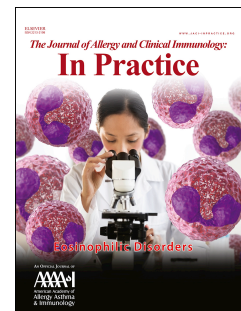


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Different patterns of foods triggering FPIES in Germany

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Abstract**Background**

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated gastrointestinal food allergy mainly affecting infants and young children. Allergic FPIES reactions differ from IgE-mediated food allergies, e.g. regarding elicitors and clinical course.

Objective

The aim of our study was to describe causative agents and development of tolerance in German children with FPIES.

Methods

We conducted a retrospective survey on children with FPIES from 14 centers in Germany assessing a 6 years period.

Results

We analyzed 142 patients with 190 FPIES reactions, 130 of which met acute FPIES criteria, and 60 defined as chronic FPIES. The most frequent eliciting food for acute FPIES was cow's milk, followed by fish, vegetables (eg. potato, pumpkin), meats (eg. beef), grains. 119 children reacted to one food only, 16 children to 2 or 3 foods, and 7 children to ≥ 4 foods. In chronic FPIES, all but 4 exclusively breastfed infants reacted to cow's milk feeding. IgE-sensitization to the triggering food was found in 21/152 (14%) cases. Two children developed additional IgE-mediated symptoms upon food challenge. Time to proof of tolerance was shortest in cow's milk-induced FPIES, and it was shorter in chronic than in acute FPIES.

Conclusion

In our national survey, we identified triggers for acute FPIES that partially differ from those reported internationally. Mainly foods introduced early in infant nutrition triggered acute reactions. Time to proven tolerance was shown to be contingent on FPIES symptomatology, and on the triggering food. These data should be considered regarding nutritional advice for infants with FPIES.

Highlights box

What is already known about this topic?

Food protein-induced enterocolitis syndrome (FPIES) is a rare disease presenting with protracted vomiting after ingestion of triggering foods. Severe reactions may lead to shock. Milk, soy, rice and fish are the most frequent elicitors worldwide.

What does this article add to our knowledge?

Besides cow's milk and fish, we identified beef, poultry, rice and potatoes as most frequent FPIES triggers in Germany. Development of tolerance is shorter in chronic than in acute FPIES, and differs between triggering foods.

How does this study impact current management guidelines?

Guidelines on the introduction of complementary foods in infants with FPIES should be based on data from regional studies, as different dietary habits in different countries may lead to different characteristics of FPIES.

Keywords: FPIES, children, Germany, food protein-induced enterocolitis syndrome, food allergy, tolerance development, IgE, triggering foods

98 **Abbreviations:** FPIES – Food protein-induced enterocolitis syndrome

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Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a rare non-IgE-mediated food allergy, which has been increasingly well described and understood since the 1980s. The majority of affected patients are infants and young children presenting with repetitive vomiting 1-4 hours following the ingestion of an offending food. Symptoms may include pallor, lethargy, and diarrhea, and, if severe, can lead to severe, life-threatening circulatory collapse.

In 2017, diagnostic criteria for acute FPIES and recommendations for diagnosis of chronic FPIES were published by an international consensus workgroup (1). The features of chronic FPIES are non-specific, can include intermittent or progressive vomiting, diarrhea, failure to thrive, or resemble a sepsis-like condition. Symptoms usually present in the first weeks of life when infants are regularly fed with the triggering food, usually cow's milk or soy formula, and occasionally breast milk.

Epidemiological data on FPIES are limited. In Australia, a population-based study reported the estimated incidence of FPIES to be 15.4/100.000 per year in infants up to age 2 years (2). Two birth cohorts from Israel and Spain found incidences for cow's milk FPIES of 0.34% and 0.7%, respectively (3,4).

