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A multicentre retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes

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Abstract

Background Food Protein-Induced Enterocolitis Syndrome (FPIES) is a non-IgE-mediated paediatric disorder triggered by the ingestion of specific food proteins. Many features of this syndrome are not yet well defined.

Objective The aim of our study was to describe demographic features, causative agents, clinical features, treatments and outcomes of children suffering from acute FPIES at three Italian of Pediatric Allergy Centers.

Methods A retrospective study was performed over a 7-year period (2004–2010). Hospital medical record databases and hospital outpatient electronic charts were screened for the diagnosis of FPIES. Information on the first and subsequent FPIES' episodes was collected.

Results We diagnosed 66 children with FPIES. The number of diagnoses significantly increased between 2008 and 2010 ($P < 0.001$). We collected a total of 165 FPIES episodes (median per child 2, range 1–10). Cow's milk was the most common trigger food (65%), followed by fish, egg, rice, soy, corn, poultry and goat's milk. Fifty-six (85%) children reacted to a single food. Mean documented time from ingestion to symptom onset was 2.4 h (SD 0.7 h). Vomiting was the most common symptom (98%). Among patients diagnosed with OFC, 78% reacted after eating a whole serving size of the trigger food per age. Skin prick tests (SPT) for trigger foods were negative in 97% of cases. Thirty-two/66 children (48%) achieved tolerance at a mean age of 29 months (SD 17 months). Age of achieved tolerance for cow's milk was significantly lower compared to that of other foods (24 ± 8 vs. 53 ± 17 months, $P < 0.0006$).

Conclusion and Clinical Relevance This article provides new insights on FPIES in Italy by describing its largest series, and shows how a significant increase in the FPIES diagnosis has been observed in the last few years. We also discussed selected management aspects of this syndrome where different phenotypes can be found.

Keywords cow's milk allergy, food allergy, food protein-induced enterocolitis syndrome, oral food challenge

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Introduction

Food Protein-Induced Enterocolitis Syndrome (FPIES) is a non-IgE-mediated food allergy that typically occurs within the 9th month of life. Children show symptoms 2–6 h after ingesting a trigger food, with profuse vomiting, pallor, lethargy and diarrhoea (1, 2). These features are not disease-specific, therefore FPIES is often misdiagnosed and treated as sepsis, metabolic disorders,

severe gastroenteritis or surgical abdominal emergencies.

FPIES is a cell-mediated food hypersensitivity. Some studies suggest that tumour necrosis factor alpha (TNF- α) is involved. A relative lack of expression in transforming growth factor-beta (TGF- β) may also be implicated. An increase in IL-4 and a decrease in IFN- γ expression have been described after a positive challenge in a child with rice FPIES, whereas an increase in

IL-10 in the same patient was demonstrated 6 months after tolerance was achieved (3).

Over the past few years, the number of reports about FPIES has increased, and new trigger foods such as rice, poultry, egg, grains, vegetables, fruit and peanuts have been described (2). Nevertheless, less than 300 cases have been reported so far in literature and the biggest series includes 44 children (4). There is still a lack of knowledge about the syndrome and its epidemiology, clinical characteristics, therapeutic options and outcomes.

In this study, we have aimed at reporting the clinical features of 66 Italian children with FPIES. The demographic features, causative agents, clinical features, managements and outcomes of these patients were collected in three Italian Pediatric Allergology Centers and subsequently described. We have also compared our findings with those found in literature to improve the clinical knowledge of FPIES.

Patient and methods

A retrospective study was performed over a 7-year period (2004–2010). All children diagnosed with FPIES at three Italian Pediatric Allergy Centers (University of Sacred Heart Agostino Gemelli in Rome, Fatebenefratelli Hospital of Benevento and Anna Meyer Children's Hospital of Florence) were enrolled. Cases of FPIES were selected from the hospitals' medical record databases, using the International Classification of Diseases Ninth Revision (ICD-9) code for allergic gastroenteritis and colitis (code 558.3), and from a selection of the hospitals' outpatient electronic charts. Information on the first and subsequent FPIES episodes was collected.

Enrolled children were self-referred in 60% cases, referred by a General Pediatrician in 30% cases and referred by a General Practitioner (GP) in 10% cases.

