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Food protein-induced enterocolitis syndrome in pediatric ages - A retrospective analysis of the cases reported to HP-CHUC

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Abbreviations

FPIES - Food protein-induced enterocolitis syndrome

GI - Gastrointestinal

HP-CHUC – Hospital Pediátrico, Centro Hospital e Universitário de Coimbra

IgE - Immunoglobulin E

NP: Not performed

OFC - Oral food challenge

sIgE - Serum-specific immunoglobulin E

SPT - Skin prick tests

UD: Undetermined

Abstract

Background: Food protein-induced enterocolitis syndrome is a non-IgE mediated food allergy that affects mostly the gastrointestinal tract. Its prevalence and physiopathology are not well known. It is typically a childhood disease, in some cases, can affect older children and even adults. The acute reaction usually occurs one to four hours after the intake of the culprit food and manifests as profuse emesis, pallor, lethargy or prostration and, in some cases, hypovolemic shock can occur. The most common triggers are cow and soy milk but rice, fish and even foods that are considered hypoallergenic like fruits and poultry can be implicated. The diagnosis is based on the identification of the clinical features of the disease. Resolution occurs in early infancy, usually between three and five years old. The oral food challenge is the recommended method to diagnose and determine resolution of FPIES.

Methods: This was a retrospective descriptive study of children with food protein-induced enterocolitis syndrome who presented to the Pediatric Allergy Clinic of HP-CHUC over approximately three years. Hospital medical record databases were screened for the diagnosis of FPIES. The data collected was analyzed using an Excel spreadsheet and IBM SPSS Statistics version 22 software.

Results: Seven patients were identified with FPIES. The age of onset was mainly before one year old (57,1%) and the mean time to achieve the correct diagnosis was 8,8 months. The most common causal food was fish and all the patients developed emesis. Symptoms initiated one to six hours after OFC. None of the sIgE or skin prick tests performed were positive and all the patients had positive oral food challenges. We noticed a strong atopy background either personal or familial, 57,1% and 42,9% respectively. Only three patients achieved resolution by the time the study was finished.

Conclusion: The delay between the beginning of the first symptoms and the correct diagnosis is considerable and its impact on the children life quality should not be disregarded. Like in other countries of the south Europe, Portugal also reports a higher fish induced FPIES which can reflect the importance of geographic differences when it comes to identify the most common food trigger associated with FPIES.

Key-words: Non-IgE food allergy; food protein-induced enterocolitis syndrome; pediatric age.

Resumo

Introdução: A síndrome de enterocolite induzida por proteínas alimentares (FPIES do acrónimo em inglês) é uma alergia alimentar não IgE mediada que afeta principalmente o trato gastrointestinal. A sua prevalência e fisiopatologia não são bem conhecidas. É uma doença tipicamente da primeira infância mas existem casos relatados de crianças mais velhas e mesmo adultos. Apresenta-se sobretudo na forma aguda que ocorre geralmente uma a quatro horas após a ingestão do alimento em causa e manifesta-se por vómitos profusos, palidez e prostração, podendo causar choque hipovolémico. Os alimentos mais implicados são leite de vaca ou de soja mas também arroz, peixe e até fruta e aves, estes geralmente considerados hipoalergénicos. O diagnóstico é baseado nas manifestações clínicas. A resolução ocorre maioritariamente na idade pré-escolar, geralmente entre os três e os cinco anos. A prova de provocação oral é o método recomendado tanto para o diagnóstico como para a sua resolução.

Métodos: Trata-se de um estudo retrospetivo descritivo de crianças com FPIES que foram seguidas na Consulta de Alergologia do Hospital Pediátrico do Centro Hospitalar e Universitário de Coimbra (HP-CHUC) durante um período de aproximadamente três anos. Foram consultados os processos clínicos dos doentes e os dados recolhidos foram analisados através do Excel e do software IBM SPSS Statistics versão 22.

Resultados: Foram identificados sete doentes com FPIES. A idade de início dos sintomas foi na maioria (57,1%) dos casos antes de um ano de idade e o tempo médio entre início de sintomas e do diagnóstico foi 8,8 meses. O alimento que mais causou FPIES foi o peixe e todos os doentes manifestaram vómitos. Os sintomas tiveram início entre uma e seis horas após a realização de prova de provocação oral (PPO). Todos os doseamentos de sIgE e testes cutâneos realizados foram negativos e todas as PPO foram positivas. Foi observado um

forte historial pessoal e familiar de atopia, 57,1% e 42,9%, respetivamente. Apenas três doentes apresentavam resolução da doença até ao momento em que este estudo foi concluído.