Milk and soy are the most frequently reported food triggers in acute FPIES. Of the large number of solid foods reported to cause acute FPIES, fish and rice are the most common triggers followed by other grains, poultry, egg, vegetables, fruits and meat. In recent years, an increasing number of published case reports and multicenter studies showed that food triggers vary according to geographic location and dietary and weaning habits. Ruffner et al. (5) and Blackman et al. (6) published the largest series of children in the United States and found cow's milk, soy and rice (5), and rice, cow's milk and vegetables (6), respectively to be

the most frequent triggers. An Australian population-based study cohort reported rice, cow's milk and egg as main triggers (2). In Spain the most frequent FPIES-triggers were cow's milk followed by fish and egg (7). Italy (8) and the United Kingdom (9) showed similar triggers with fish following milk, while in Greece, fish was the most common trigger, followed by cow's milk and rice (10). There are no published data concerning FPIES-triggers in Germany. As the frequency of triggering foods are different in various countries, most probably depending on the local dietary habits, we aimed to identify relevant triggers of FPIES in German children in order to provide relevant feeding advice to families. Furthermore, we aimed to gather information about the development of tolerance, depending on the food, the existence of IgE-mediated sensitization, and the clinical characteristics of the disease.

Methods

A retrospective study was performed over a 6-year period (2014-2020). All members of the Food Allergy Working Group of the German Society of Pediatric Allergology (GPA) were invited to participate in the study in the beginning of 2019, and to contribute their cases. Data on patients having been presented to the hospital or outpatient clinic with the diagnosis of acute or chronic FPIES based on the criteria published in the international consensus guidelines (1) were included. The diagnosis of acute FPIES was made when patients showed repetitive vomiting 1-4 hours after ingestion of a suspected food in absence of classic IgE-mediated allergic skin or respiratory symptoms and met 3 or more minor criteria. All patients had multiple reactions to their first allergen before a diagnosis was made. Challenges to confirm the diagnosis were

not usually performed. If patients reacted to further triggers, usually only one reaction occurred because the patients avoided the allergen in the further course.

All patients with chronic FPIES were admitted to a hospital with signs of a severe disease with chronic vomiting, diarrhea and dehydration. The children improved rapidly with elimination of cow's milk or breast milk. Infectious diseases and other possible triggers of the symptoms were thoroughly investigated and excluded. Not all parents consented to prompt challenges to confirm the diagnosis. Thus, the diagnosis of chronic FPIES remained presumptive in some children. No patient with a mild form of chronic FPIES was included and doubtful cases were excluded from the analysis.

Data were drawn from the patient record, anonymized, and sent to the analysts (SG, LL). We collected numerous data including gender, age at reaction, clinical symptoms, suspected food triggers, skin prick test, specific IgE to the suspected food (ImmunoCAP, Phadia, Freiburg, Germany), age at the time of oral food challenge (if applicable), result of oral food challenge (including cumulative dose of food at reaction, time to reaction and clinical picture), and age at tolerance.

Food challenges were performed according to the national guidelines (11) on an inpatient basis. The majority of the food challenges were performed to determine whether FPIES had been outgrown. Depending on the presence of IgE-mediated sensitization to the culprit food, a 3- or 7-step open food challenge was planned. Patients presenting with positive specific IgE or skin prick test underwent a 7-step challenge according to the PRACTALL-guidelines (12). For the 3-step challenge, the meal (an age-appropriate serving) was divided in 3 parts: 10%, 30%, and 60% of the total serving. The 3 doses were consecutively fed in 90 to 180 min intervals, depending on the patients' individual reaction time in previous

reactions. The outcome of the challenge was assessed according to the international guidelines (1). Re-challenges were conducted at different time intervals, depending on the assessment of the pediatrician. The study was approved by the local ethic committee of the medical association of North Rhine-Westfalia.

Statistics

Statistical analysis was carried out using R (R System for Statistical Computing, version 3.6.1). Categorical variables are described by absolute and relative frequencies; continuous variables are described by median and range. Kaplan-Meier survival curves were used to estimate the time to tolerance after reaction; log-rank tests were performed for associated group comparisons.