Diagnosis was based on Powell's criteria published in 1986 (5) and updated by Sicherer *et al.* in 1998 (6).

After FPIES was suspected by a Pediatric Allergy Specialist, diagnostic OFC was performed in a hospital setting within 4 weeks after a suspicion of FPIES was stated. While waiting for OFC, all children were prescribed a trigger food-free diet. At the Allergy Center of Rome, after the 2008, the diagnostic OFC was avoided in those patients with a history of two or more FPIES typical reactions; a diagnosis was stated at the Outpatients Clinic and a trigger food-free diet was prescribed.

All Centers modified Powell's OFC guidelines (5) and only 17% of patients, all enrolled at the Center of Benevento, underwent OFC with an intravenous line in place from the beginning of the test. In this Center, the OFC protocol was as follows: 0.4 g/kg of protein divided into three equal doses were administered over 3 h; if no adverse reaction occurred over the following 4 h, a whole meal of trigger food was given and clinical

observation lasted for another 2 h. In Florence, a dose of food equal to 25% of the serving size per age was given, followed by a 4-h clinical observation; then a dose equal to 50% of the serving size per age was given, followed by another 4-h clinical observation; finally, the whole meal was given the day after, followed by a 4-h clinical observation. In Rome, a dose of food equal to 50% of the serving size per age was given, followed by a 2-h clinical observation; then a second dose equal to 100% of the serving size per age was given, followed by 4-h clinical observation. Only in Florence, Sicherer's (7) dietary suggestions were given to children with FPIES, unless they were already eating those foods without adverse reactions.

Skin prick tests (SPT) were performed in all children using commercial allergen extracts (Lofarma, Milan, Italy) and fresh food.

Data were analyzed at University of Sacred Heart Agostino Gemelli in Rome using the Prism software version 5.00 (GraphPad, San Diego, CA, USA). All statistical tests were two tailed using 0.05 level of significance. Data were expressed as mean values $\pm$ standard deviation, unless otherwise stated.

The study was approved by all the hospitals' ethics committees.

Results

Population

We found 66 children with FPIES between January 2004 and December 2010. We screened 5234 Outpatients' electronic charts searching the key words 'FPIES', 'Allergic Enterocolitis', 'Food Allergy', 'Cow's Milk Allergy', 'Egg Allergy', 'Fish Allergy', 'Soy Allergy', 'Rice Allergy'- and 250 medical records from the hospitals' databases using the International Classification of Diseases Ninth Revision (ICD-9) code for Allergic Gastroenteritis and Colitis (code 558.3). Over the study period, 346 new diagnoses of paediatric food allergy were made at the three Italian Centers, therefore it is possible to estimate a FPIES prevalence of approximately 19% (66/346). Population characteristics are summarized in Table 1.

Thirty-five children (53%) were diagnosed after a positive OFC, a suggestive clinical history and negative SPT for FPIES trigger foods (except one case with weakly positive SPT). Challenge foods included cow's milk (n 24), fish (n 4), rice (n 2), egg (n 2), chicken (n 2) and corn (n 1). Median time to the onset of reactions was 2 h (range 0.5–4) (Fig. 1). Intravenous fluid resuscitation and/or steroids were administered in 15/35 (43%) cases: 2/18 in Rome – of which one also received i.m. epinephrine; none received any treatment after 2008, 7/11 in Florence and 6/6 in Benevento. Symptoms and symptom evolution shown after OFC were

Table 1. Population characteristics

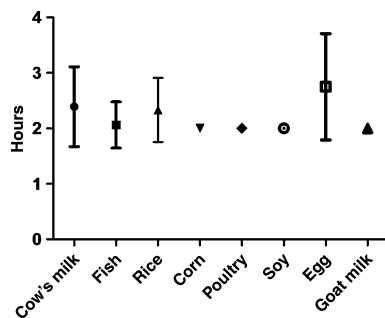
Male No. (%)	40 (61)		
No. Episodes of FPIES	165		
Atopic dermatitis, No. (%)	6 (9)		
Positive atopic family history, No. (%)	13 (20)		
Breastfed, No. (%)	63 (95)		
Duration of breastfeeding in months, median and range	4 (0.5–12)		
	All patients (No. 66)	OFC patients* (No. 35)	No-OFC patients† (No. 31)
No. of FPIES episodes before diagnosis, median (range)	2 (1–10)	2 (1–10)	2 (1–6)
Age (months) at first FPIES episode, mean $\pm$ SD	5.7 $\pm$ 5.1	4.6 $\pm$ 3.4	7 $\pm$ 6.5
Age (months) at FPIES diagnosis, mean $\pm$ SD	14.1 $\pm$ 14	11.2 $\pm$ 9.5‡	17 $\pm$ 17.5‡

*diagnosed after OFC;

†diagnosed without OFC;

‡ $P = \text{NS}$.