Conclusão: O atraso entre o surgimento dos primeiros sintomas e o diagnóstico foi considerável e o seu impacto na qualidade de vida destas crianças não pode ser negligenciado. Tal como em outros países do sul da Europa, em Portugal também se observou um maior número de crianças com FPIES a peixe, o que pode refletir a importância das diferenças geográficas no padrão de alimentos mais comuns envolvidos na FPIES.

Palavras-chave: Alergia não-IgE mediada; síndrome de enterocolite induzida por proteínas alimentares; idade pediátrica.

Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated gastrointestinal (GI) food allergy that affects mostly the gastrointestinal tract[1-4].

Rubin [5] in 1940 reported intestinal bleeding in newborns due to milk allergy and later Gryboski *et al.* [6] and Powell [7] described the first cases of FPIES. Powell [8] established for the first time the diagnostic criteria for FPIES, later modified by Sicherer *et al.* [9]. An important difference between non-IgE mediated and IgE mediated allergies are the fact that the first one doesn't involve the respiratory tract and skin [2, 4, 10].

FPIES can be divided in various forms, we can have typical or atypical FPIES and also according to the type of presentation, an acute or chronic form.

Atypical FPIES, often mistaken by an IgE mediated allergy, occurs when a child has positive sIgE tests and it is associated with a protracted course of the disease [1, 11-13].

Acute presentations are more common than the chronic forms and better characterized [1, 12, 13].

An acute presentation typically manifests as profuse vomiting, usually one to four hours after intake of the culprit food, pallor, lethargy or prostration. Diarrhea usually develops after five to 10 hours and can last up to 24 hours [1, 4, 11, 14, 15]. Some children become hypotensive and in severe cases hypovolemic shock occurs [3, 11, 15]. Methemoglobinemia and acidemia were also reported [1, 4, 16]. The chronic form presents with vomiting, watery or bloody diarrhea and failure to thrive and it usually affects younger infants [2, 3, 17].

FPIES is an uncommon and not well known disease that usually begins in the first year of life of infants, being less common in older children and adults [9, 3, 12, 14].

A lot of foods can induce FPIES in infancy, the most common being cow's milk and coexisting allergy to soy, but other foods such as rice, fish, barley, fruits, vegetables, grains,

poultry can also be implicated [9, 14, 15, 18]. In adulthood the most reported food was shellfish [3, 17].

The diagnosis of FPIES is mainly based on the clinical features, but skin prick tests and sIgE tests are usually performed to exclude an IgE mediated allergy and to proceed safely to an oral food challenge (OFC). OFC is considered the gold-standard diagnostic test to identify FPIES [1, 11, 18].

Performing an OFC is not only important to be sure of the diagnosis and culprit food but also to determine if tolerance was achieved or not. The reintroduction of the culprit food into the infant's diet is usually performed at the hospital with an OFC. It should be performed after the period of at least one year, [11, 18, 19] to determine if tolerance has been achieved. Exceptionally the reintroduction of the culprit food in the infant's diet can be performed at home, generally in mild cases [15, 17]. Reintroduction of the culprit food at the hospital is more advisable since the child can develop moderate to severe symptoms and require intravenous fluid therapy [1, 12].

The prevalence of this disease is not well known, one large population study in Israel done by Katz *et al.* [14] showed a prevalence of cow's milk FPIES of 0.34%. Mehr *et al.* [4] in Sydney also noticed an increase in FPIES between the periods of 1992-1995 and 2004-2010. Despite this increasing in FPIES prevalence, we cannot be certain if it is a true incidence rise or only increasing awareness of this condition and consequently being more reported [18]. There are no population studies about FPIES in Portugal.

In some studies there seems to be a slightly male prevalence [4, 11, 14].

The age of onset is usually under 12 months, but varies depending on the culprit food. Usually solid foods have a later onset than the liquid ones [3, 14, 18, 20]. However there are cases of FPIES affecting teenagers and adults, in which the most common causal food is shellfish.[3, 12, 17, 20]

It has a very good prognostic with the majority of children overcoming it around the age of three years old. Achievement of tolerance occurs earlier for liquid than for solid foods [3, 14, 18]. The physiopathology of FPIES is not well known, but it's thought to be T cell mediated [3, 21].