Results

We included data from 142 children from 14 sites in Germany. Forty-four percent were female. The patients had had 190 reactions to different foods. Of these, 130 reactions met the criteria for acute FPIES, 60 for chronic FPIES. The median age for the first reaction in acute FPIES was 8.0 months (range, 1 - 50 months), whereas for chronic FPIES it was 1.0 month (range, 0 – 6 months). The children were followed for a median period of 12 months (range, 0 – 108 months).

Elicitors

Main eliciting foods of an acute reaction were cow's milk and fish, followed by vegetables, meat, and grains (Figure 1). Reactions to fish were mainly triggered by salmon. In the group of meat-allergic patients, the main trigger was beef, followed by poultry and pork. Potato, pumpkin, and carrot were the most common triggering vegetables. Rice and wheat together were the most common triggering grains (Table 1).

In 56/60 (93%) children suffering from chronic FPIES, cow's milk was the triggering food. There were four cases of chronic FPIES in exclusively breastfed infants. In one of these children we assumed cow's milk protein passed through breast milk to be the trigger, as the child reacted to cow's milk in a challenge after 10 months. A few ($n=4$; 6.7%) of the children having presented with chronic FPIES developed symptoms of acute FPIES to a different food later.

Looking at the whole cohort, reactions to only one food was observed in 119 patients, to 2 or 3 foods in 16 patients, and to 4 or more foods in 7 patients. In patients reacting to more than one food, one child reacted only to food from the same food group (grains), 9 to foods from the same group and an additional group, and 13 to foods from different groups.

Some children developed reactions to related allergens. Of 22 patients reacting to meat, 4 reacted to more than one type of meat and 6 additionally to fish. Five children reacted to beef and cow's milk and 2 children to related vegetables. One child reacted to 3 different cabbage varieties (red cabbage, cauliflower, and turnip cabbage). Another child reacted to courgette and pumpkin, 2 members of the cucurbit family.

Looking at all children reacting to cow's milk (chronic and acute), 10 % (9/88 children) had additional reactions to solid foods, whereas in children who had their first reaction to a solid food, 25.9% (14/54 children) later reacted to other solids.

Timing of symptoms

In children suffering from acute FPIES the median time interval between food ingestion and reaction was 2 hours (range 0.5-5 hours). There was no significant difference concerning the reaction interval looking at different food groups ($p=0.07$).

Sensitization

In 152/190 cases, IgE-mediated sensitization to the culprit food was tested, with a positive result in 14% (21/152 foods) either by skin prick test or food-specific IgE at any time of the study. Sensitization to milk was demonstrated in 15 children, to egg in 3 children, to wheat in 2 children, and to banana in 1 child. Ten of the sensitized children were diagnosed with chronic FPIES, 11 with acute FPIES. Subsequent tests showed that 5 of the sensitized children developed a sensitization in the course of time after an initially negative test, whereas 4 children lost sensitization.

Challenge results and factors influencing tolerance

One hundred and sixteen oral food challenges were done in 100 children. The median age at challenge was 17 months (range 2 – 104 months). In 49% ($n=57$), the challenge was judged as positive, in 49% ($n=57$) negative, and in 2 challenges the outcome was not documented. In the 3 step challenges, reactions occurred after the first dose (10% of the challenge meal) in 41%, after the second dose (cumulative 40%) in 41%, and after the last dose (cumulative 100%) in 18%.

Because of an existing sensitization, 12 of the 116 challenges were performed in a 7-step approach. A switch of symptoms from typical FPIES to urticaria and angioedema as symptoms of an IgE-mediated reaction during the food challenge was observed in 2 patients. One of these had additional FPIES-typical symptoms after 3 hours with pallor and vomiting appearing to be a combined IgE-mediated and FPIES reaction.