FPIES, Food protein-induced enterocolitis syndrome.

Fig. 1. Time from trigger food exposure to symptom onset (hour, mean $\pm$ SD).

similar in the three Centers, independently from how severe the previous FPIES episodes were, and which OFC protocol was chosen. In all children, the symptoms subsided within 6–12 h (data not shown).

Thirty-one children (47%) were diagnosed without diagnostic OFC. They all fulfilled the first four of Powell's criteria. Twenty-eight of them had a typical clinical history consisting of two or more episodes. Two were diagnosed by the Allergy Specialist even if having had only one FPIES episode because they had severe symptoms, i.e. collapse, requiring fluid resuscitation and further hospitalization (Table 2). Diagnostic OFC was commenced, but never completed due to a child's refusal to eat in one case.

FPIES diagnosis significantly increased in 2008 (Fig. 2). This increase was observed mostly in Rome (Tables 2 and 3), where the diagnostic strategy was only partially modified (see Methods section). After 2008, the number of new diagnoses remained somewhat stable.

Foods

Cow's milk was the most common trigger food, followed by fish and egg (Table 4). Fifty-six (85%) chil-

Table 2. Characteristics of 12 patients diagnosed in Rome in 2008 (if hospitalization, no OFC was performed due to severity of reaction)

Pt No.	No. prediagnosis reactions	Diagnostic OFC
Pt 1	3	No
Pt 2	2	No
Pt 3	2	No
Pt 4	4	No
Pt 5	4	No
Pt 6	1	Yes
Pt 7	3	No
Pt 8	2	No
Pt 9	1	Yes
Pt 10	2	Hospitalization
Pt 11	1	Hospitalization
Pt 12	1	Hospitalization

dren reacted to a single food. No child had reactions to both cow's milk and soy (Table 5).

Eight children resulted with fish FPIES, three of whom with multiple fish FPIES (Table 6). When tested for tolerance to other fish types, three were tolerant to different fish types, eaten during an OFC within 4 weeks from the last FPIES reaction (Table 6). The other five children refused to undergo OFC with fish other than the trigger one.

Overall, 44 (67%) children reacted to cow's milk vs. 22 (33%) who reacted to foods other than milk. The mean age of children with cow's milk FPIES is significantly lower than the one of children with FPIES triggered by other foods (3.5 ± 2.4 vs. 10.6 ± 6.7 months, $P < 0.0001$) (Fig. 3).

SPT for trigger foods were performed in all children and resulted negative in 97% cases. In two patients with cow's milk FPIES, the prick-by-prick with fresh milk resulted weakly positive (4 and 3 mm), whereas the prick-with -allergen extracts (casein, beta-lactoglobulin and alpha-lattoalbumine) were negative. In

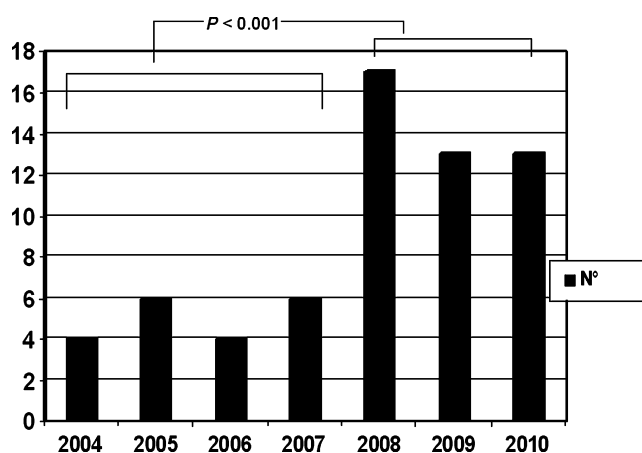


Fig. 2. Distribution of food protein-induced enterocolitis syndrome diagnosis over 7 years.

