Spanish Survey of Food Protein-Induced Enterocolitis Syndrome

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Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy characterized by delayed and reproducible gastrointestinal symptoms. It is a heterogeneous disorder with a wide spectrum of clinical phenotypes[1]. The typical symptoms and the offending triggers vary depending on the age of the onset of the disease and the geographic area[2]. The aim of this study was to establish the characteristic of FPIES and clinical management in Spain.

We performed an online cross-sectional survey completed by members of the Spanish Society of Allergy and Clinical Immunology (SEAIC) and of the Spanish Society of Paediatric Clinical Immunology, Allergy and Asthma (SEICAAP). The survey (online repository text) was created using SurveyMonkey® and it was launched in early March 2020 and ended in July 2020. The data were recorded in an anonymized database. The survey was fulfilled by 122 physicians (Table E1).

Most of the participants (74.4%) only treat pediatric patients diagnosed with FPIES, 4.9% only adults and 20.7% treated both. Most (81.2%) used the diagnostic criteria proposed by the International Consensus[3].

Almost all physicians (90%) carried out an oral food challenge (OFC), 41.7% during the follow-up to check tolerance to the offending food, 16.7% to check tolerance to other foods, 24.1% in both cases and 7.5% only for diagnosis. Period they considered adequate to perform the OFC varied according to patient’s age, food involved, and the purpose of the OFC, but most wait 12-18 months from the last reaction. A 39.1% performed the OFC giving several equal doses on the same day, following the consensus recommendations, while 36.5% did it on the same day or in two days, but in increasing doses. Only 15% performed it giving a single dose per day in 2 different days. Most clinicians (77.5%) canalized a peripheral line before the OFC, but only 31% of them always did it.
Fish was the food most frequently involved in FPIES in children, followed by cow’s milk proteins (CMP) and egg, while in adults the most offending triggers were fish and shellfish. In fish FPIES, most respondents (62.2%) performed OFC with an alternative fish, being canned tuna the most frequently used, followed by swordfish and salmon. However, in shellfish and cereals FPIES, only 33.3% and 32.3% of the respondents respectively, carried out the OFC with an alternative. Cephalopods were the most frequently used in the case of shellfish, followed by bivalves, and in the case of cereals, corn, and rice. Interestingly, in CMP-FPIES, 14.2% of the respondents used cooked milk as the first option in the OFC, and in egg-FPIES, 28.1% carried out with baked forms. As to the acquisition of tolerance, most respondents (36.5%) reported that the tolerance age of their patients with CMP-FPIES was between 2-3 years, in the case of hen’s egg and cereals above 3 years (50.5% and 53.9% respondents, respectively), and for fish over 5 years (64.7%). (Table 1). Finally, regarding the treatment of the acute reaction most responders (40.5%) chose intravenous fluid reposition, ondansetron and corticosteroids.

FPIES is not only a heterogenous disease due to its different clinical presentations (acute, chronic, atypical, adult-onset)[1]. There are geographical and age dependent differences that make some foods more prevalent in some populations than others[2]. These differences are highly relevant to establish an accurate diagnosis, treatment, and diet. This study describes the characteristics of patients with FPIES in Spain. The survey carried out, answered by a representative sample of physicians from all over the national territory, gives us a global vision of the disease in our country. FPIES is considered an infrequent disease. The few prospective epidemiological studies published estimate an incidence of 0.34-0.7% in children and 0.2% in adults[4]. In our study, one third of the respondents perceived FPIES as a common disease and, even though most of the cases they attend are children, up to 25% of physicians had adult patients with FPIES. So probably, FPIES is a more frequent disease in this age group than what has been described so far.

Diagnosis is based on clinical history. There are several unvalidated diagnostic criteria sets published to assist in clinical diagnosis[5]. Interestingly, 80% of those surveyed answered that the most useful to them were the International Consensus one’s[3]. This is striking since Vazquez-Ortiz et al[6] showed that with these criteria 25% of our paediatric population would not be correctly diagnosed. And in the case of adults, diagnostic
profitability would be even worse since, according to published series, vomiting may be absent in many patients so we could leave up to 50% of adults with FPIES undiagnosed[7]. In the latest published criteria[5], crampy abdominal pain, a very common symptom in adults, replace vomiting in this age group.

In our study, fish followed by milk and hen’s egg were the most common offending foods in children, while in adults the most common ones were fish and shellfish. These data agree with those previously published[3]. However, FPIES due to vegetables does not seem to be so infrequent in our country, since almost 40% of the respondents attend patients with FPIES by vegetables, especially legumes. Interestingly, soy FPIES, frequent in other countries is extremely rare in Spain[2], and yet mushroom seem to be an emerging trigger.

Regarding OFC, most professionals choose to administer several doses of food, at variable time intervals, throughout the same day. This, which was one of the recommendations given so far, has been shown to be meaningless unless it is an atypical FPIES, as a dose of 25% to 33% of the standard serving size is sufficient to trigger a reaction in most patients with FPIES[8].

The age at which Spanish children outgrow their FPIES is like that described globally[9], although it is maybe biased because OFC are performed at long intervals (12-18 months) and there is a lack of prospective studies.

Although several studies[10,11] have shown that most children in southern Europe had single FPIES and that it is possible to tolerate other food from the same group, only 18% of the respondents performed the OFC to check tolerance to them.

In conclusion, this national survey has allowed us to establish areas for improvement to work on in the coming years. Specifically, in the diagnostic criteria and how and when to perform the OFC.

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**Conflict of interest**
None of the authors have any conflict of interest regarding this study.
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