The age of tolerance to the offending food was known in 70% (133/190 foods). In 30% (57/190 foods) either the challenges were positive or no challenge was done until the end of the observational time. Children suffering from acute FPIES achieved tolerance at median age of 19.5 months (range 7 - 120 months), whereas children with diagnosis of chronic FPIES achieved tolerance at 16.5 months (range 4 - 39 months). Estimating the time to proof of tolerance using Kaplan-Meier-analysis yielded a significant difference between the two groups ($p < 0.0001$, Figure 2).

With regard to each particular food trigger, we found that patients allergic to cow's milk were significantly earlier tolerant than other patients ($p < 0.0001$, Figure 3). IgE-mediated sensitization against the offending food did not influence the probability of tolerance development (Figure 4).

We also analyzed, whether children reacting to more than one food had a delayed tolerance development. For this, we compared the time to tolerance for milk in patients with only milk as trigger or with milk and additional triggers (Figure 5). In fact, children with multiple triggers achieved tolerance to milk earlier than the children only reacting to milk ($p = 0.039$). This result may have been influenced by the allergist's decision of when challenge was performed and by the small number of patients.

Discussion

Our study presents the largest data set from a European population consisting of 142 children that presented with 60 reactions of chronic and 130 reactions of acute FPIES. The main aim of our study was to provide information about the triggering foods of FPIES in Germany in order to give parents advice about how to introduce new foods in children with FPIES depending on their individual risk. Many parents are worried to introduce new foods after their children have had a first reaction. Furthermore, it is well known that children suffering from FPIES to multiple foods may develop feeding difficulties due to food aversion (13). The early introduction of a broad variety of food textures and tastes can prevent feeding difficulties (14).

The international guideline suggests a list for selecting weaning foods in infants with FPIES with low, moderate, and high risk for eliciting an FPIES-reaction (1). This list is based on data mainly derived from populations observed in the US and Australia. With more studies from other countries being published, it has become obvious that the frequency of varying elicitors differs, possibly depending on local dietary habits of the population. Studies from different countries identified cow's milk as the most or second most frequent eliciting food for both acute and chronic FPIES (2-10, 13,15). According to our data, the same applies to Germany. All cases of chronic FPIES, except 4 cases of exclusive breastfeeding, were induced by cow's milk. In one of the 4 breast-milk induced reactions, cow's milk could be identified as the presumed triggering food through a positive cow's milk food challenge at the age of one year. Similar cases of FPIES induced by cow's milk proteins passed through breast milk have already been described by Sopo et al. and Baldo et al. (16,17), but it seems

to be very rare in general. Cow's milk protein in the maternal diet is probably the most important trigger for breast-milk induced FPIES. Therefore, in exclusively breastfed infants with moderate chronic FPIES, a cow's milk-free diet for the mother is a possible treatment approach.

Comparing our results to the published consensus guidelines and reviews that deal with the introduction of complementary foods in patients with FPIES (1,18), there are interesting aspects that need to be addressed. As in other European countries (7-10,19), we identified fish as the most frequent solid food trigger for acute FPIES in Germany. According to the German weaning guidelines (20), fish is an integral part of the early infants' diet.

Furthermore potatoes, pumpkins, and carrots are the first vegetables introduced to infants and beef and chicken are the first meats. These foods are found to be the most frequent triggers in Germany in contrast to other countries where weaning recommendations are different (21). This may be one possible explanation for different frequencies of solid food triggers in different countries. It can be speculated that foods that are introduced first have a higher risk of triggering FPIES. Thus, timing could be another risk factor in addition to the allergenic potential of food proteins. A first indication for this assumption was provided by the EAT study (22), in which some children developed FPIES to egg after early introduction.

The same was recently shown in a study that found evidence that early introduction of peanut leads to increased rates of FPIES to peanut (23). Further studies should examine the relationship between the exact timing of introduction of complementary foods and the development of FPIES. The international guidelines categorize beef, pumpkins, carrots, and potatoes as foods with low or moderate risk, whereas eggs and soy as high-risk foods. This categorization does not apply for German children according to our results. Following these

considerations, lists with low- or high-risk foods are debatable and risk assessment of foods should be more adapted to feeding habits in different countries.