In this study we decided to focus on the clinical aspects of the disease of the patients attending a Pediatric Allergy Clinic. We consider these children should be followed in a differentiated clinic to avoid extensive work-up and unnecessary procedures or diet restrictions. We also believe this disease is still greatly underdiagnosed, not only worldwide, but also and particularly in Portugal due to the fact that most physicians have not become aware of it yet.

Methods

This thesis is a retrospective descriptive study of patients identified with FPIES, followed at HP - CHUC Allergy Clinic. The purpose of this study is to characterize the patients with FPIES attending this Clinic.

Sample Selection

The inclusion criteria for the collection of the sample were patients under 18 years old identified with FPIES and followed at HP - CHUC Allergy Clinic from 1/10/2014 until 1/08/2017.

Data extraction

The sample selection was performed between the April 1st and August 1st 2017. It was obtained after analyzing the medical records of the patients followed by this clinic using the hospital electronic clinical databases. The data collected corresponds to the period between 1/10/2014 and 1/08/2017. The information collected was gender, current age, age at presentation, culprit food, symptoms, delayed diagnosis, results of the OFC, current status of the disease, the results of skin prick tests (SPT) and serum-specific IgE (sIgE) as well as family and personal history of atopy. This information was transcribed to an Excel spreadsheet and the data was analyzed using IBM SPSS Statistics version 22.

Bibliographic research

The bibliographic research was made between 1/05/2017 and 20/12/2017 in two electronic medical databases, *PubMed* and *Embase* with the key words “food allergy” “non-IgE-mediated food allergy” and ”food protein-induced enterocolitis syndrome” for the

maximum period of 10 years and restricted to pediatric age (< 18 years old). The inclusion criteria for the studies selection were: (a) population: FPIES in pediatric age; (b) intervention: diagnosis and treatment; (c) outcomes: symptoms and resolution.

The duplicates were eliminated and we had a total of 86 articles, 66 articles from Pubmed and 20 from Embase. Initially the articles were screened by title, abstract and language (English, French and Spanish). After this initial screening and if any doubt remained the full papers were assessed. Articles that were not available were excluded. Of a total of 22 articles, 20 were from *Pubmed* and 2 were from *Embase*.

Five historical articles that were not included in that time frame were also used, specifically articles from Rubin, Gryboski, Powell and Sicherer, so we ended up with a total of 27 articles.

Results

Sample

Seven patients attending HP - CHUC Allergy Clinic were included in our sample and it's unknown if other children were followed at other Pediatric Clinics. No new cases appeared while the research was going on (1/04-1/08 of 2017).

This sample (n=7) is constituted by four female and three male children.

Tabela 1 – Characteristics of the children indentified with FPIES.

Patients	Gender	Age at onset (months)	Causal food	sIgE	SPT[1]	OFC	Resolution
1	M	2,5	Cow's milk	-[2]	-	+[3]	Yes
2	F	5	Cow's milk	-	-	+	Yes
3	M	7	Fish	-	-	+	No
4	M	8	Egg white	NP[4]	-	+	Yes
5	F	24	Fish	-	-	+	No
6	F	48	Molluscs	-	-	+	No
7	F	48	Fish	NP	NP	+	UD[5]

[1] SPT: skin prick tests; [2](-): Negative; [3] (+): Positive; [4] NP: Not performed; [5] UD: Undetermined

The age of onset was variable with the majority (57,1%) of the children being under 12 months. The maximum age reported was four years old and the mean age was 20,4 months.

The most common causal food was fish followed by cow's milk. FPIES triggered by molluscs and egg white were also reported (Table 1 and 2).

Tabela 2 – Culprit food.

Culprit food	Frequency (n)	Percentage (%)
Fish	3	42,9
Cow's milk	2	28,6
Egg white	1	14,3
Molluscs	1	14,3
Total	7	100

It was mentioned previously that this disease is not well known by pediatricians and the same occurred in our study, with the first report about FPIES being made back in 2014. The mean time to achieve the correct diagnosis of FPIES was 8,8 months, with two children diagnosed more than 20 months after the initial presentation (Table 3).