Table 3. Patients per year per center and relative number of diagnostic OFC performed

Year	Rome		Florence		Benevento	
	No. FPIES	OFC	No. FPIES	OFC	No. FPIES	OFC
2004	4	4	0	0	0	0
2005	1	0	0	0	3	0
2006	2	1	2	2	2	0
2007	2	2	2	2	2	1
2008	12	2	3	2	2	2
2009	9	5	5	3	2	2
2010	7	2	4	2	2	1
Total	37	18	16	11	13	6

FPIES, Food protein-induced enterocolitis syndrome.

Table 4. First food protein-induced enterocolitis syndrome episode to trigger foods

Food	No. of children (%)	Mean No. prediagnosis reactions
Cow's milk	44 (67)	2.7
Fish	8 (12)	2.8
Egg	4 (6)	2.5
Rice	3 (4)	3
Soy	3 (4)	2
Poultry	2 (3)	4
Goat's milk	1 (2)	1
Corn	1 (2)	1

these two children, FPIES later shifted into an IgE-mediated allergy, described elsewhere (8). The IgE serum levels for trigger foods were tested in 25 patients and were negative in all. Personal patient histories for IgE-mediated food allergies were negative in all, but 1/66 patient, who had a kiwi allergy.

Table 5. Multiple food protein-induced enterocolitis syndrome to trigger foods (to note that primary trigger food is reported as first)

Trigger foods (No. of patients)
Cow's milk & wheat (2)
rice (1)
fish (1)
banana (1)
banana and tomato (1)
Rice & corn (2)
Poultry & fish (2)

Table 6. Fish food protein-induced enterocolitis syndrome (to note that primary trigger fish is reported as first)

Trigger fish (No. of patients)	Tolerated fish after OFC
Codfish (4)	Not tested
& sole (1)	Salmon, swordfish
& sea bream and salmon (1)	Not tested
Sole (1)	Codfish, tuna
& trout (1)	Sea bream, codfish, perch

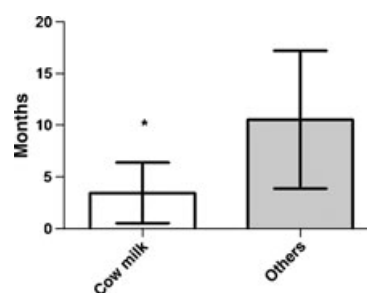


Fig. 3. Age at food protein-induced enterocolitis syndrome presentation (months, mean $\pm$ SD).

Clinical features

We collected a total of 165 FPIES episodes. Median pre-diagnosis episodes were two (range 1–10) (Tables 1 and 4; Fig. 4). The mean number of pre-diagnosis reactions per child did not vary over the years (data not shown). Mean time from trigger food ingestion to symptom onset was 2.4 h (SD 0.7 h) and there was no significant difference between trigger food reaction times (Fig. 1). Repeated vomiting was the most common clinical feature (Table 7); it was present in all patients except one who had isolate diarrhoea. This patient had a history of two episodes and was diagnosed after a diagnostic OFC performed within 2 months from the last episode. Seventeen/36 (47%) patients with diarrhoea and 8/30 (27%) patients without it were hospitalized and received i.v. fluids ($P = \text{ns}$). Pallor and hypotension/lethargy never occurred alone. Repeated vomiting was isolated in six cases.

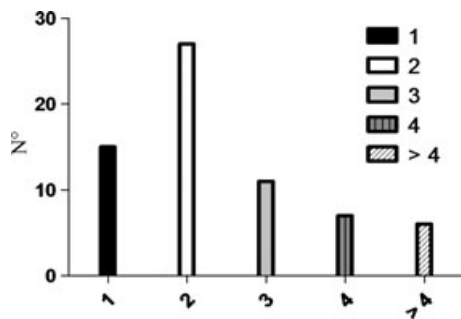


Fig. 4. Number of food protein-induced enterocolitis syndrome episodes before diagnosis.