We made several new observations concerning reaction patterns in our patients. In patients with chronic FPIES only 4 children (6,7%) had further reactions during introduction of complementary foods. Second, of the 23 children with multiple food triggers 22 reacted to foods from different groups (*e.g. milk, meat and vegetables*) without a clear pattern being apparent. In some children with multiple reactions there might be a common antigenic structure in the eliciting foods like a protein found in muscle tissue in the meat- and fish-allergic patients or a bovine protein in the beef- and milk-allergic patients. Also, in the two children with reactions to different vegetables of one family, there could be a common allergenic protein as a trigger. Overall, however, there is no clear pattern to predict further reactions.

Data on the influence and development of IgE-mediated sensitization are conflicting. In our study 14% of the patients were sensitized, most of them to cow's milk. Most of the cow's milk sensitized children (10/15) were initially diagnosed with chronic FPIES.

Only 2 of 12 sensitized and challenged patients experienced immediate-type allergic symptoms during the challenge despite a clear FPIES reaction as initial symptom.

Interestingly, one additionally showed typical FPIES symptoms after 3 hours. This has not been described in the literature before. Both children were sensitized continuously.

Regarding tolerance development there was no influence of being sensitized or not.

Diaz et al. (7) in Spain reported 15.7% of sensitization, mainly against cow's milk, but also against egg, however they did not report different symptoms or a delayed tolerance in these patients. Sopo et al. (8) described 2 children in their cohort who switched from typical FPIES-

symptoms to an IgE-mediated reaction. In one Greek study (10) the influence of IgE-sensitization on tolerance was calculated and associated with delayed tolerance development. The authors did not mention if IgE-mediated symptoms occurred during the challenges. In the other Greek study (19) only 4 children were sensitized (all to cow's milk). All of these children had negative food challenges. The largest data set analyzing the influence of sensitization was published by Caubet et al. (15). In their group of 160 FPIES patients, 24% were sensitized to their FPIES trigger, mostly to cow's milk or soy. Sensitized children reacted earlier than 120 min after the challenge dose, but IgE-mediated symptoms were not reported. Furthermore, no children with sensitization to cow's milk achieved tolerance within the study time.

Even if our results do not suggest an influence of sensitization on tolerance development, there might be, in rare cases, an influence on clinical symptoms. Specific IgE to the FPIES trigger can develop over time. Therefore, we suggest to do repetitive IgE-testing, especially in preparation of a challenge procedure.

We found no evidence that children who reacted to multiple foods took a longer time to develop tolerance or had a more severe or prolonged clinical course. However, since only a small number of patients were involved in this analysis and there were no predetermined intervals between challenges, these data should be taken with caution.

As described in the literature (8,15,19), the time to tolerance is different for different foods. Like in the Italian study by Sopo (8), our results show a delayed tolerance development for fish, meat, vegetables, and egg compared to milk and grains. The type of food rather than the number of triggers appears to be relevant for the length of time until tolerance develops. Based on this, we suggest planning food challenges for milk and grains 1-2 years

after the latest reaction and for other foods like meat, vegetables, or fish 2-3 years after the latest reaction.

Although chronic FPIES can be a severe disease, the natural course is more benign than in acute FPIES. Only 7% of our patients initially suffering from chronic FPIES developed an acute FPIES to another food in the course of the disease. In contrast, 19% with primary diagnosis of acute FPIES developed acute FPIES to another food. In general, infants suffering from cow's milk FPIES experienced less reactions to other foods than children with solid food FPIES (10% vs. 25.9%, respectively). Furthermore, a significant earlier tolerance development was observed in children with chronic FPIES compared to acute FPIES ($p < 0.0001$). From our findings we suggest that the introduction of complementary foods in patients suffering from chronic and acute FPIES to cow's milk can be done with more confidence.