Tabela 3 – Delayed diagnosis.

Patients	Age at onset (months)	Delay (months)	Frequency(n)	Percentage (%)
1	24	1,5	1	14,3
2	5	2,0	1	14,3
3	2.5	2,0	1	14,3
4	8	4,0	1	14,3
5	7	7,0	1	14,3
6	48	21,0	1	14,3
7	48	24,0	1	14,3
Total	__	__	7	100

The symptoms reported by parents were the same provoked by the OFC at the hospital and were mainly four. The most common and present in all the patients was emesis, followed by prostration and cutaneous lesions (rash like lesions) and finally by acute diarrhea (Table 4).

Tabela 4 – Symptoms frequency.

Symptoms	Frequency (n)	Percentage (%)
Emesis	7	100
Cutaneous lesions	2	28,6
Prostration	2	28,6
Diahrrea	1	14,3
Hypovolemic shock	1	14,3

As mentioned before FPIES is a non-IgE mediated food allergy and according to that the sIgE and SPT tests should be negative. Our results met these criteria, with all the tests performed being negative (Table 1).

The OFC, usually performed to identify the culprit food and to confirm FPIES, was positive in all of our patients.

We also took into account the personal and familiar background of atopy. The majority of patients had a personal background of atopy, on the other hand the family history of atopy is less relevant (Tables 5 and 6).

Tabela 5 – Personal background of atopy.

Answers	Frequency (n)	Percentage (%)
Yes	4	57,1
No	3	42,9
Total	7	100

Tabela 6 – Family background of atopy.

Answers	Frequency (n)	Percentage (%)
Yes	3	42,9
No	4	57,1
Total	7	100

FPIES usually is a self-limited disease, with children achieving tolerance between the ages of three and five years old. In our study by the time we finished collecting all the data only three patients achieved tolerance to the culprit food. The parents of one patient decided that they did not want to perform more OFCs, so the outcome is unknown (Table 1).

From the three patients that achieved resolution, all three were older than one year old, more precisely at 13, 17 and 24 months.

The time of symptoms onset in FPIES is usually between one to four hours after the ingestion of the causal food. In our study 85,7% of the patients started the symptoms at least two hours after the OFC (Table 7).

Tabela 7 – Time of onset of symptoms after OFC.

Onset after OFC (hours)	Frequency (n)	Percentage (%)	Cumulative Percentage (%)
1	1	14.3	14,3
2	3	42.9	57,1
3	2	28.6	85,7
6	1	14.3	100,0
Total	7	100	

Discussion

FPIES diagnosis is mainly clinical and there is usually a delay in the diagnosis[4, 15, 20]. In our department there has been an increasing awareness of this disease but we believe that this entity is not well known by primary care physicians and general pediatricians.

Some studies refer a slightly male predominance [4, 14, 15], in our study due to the small sample of patients we cannot make any conclusions.

The age of onset is usually under 12 months but we had two patients with a late onset, at four years old, to fish and mollusks which is unusual especially considering that Portugal follows a typical Mediterranean diet and fish is usually introduced before one year old. This finding could be explained by a later introduction of that specific type of fish and mollusc and by a delayed diagnosis.

As mentioned before Portugal follows a typical Mediterranean diet and fish is introduced early in the children's diet. This could explain why fish is the most common culprit food that we found. Despite not statistically significant our results are consistent with other studies reported in Spain and Italy which also follow a Mediterranean diet[4, 11, 22]. Although in these studies the fish induced FPIES was reported at earlier ages and in our study occurred at later ages, except in one patient that was reported at seven months old. As reported before it could be due to a later introduction of that specific species of fish, delayed diagnosis or family alimentary habits. In our study cow's milk is the second most reported culprit food and as expected is found in earlier ages, usually before one year old, [23-25] in our case at one month and a half and five months.