Table 7. Food protein-induced enterocolitis syndrome (FPIES) symptoms

FPIES symptoms	No.	%
Vomit	65	98
Pallor	53	80
Hypotension	51	77
Diarrhoea	36	54

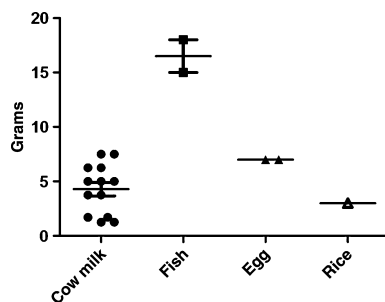


Fig. 5. Grams of food proteins triggering reactions at diagnostic OFC (grams of proteins, mean $\pm$ SD).

The range of threshold doses, expressed as estimated grams of protein, to different foods in those who reacted to the challenge, was available only in the Rome Center and is shown in Fig. 5.

Outcomes

Among all 66 children, 39 (59%) underwent OFC after 12 months from the last FPIES episode to verify if tolerance to trigger food was achieved. Fourteen did not perform it because: (a) five children patients did not complete the 12 month cycle, (b) parents of eight patients refused it and (c) one OFC was not completed because of the child's insufficient compliance. Nine had already started introducing the causative food at home without previous OFC. Four children were lost at

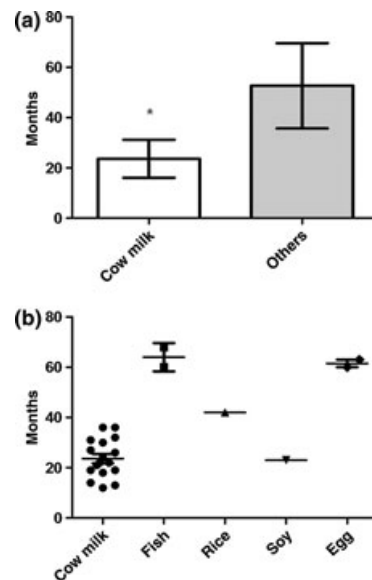


Fig. 6. (a) Age at achieved tolerance (months, mean $\pm$ SD). (b) Age at achieved tolerance (months, mean $\pm$ SD) per trigger food.

follow-up. Among the 39 who performed OFC, 23 (59%) tolerated the trigger food. Sixteen were not yet tolerant. Challenge foods included: cow's milk (n 31), fish (n 3), egg (n 2), soy (n 2) and rice (n 1); tolerance was achieved, respectively, in 17, 2, 2, 1 and 1. All nine children who reintroduced the trigger food at home under no medical supervision tolerated it. Foods reintroduced at home were cow's milk (4), fish (2), rice (1), corn (1) and poultry (1). These foods were reintroduced by parents after a median of 20 months from the last reaction (range 19–24 months). Overall, 32/66 (48%) children achieved tolerance, 23 demonstrated tolerance with an OFC, nine demonstrated tolerance at home under parents' own decision, initiative and control. The mean tolerance age of the group undergoing an OFC and of the group who reintroduced the food at home was 29.3 months and 37.5 respectively ($P = \text{ns}$). The achieving tolerance age of the cow's milk group was significantly lower compared to that of all other patients (24 ± 8 vs. 53 ± 17 months, $P < 0.0006$) (Figs 6a and b). Cow's milk FPIES tends to last less than the others (20 ± 5 vs. 42 ± 10 months, $P = 0.001$).

Discussion

Current knowledge of FPIES is based on the publication of a few hundred cases; 3 years ago Nowak-Węgrzyn et al. (2) counted about 200 patients. Before our series was published, the largest were those by Mehr (9) and Katz (4). Mehr et al. (9) reported about 35 FPIES, and described that rice was the most frequent solid trigger food and hypothermia was associated with more severe symptoms. Later, Katz et al. (4) published 44 cases,

prospectively enrolled and more recently cited in two reviews by Caubet (10) and Leonard (11). Our series is the largest at present, counting 66 cases that, added to those previously published (4, 9), make it possible to have a good amount of new data and to discuss epidemiology, clinical aspects and FPIES management.

