consent to participate in the study.

Enrolled children performed skin prick test (SPT) with legumes (lentils, beans, soybeans, peas), cereals (wheat, rice), and chicken, if not yet introduced into the diet, and with histamine and negative control (Lofarma, Milan, Italy). The SPTs were performed according to internationally standardized methodology (10) with commercial extracts (Lofarma, Milan, Italy) if available and always by prick by prick (PbP) with the cooked food. All children performed an OFC with a mixture of 'at risk' foods not yet introduced into the diet. The mixture was composed as follows: half a tablespoon of lentils (about 1 g of protein), half a tablespoon of beans (about 1 g of protein), one teaspoon of soybeans (about 2 g of protein), half a tablespoon of peas (about 1 g of protein), two teaspoons of wheat (about 1 g of protein), three teaspoons of rice (about 1 g of protein), and 15 g of chicken meat (about 3.5 g of protein). The amount of proteins for each food was established trying to balance the usually suggested range for FPIES (0.06–0.6 g/kg) with a final volume of the mixture suitable to be eaten by the little patient. If a patient had already eaten one or more of the 'at risk' foods, these were not tested. All foods were steamed and smoothies. The patients ate the mixture in a single dose, and then, they were observed for 4 h. The patients who passed the OFC with the mixture were contacted by telephone after 3 months. We asked them whether they had eaten all the food included in the mixture and whether they had presented any adverse reaction.

To calculate sample size, we considered a prevalence of 50% of multiple FPIES in USA case studies, and we compared it with our experience, in which the prevalence of multiple FPIES is equal to 2%. Considering an alpha error of 0.05 and a beta error equal to 0.20, 12 individuals were needed. The program 'Statistics for biomedical disciplines' of Stanton A. Glanz has been used. The study was approved by the ethics committee of the hospital.

Fourteen patients (six males, eight females) with diagnosis of CM FPIES (13 children) and wheat FPIES (one child) were enrolled. The first episode of acute FPIES has occurred at an average age of 3.8 months, while the definitive diagnosis of FPIES (made in 6/14 by OFC) was formulated at an average age of 6.9 months. Considering all the reactions ever presented by the 14 patients after the ingestion of culprit food, both at home (as reported by parents) and during OFC, the mean number of vomits was 4.6, pallor was present in 75% of cases, lethargy in 75%, diarrhea in 28%. In one case, during an OFC, hypotension was registered.

The patients performed SPT and the OFC with the mixture at a mean age of 7.8 months. All patients had negative SPT and passed the OFC with the mixture. Tested foods were liberalized in the diet of all 14 patients. At phone follow-up after 3 months, patients reported they had eaten all tested foods several times, without ever presenting adverse reactions.

Multiple foods FPIES is much less common in some countries, that is, Italy, Israel, and Australia (6–8), than in the USA (4, 5). These differences are only partially explained by the different eating habits, and it is assumed that multiple genetic and environmental factors are involved (11). The preventive diet (2, 9) therefore does not seem to be justified in countries with low prevalence of multiple foods FPIES.

Our study showed a 100% of tolerance of 'at risk' foods, and all 14 children passed mixture OFC. Although in many cases the adverse reaction does not occur upon the first introduction of the offending food (12), our patients liberalized all tested foods in their diet without presenting any adverse reaction even in a 3-month follow-up.

Multiple FPIES are more common with solid foods than with milk (12); therefore, the fact that our series is composed by 13/14 CM FPIES decreases clinical relevance of our results and their transferability. This happened because solid foods FPIES tends to appear at a later age (12), so almost all our patients with solid foods FPIES had already eaten all the 'at risk' foods without any problem.

We did not test fish, although it is the solid food most frequently culprit of FPIES in Italy (13), because we meant to test foods which are considered 'at risk' in the international literature, and mostly because in our experience, only 5% of children with fish FPIES presented episodes of acute FPIES with other foods.

In conclusion, to perform an OFC with a mixture of 'at risk' foods for children with acute FPIES is a convenient and safe practice in countries where the prevalence of multiple foods FPIES is low. This procedure can avoid unnecessary elimination diet.

To date, we believe prudent to test 'at risk' foods by OFC before authorizing the free ingestion at home. Nevertheless, considering the complexity of the challenge procedure for FPIES, this suggestion may be realized only for infants with very severe episode of FPIES or for those who live in countries where medical facilities are not readily available, at least in countries with low prevalence of multiple foods FPIES.

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