This disease is often mistaken by an IgE-mediated food allergy but usually the SPT and sIgE are negative. SPT and sIgE are recommended at diagnosis and follow-up, first because if an OFC is going to be performed we should guarantee that it is not an IgE mediated

allergy and second because children who have positive SPT and/or sIgE tests tend to have a more protracted course [2]. After that an OFC is usually performed and if positive confirms the diagnosis of FPIES. If the clinical history is very suggestive of FPIES, there is no need to perform an OFC[2, 12, 17]. However in our Clinic we usually do it not only because it allows us to identify correctly the culprit food but also to prove the parents that the single treatment that needs to be done in this disease is avoiding the food responsible for the symptoms. Sometimes the culprit food suspected by the children's parents is not the one that causes FPIES and this is why the OFC is sometimes very important, to identify correctly the culprit food and avoiding misunderstandings in the treatment as well as avoid unnecessary diet changes. The mean time to achieve the correct diagnosis was 8,8 months, with two patients taking more than one year to be correctly diagnosed. These delays in diagnosing a child with FPIES can have some serious implications, with a lot of work-up behind it and sometimes even invasive procedures are performed in the searching for the correct diagnosis. In our study we classified the delay in diagnosing FPIES since the first time the symptoms were reported by the parents and the time were the hypothesis of FPIES was first considered and subsequently the work-up to achieve this diagnosis began. This means that the delay is not restricted to the time that the patients were followed by our Clinic or others, but to the beginning of symptoms consistent with FPIES.

FPIES is an exclusion diagnosis, especially if the child presents to the emergency room (ER) in a shock-like status, usually a hypovolemic shock and easily reversible with intravenous hydration [4, 12, 16].

The most common symptom and present in all patients was emesis, followed by prostration and skin lesions. Skin lesions are not supposed to happen in FPIES as is a more common finding associated with IgE mediated allergy. Despite skin lesions being reported in two

patients their IgE and SPT were negative, so there is a possibility that these skin lesions were not related to the food allergy. In fact all SPT and sIgE tests performed in our study were negative. These results, except the skin lesions, are consistent with the diagnosis criteria of FPIES [2, 11, 12]. Skin lesions have been reported as well in FPIES, but the reason why they appear is not clear [26]. Diarrhea was reported in only one patient. Diarrhea is usually a less common finding and its onset occurs later, approximately five to 10 hours after the OFC is performed. Moreover, diarrhea is more associated with chronic FPIES rather than an acute episode [2, 12, 27]. We had one patient that developed hypovolemic shock and needed intravenous bolus of saline solution.

In our study we didn't identify any case of chronic FPIES, mostly because the parents recurred rapidly to the hospital after the symptoms and despite not being diagnosed with FPIES right away, usually it was advised to avoid that food.

As mentioned previously OFC is not mandatory to diagnose FPIES, although it is considered the gold-standard to diagnose FPIES. The onset of symptoms is generally between one to four hours, [1, 12, 17] in our study 85,7% of the patients started the symptoms up to four hours after the OFC was performed and only one started the symptoms six hours after the OFC.

Atopy is a condition were individuals may produce antibodies against harmless environmental substances, it has a strong familial basis and individuals are genetically predisposed to develop one or more atopic diseases like allergic rhinitis, asthma, atopic eczema, etc. In this study we considered family atopy as that restricted to the parents and brothers or sisters and defined as asthma, atopic eczema, allergic rhinitis or hypersensitive reactions to foods. The family and personal history of atopy are often asked to the patients and in our study 57.1% of the patients had an history of atopy and 42,9% had a family

background of atopy. The frequency of this family or personal atopy varies greatly among different studies [12, 17]. Nevertheless, we see that FPIES can be in some extent related to patients that have some atopic background either personal or familiar.

As mentioned before the resolution of FPIES varies according to different studies and also depends on whether the food is solid or non-solid. In our study three children achieved resolution, other three didn't by the time we finished our investigation and the parents of one patient decided to stop the investigation and decided to avoid the food instead.

Conclusion

There are several limitations in this study, starting with the sample size that could not allow us to make statistically significant conclusions. Also we restricted our sample to the patients followed by the Pediatric Allergy Clinic and there must be other patients with FPIES followed by other Clinics such as Gastroenterology and General Pediatric Clinics.

More studies should be done to determine the prevalence of this disease, that apparently is not so uncommon as initially thought. The physiopathology of the disease also needs to be clarified. Further studies can be performed to identify the characteristics of Portuguese children that develop FPIES and compare it to other studies.

However with our study we could notice that the food triggers of FPIES may indeed vary geographically according to the diet habits of each region or culture, as suggested by other studies.

We hope that with our study we'll bring a general awareness about this disease in Portugal or at least in our hospital and with this allow patients with FPIES to be correctly diagnosed and oriented.

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