Some of the findings in our study are similar to those in literature. Indeed, in our study, we found that there was a delay in FPIES diagnoses in Italy, as well as in Australia (9). We also found that the mean number of pre-diagnosis reactions per child did not change over the years (data not shown). Nowak-Wegrzyn et al. (2) hypothesized that this could be due to clinicians' low index of FPIES suspicions and a lack of specific confirmatory tests. In fact, FPIES diagnosis is clinical, and neither the atopy patch test (12, 13) nor other tests have a relevant, positive or negative predictive value for this syndrome.

We found an increase in diagnoses between 2008 and 2010, similarly to what was described in Australia between 2004 and 2007 (9). The Allergy Center of Rome was the institute where the number of diagnoses increased the most. FPIES here went up from two in 2007 to 12 in 2008 (see Tables 2 and 3). Since 2008, in line with diagnostic procedures suggested by other authors (4, 9), in Rome, an OFC was not performed on children with ≥ 2 typical FPIES reactions. All 12 patients in 2008, but two had ≥ 2 FPIES episodes or a positive OFC (see Table 2), whereas two children had one severe FPIES episode requiring hospitalization. We would suggest that this increase in FPIES diagnosis was due to clinicians' spread of knowledge and increased awareness of the syndrome. However, we consider that the FPIES awareness has increased among allergy specialists only, as children were usually self-referred or came from the Emergency Department and were rarely referred by GP or general paediatricians (14). We also consider that, at least in Italy, FPIES in the past was considered a pure gastrointestinal disease, named as an 'intolerance' to a trigger food and managed by Pediatric Gastroenterologists (15). Only recently, it has been clearly recognized as a separate entity from other food intolerances and managed by allergists.

Our study also underlined some differences with previously published works. With regard to diagnostic FPIES' OFC, it is suggested (2) to gradually increase (over 1 h) the food protein intake, so to give 0.06–0.6 g/kg of food protein; if no reaction occurs within 2–3 h, it is allowed to administer a normal serving size per age of food, followed by a few hours of clinical observation. Katz et al. (4) and Zapatero et al. (13) have instead followed an OFC that was similar to the one for IgE-mediated food allergies. They started with a low food protein dose, 5 mL of cow's milk or the eighth portion of a normal serving size of fish per age, and

increased this dose every 20–30 min until they reached a normal serving size per age. In our study, cases were collected in three Pediatric Allergy Centers, and three different OFC protocols were adopted. The protocol adopted in Florence was the most prudent, but required considerable input regarding time and human resources. Choosing the most appropriate diagnostic OFC protocol is complex; in fact, a variety of protocol is reported in literature because of FPIES reaction features themselves. First of all, to know the smallest FPIES symptom trigger dose is difficult, as the onset of FPIES symptoms is always delayed. Patients can eat a whole meal before there is an onset of reactions, and it is not yet known if the same reactions would have occurred even after eating small doses of trigger foods. In our study, we have documented that most patients (14/18 [78%]) diagnosed in the Centre of Rome with OFC reacted after eating a whole meal (i.e. 200 mL cow's milk, a whole egg, 100 g fish; see Fig. 6). In line with our findings, Katz et al. (4) reported that most of their patients (15/28 [53.6%]) tolerated 121 mL or more of milk before showing FPIES symptoms. Regarding treatments, intravenous fluid resuscitation and steroids were administered in 15/35 (43%) diagnostic OFC. As three different OFC protocols were adopted in this study, we compared medical practices. In the Centre of Rome, therapies were administered more rarely, never beyond 2008, despite the audacity of OFC protocol. Moreover, in Rome, we had no increase in post-OFC hospitalizations and most children were successfully treated with clinical observations only – with no intravenous line in place. Katz et al. (4) also reported that all reactions during OFC were successfully treated with oral rehydration without hospitalization, and that there wasn't any case of significant hypotension, although intravenous access, oxygen delivery, vital-sign monitoring equipment and other resuscitation equipment were readily available. Zapatero et al. (13) as well reported that only 3/9 patients with failed OFC required emergency treatment, and that the other six patients clinically improved with oral hydration only. After all, we would suggest personalizing FPIES diagnostic OFC protocols: (a) in those cases with a history of mild/moderate reactions and in children above 4 years of age, who are very likely tolerant, a normal serving size amount per age could be given at once without an intravenous line in place; (b) in those cases with a history of severe reactions, OFC protocol should be prudent, doses administered over 2 days with an intravenous line in place.