There are some limitations of our study. Due to the retrospective and multicenter design, there was no study protocol with homogeneous procedures, for instance, the timing of food challenges. The point of time for the challenge was decided by the allergist and the children's parents. For that reason, some children might have achieved tolerance earlier than confirmed in their food challenge. Regular conducted challenges could have resulted in different outcomes.

Furthermore, not all patients with chronic FPIES were promptly challenged to confirm the diagnosis. Thus, overdiagnosis of chronic FPIES may have occurred as some children were already tolerant at time of the challenge.

The major strength of this study is the large set of patients from 14 centers in various regions of Germany, providing an instructive overview on eliciting foods, the pattern of

triggers and the time course of tolerance development. We assume that these data will help to improve nutritional advices given to patients.

In conclusion, we found that food triggers for acute FPIES in Germany partly differ compared to other countries. In our database, the most frequent triggers are foods that are introduced early in the infants' diet such as cow's milk, fish, potatoes, pumpkins, and beef. From our data, we hypothesize that the eliciting foods depend on the dietary habits and the timing of introduction in addition to the allergenic potential of the food.

Although IgE-sensitization to FPIES triggers occurred frequently, children suffering from FPIES rarely develop IgE-mediated symptoms.

Patients with chronic FPIES have a lower risk for multiple trigger FPIES compared to those with acute FPIES. The outcome of the disease in terms of development of tolerance is more favorable in patients with chronic and acute FPIES to cow's milk compared to those with acute FPIES to solids.

With these data on the frequency of triggers and tolerance development, we hope to help improve counseling for children with FPIES and adapt it to local dietary habits.

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Table legend:

Table 1: Distribution of particular food triggers in different food groups (fish, meat, vegetables, grains) in absolute and relative frequency.

Figure legends:

Figure 1: Elicitors of acute FPIES in German infants and children. Similar foods were combined in groups. Number of cases.

Figure 2: Kaplan-Meyer survival curves for time to proof of tolerance from first reaction comparing acute and chronic FPIES in months. Probability of still being not tolerant after one year: 0.532 (acute FPIES), 0.186 (chronic FPIES).

Figure 3: Kaplan-Meyer survival curves for time to proof of tolerance from first reaction comparing different food groups. Probability of still being not tolerant after one year: 0.844 (fish), 1.000 (meat), 0.687 (vegetables), 0.347 (grains), 1.000 (egg), 0.143 (cow's milk), 1.000 (others: banana, almond, hazelnut, coconut milk, sunflower seed).

Figure 4: Kaplan-Meyer survival curves for time to proof of tolerance from first reaction comparing IgE-positive vs. IgE-negative patients.

Figure 5: Kaplan-Meyer survival curves for time to proof of tolerance to cow's milk in cow's milk allergic patients comparing patients reacting only to milk vs. patients reacting to multiple foods

Food trigger	Absolute (relative) frequency
Fish	n=27
salmon	12 (44.5%)
fish, not specified	10 (37.0%)
pollack	4 (14.8%)
cod	1 (3.7%)
Meat	n=23
beef	12 (52.2%)
poultry	7 (30.4%)
pork	3 (13.1%)
lamb	1 (4.3%)
Vegetables	n=24
potato	6 (25.0%)
pumpkin	4 (16.7%)
carrot	3 (12.5%)
sweet potato	2 (8.3%)
pea	2 (8.3%)
turnip cabbage	1 (4.2%)
soy	1 (4.2%)
red cabbage	1 (4.2%)
mushroom	1 (4.2%)
courgette	1 (4.2%)
cauliflower	1 (4.2%)
green bean	1 (4.2%)
Grains	n=16
rice	6 (37.5%)
wheat	5 (31.2%)
oat	3 (18.7%)
spelt	1 (6.3%)
millet	1 (6.3%)
Others	n = 6
banana	2 (33.3%)
almond	1 (16.7%)
coconut milk	1 (16.7%)
hazelnut	1 (16.7%)
sunflower seed	1 (16.7%)