Many authors prefer avoiding performing diagnostic OFC; Katz et al. (4) performed it in 63.6% of children (which is the highest percentage ever published), we did it in 53%. One of the reasons for avoiding diagnostic OFC, in our opinion, is the diagnostic FPIES delay. Most

children have various episodes before diagnosis and it is unlikely that parents of a child who has already had two or more severe episodes would consent to perform it. In fact, it has already been suggested (2, 11) not to perform confirmatory challenges in those children with a typical history who became asymptomatic after an elimination diet. The open question is if it would be possible to avoid diagnostic OFC with a history of one severe episode only. Mehr et al. (9) and Katz et al. (4) avoided OFC in few of their cases. However, we do not have enough data to suggest either this or the other practice, therefore we would suggest avoiding diagnostic OFC only in the presence of a history of at least two episodes of typical FPIES.

A special situation can be the presence of IgE for the trigger food – atypical FPIES (2). In our population, two patients with cow's milk FPIES had weakly positive (4 and 3 mm) prick-by-prick, whereas prick-with-allergen extracts (casein, beta-lactoglobulin and alpha-lactalbumin) were negative. In these two cases, a form of immediate cow's milk hypersensitivity developed 1 year after FPIES diagnosis (8). Katz et al. (4) and Kessel et al. (17) reported a similar evolution in eight and three cases respectively. As also suggested by Israeli authors (4), in these cases, we would suggest following OFC guidelines for IgE-mediated food allergy. Therefore, testing specific IgE for trigger food is compulsory before performing OFC in FPIES.

Whether or not to judge a diagnostic OFC positive is still a matter of debate. Nowak-Węgrzyn et al. (2) considered it positive in the presence of at least three of the following criteria: vomiting, diarrhoea, increased neutrophil and/or eosinophils count in the stool, increased neutrophils count in the blood, increased leucocytes count in the gastric juices. In our series, diarrhoea was present in only about 50% of the cases, and in others (4, 9, 13) even in a lower percentage. Therefore, if the above advice (2) is followed, stools, gastric juices or blood tests would be needed to make a diagnosis. On the contrary, and in agreement with Katz et al. (4), we think that repeated vomiting accompanied by pallor and lethargy are adequate and sufficient clinical tips to consider an OFC as positive for FPIES. As a matter of fact, when we issue the diagnosis of FPIES solely on the basis of a suggestive history, we never have laboratory exams to base the diagnosis on.

If diagnostic OFC can be avoided in selected cases, performing it to test tolerance is compulsory. Nowak-Węgrzyn et al. (2) reported that 60% cow's milk FPIES resolved within 2 years. Katz et al. (4) were more encouraging, as 75% (27/36) patients with cow's milk FPIES recovered by the age of 18 months. Hwang et al. (16) reported that cow's milk and soy FPIES resolved by the age of 20 and 14 months respectively. In our study, we performed a tolerance OFC 1 year after the last

FPIES reaction. Children (63%) with cow's milk FPIES achieved tolerance at the age of 18–24 months. Therefore, we would suggest performing a tolerance OFC for cow's milk at 18 months of age. The age for achieving tolerance to other foods, especially fish and egg, is significantly higher than for cow's milk (around 53 months), because solid foods are introduced later in life, but also because solid food FPIES itself lasts longer (Figs 6a and b). Unfortunately, not enough data are available in this study and in literature to further discuss solid trigger foods.

In our series, cow's milk was the most common trigger food, followed by fish. Cow's milk was also the most frequently involved in a series from the USA, followed by soy, whereas rice was more common in another series from Australia. Fish is mentioned only in our series and in one published by Zapatero et al. (13) in 2005, who justified this data by stating that Spain holds second place among European Union's fish consumers, and that fish is usually introduced in Spanish infants' diets before 1 year of age. In Italy, fish is also introduced in the diet and at an early age, but this can be said for rice as well. Nevertheless, we have not found a high number of rice FPIES, and therefore we do not think that these differences in trigger foods among countries can be satisfactorily explained by different dietary habits. We think, in line with Katz et al. (4), that various phenotypes of FPIES exist in the world, and that this could be why different trigger foods are involved, as well as why there is such a different prevalence of allergic family histories, a different prevalence of single-food FPIES and different needs of drug use due to the wide spectrum of reactions' severity. FPIES phenotypes could also be explained by country-specific baseline differences regarding a wide range of factors that are hypothesized to play a role in the development of a food allergy, including obstetrical practices and pre- and post-natal environmental exposures, as stated in the 2011 EuroPrevall birth cohort study (18).

Interestingly, three of eight children who reacted to one or more fish, tolerated other fish (see Table 6). It is well known that cross-reactivity between fish is not absolute in IgE-mediated allergies (19), and therefore it is possible that a child with fish FPIES does not necessarily have to exclude all fish from the diet, which, on the contrary is usually suggested.

In our series, we did not observe patients with both cow's milk and soy FPIES. Burks et al. (20) and Sicherer et al. (21) showed instead that most children enrolled in their series with cow's milk FPIES reacted to soy, and were therefore prescribed both cow's milk-free and a soy-free diet. Nowak-Węgrzyn et al. (2) also pointed out that concomitant cow's milk and soy FPIES occurred in over 60% of cases, and that extensively

hydrolyzed casein formulas should be recommended for infants that cannot be breastfed. But larger series (4, 9) did not show similar results. Katz et al. (4) reported that 35/44 of their cow's milk FPIES were taking soymilk at the time of formal diagnosis, and that out of the remaining nine, five went to soymilk after a negative OFC with this food. Mehr et al. (9) did not have a single patient with both cow's milk and soy FPIES, just as in our series. Therefore, we would suggest that soymilk can be offered as alternative to cow's milk in a child over 6 months of age who cannot be breastfed, as long as an OFC in hospital setting has been passed.

Regarding the so-called 'extended dietary restrictions' published by Sicherer (7) – particularly advisable in those infants with solid food FPIES, who might be more likely to react to different foods and benefit from avoiding grains, legumes and poultry, they were given to patients only at the Center in Florence. Nevertheless, we did not see an increase in multiple-food FPIES at the Centers in Rome and Benevento, but, paradoxically, multiple FPIES were only seen in the Center where restrictions were prescribed. Katz et al. (4) and Mehr et al. (9) did not describe details on dietetic restrictions in their published series. Katz et al. (4) only reported that none of the patients with cow's milk FPIES had FPIES to any other solid foods, as well as what is shown in the series from South Korea (16) and Spain (13). We would therefore suggest avoiding prescribing dietary restrictions, and to perform an OFC in hospital setting for foods considered to be at higher risk of adverse reactions, such as cow's milk, cereals, legumes and poultry, only in infants over 6 months of age with solid food FPIES.

In summary, we found 66 new FPIES for which diagnoses were quite delayed. Diagnoses significantly increased between 2008 and 2010. After analyzing these patients' data, we would suggest personalizing FPIES' OFC protocols, and more specifically: (a) giving a normal serving size per age for each trigger food at

once without an i.v. line in place to those children with mild/moderate reactions and to those above 4 years of age; (b) administering the trigger food in small doses over 2 days with an i.v. line in place to those patients with severe reactions; (c) not performing confirmatory OFC in those children with at least two episodes of typical FPIES in their personal medical history; (d) considering repeated vomiting accompanied by pallor and lethargy, an adequate and sufficient clinical tip for FPIES diagnosis; (e) generally avoiding prescribing extended dietary restrictions, and performing an OFC in a hospital setting for foods considered as giving more adverse reactions, such as cow's milk, cereals, legumes and poultry, only in infants over 6 months of age with solid food FPIES; (f) testing specific IgE for the trigger food before performing tolerance OFC to exclude that FPIES shifted into an IgE-mediated allergy; (g) performing tolerance OFC for cow's milk at around 18 months of age.

Conclusions

Thanks to this new series and to the recently published literature (4, 9), FPIES management has been discussed and specific modifications have been proposed. Diagnostic criteria, OFC protocols, dietary restrictions and follow-up timings should be based on the new concept that various FPIES phenotypes can exist. Nevertheless, FPIES still needs to be studied further, and a collective review of its management would be desirable. To do so, with the cooperation of the Italian Association of Paediatric Allergists (APAL, www.apalweb.it), we have set up an online database opened to all Italian Pediatric Allergists, that we hope will be the first step to an international database on FPIES.

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