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Food Protein-Induced Enterocolitis Syndrome (FPIES): Clinical Outcomes

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Abstract: Background/Objectives: Food Protein-Induced Enterocolitis Syndrome (FPIES) is a rare and poorly understood condition that primarily affects infants and young children. This study aimed to evaluate the clinical characteristics and outcomes of oral food challenge (OFC) tests in patients diagnosed with FPIES. **Methods**: A retrospective cohort study was conducted on pediatric patients who underwent OFCs for FPIES at a tertiary health service from January 16, 2018, to June 20, 2024. Both accidental and scheduled in-hospital OFC results were considered. **Results**: Five patients were included, and 19 OFCs were evaluated. Four patients underwent 4 OFCs each, and one patient underwent 3 OFCs. The mean age of the first symptom onset was 35 days (ranging from 3 days to 2 months). Before the first OFC, the mean duration of the elimination diet was 7 months, and for patients who required additional OFCs, was 11.6 months. Four patients were admitted to the intensive care unit. Two patients were being fed on formula, and three were having mixed feeding. Two patients had a personal and family history of atopy, and one had only a family history of atopy. Two patients had genetic syndromes. All patients developed tolerance to cow's milk protein within a mean time of 44 months, ranging from 17 to 103 months. The two patients with genetic syndromes had a longer time to develop tolerance. **Conclusions**: FPIES may require multiple OFCs for diagnosis and management. The time to develop tolerance was longer in patients with genetic syndromes.

Keywords: cow's milk allergy; diagnosis; outcomes

1. Introduction

Food Protein-Induced Enterocolitis Syndrome (FPIES) is a rare immune-mediated condition that primarily affects infants [1,2]. It is characterized by severe gastrointestinal reactions triggered by food proteins, most commonly found in milk formulas and solid foods introduced in early childhood [3]. Unlike IgE-mediated allergic manifestations, FPIES symptoms include intense vomiting occurring 1-4 hours after ingesting the allergen, diarrhea (after 5-10 hours of exposure), dehydration, and, in severe cases, hypovolemic shock, often leading to hospitalizations [4–6].

Despite challenges in diagnosing and managing of FPIES, the oral food challenge (OFC) remains a crucial tool for diagnosis and evaluating food tolerance acquisition [3,5,7]. In general, these patients require elimination diets, and food reintroduction must be carefully controlled and monitored [1,7]. Knowledge of clinical outcomes after OFCs in FPIES patients remains limited, particularly in the Brazilian context.

This study aims to evaluate the clinical characteristics and outcomes of OFCs performed in pediatric patients diagnosed with FPIES at a tertiary health service, contributing to the understanding of factors involved in clinical progression and the time needed to acquire food tolerance.

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2. Materials and Methods

This retrospective cohort study was conducted on pediatric patients who underwent OFCs for FPIES at a tertiary health service from January 16, 2018, to June 20, 2024. Data from both accidental and scheduled OFCs, conducted in a controlled hospital environment, were analyzed.

For OFCs done in the hospital, a protocol similar to the one published by Nowak-Węgrzyn *et al*. was used. All patients had a peripheral venous access inserted before starting the test. The cow's milk protein dose ranged from 0.06 to 0.6 g/kg (mean of 0.3 g/kg), divided into 3 equal doses, administered every 30 minutes. A maximum limit of 3 g per step or 10 g for the entire test was established. All patients were monitored for at least 4 hours after the last dose of formula [8].

The analysis included patients with complete clinical records, covering age of the first symptom onset, duration of the elimination diet before the first OFC, total number of OFCs performed and the time to acquire food tolerance. Initial symptoms during the reactions, family history of atopy, clinical data on prematurity, genetic syndromes, and symptoms presented in positive tests were also documented.

OFCs were considered positive with the presence of one major criterion and two or more minor criteria. The major criterion includes vomiting 1-4 hours after ingestion of the causative food, and minor criteria include diarrhea (after 5-10 hours of exposure), lethargy, pallor, hypotension, hypothermia, and increased neutrophil count (> 1500 neutrophils above baseline) [9].

Data were extracted from electronic medical records and organized in tables for descriptive analysis and comparison of variables. Mean and standard deviation were calculated for continuous variables, while frequency analysis was conducted for categorical variables.

The study was approved by the Local Research Ethics Committee under Number: 6.216.007.

3. Results

Five patients diagnosed with FPIES were included in the study, totaling 19 OFCs, of which 13 were accidental and 6 were conducted in a hospital setting. Four patients underwent 4 OFCs each, and one patient underwent 3. The mean age at the first manifestation of FPIES was 35 days, ranging from 3 days to 2 months. The mean duration of the elimination diet before the first OFC was 7 months, while patients needing additional OFCs had a mean duration of 11.6 months. Initial symptoms often included diarrhea, dehydration, large-volume vomiting, hypovolemic shock, and metabolic acidosis, with four patients requiring intensive care unit admission. Two patients were being fed on formula, and three were having mixed feeding. Regarding atopic history, two patients had personal and family history of atopy, one had a family history, and two had no atopic background. The symptoms presented during OFCs included vomiting, diarrhea, hypotension, and lethargy. Diarrhea was present in only 6 of the 14 positive tests (43%). All patients were term infants with appropriate weight for gestational age. Two patients had genetic syndromes, including Down Syndrome (DS) and a microdeletion on chromosome 3p associated with a duplication on chromosome 16q. All patients eventually acquired food tolerance, with a mean time of 44 months, ranging from 17 to 103 months. Patients with genetic syndromes had a prolonged time to acquire tolerance (103 and 42 months, respectively). Table 1 presents the data of the patients.

Table 1. Clinical characteristics of patients with FPIES undergoing Oral Food Challenge (OFC)

	1	**2**	**3**	**4**	**5**
Sex	Male	Male	Male	Female	Male
Age of first symptoms (days)	40	60	20	3	53

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Breastfeeding at the onset os symptoms	Mixed feeding	Mixed feeding	Infant Formula	Infant Formula	Mixed feeding
Symptoms	Diarrhea, vomiting, dehydration, metabolic acidosis	Vomiting and dehydration	Diarrhea, dehydration, malnutrition	Diarrhea, dehydration and metabolic acidosis	Diarrhea, vomiting, dehydration, metabolic acidosis and hypovolemic shock
Exclusion diet	Amino acid formula	Breast milk and soy-based formula	Soy-based formula	Amino acid formula	Amino acid formula
Follow up time (months)	60	72	100	45	28
Time of exclusion (months)	2	1	8	12	1,5
Time between the first and second OFC (months)	10	5	24	11	8
Total os OFC	3	4	4	4	4
Accidental OFC	2	4	3	0	4
Schedule OFC	1	0	1	4	0
Age of tolerance (months)	17	34	103	42	24
Atopy personal history	Yes	Yes	No	No	No
Atopy familiar history	Yes	Yes	No	Yes	No
Comorbidities	No	No	3p Microdeletion / 16q Duplication Chiari type 1	Down syndrome and hear disease	Swallowing disorder / immune system dysregulation

4. Discussion

Our data on FPIES patients highlight the importance of early and appropriate management of acute episodes. Dehydration and shock can occur rapidly in severe cases, requiring immediate medical intervention, such as intravenous rehydration and hemodynamic support. Being a rare disease with nonspecific allergy symptoms, it is not a diagnosis frequently suspected in the initial approach, leading to underdiagnosis and often confusion with other pathologies, such as sepsis and acute abdomen [9,10].

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In our study, the mean age of the first manifestation was 35 days, earlier than some studies in the literature that report a median onset at 5.5 months [2]. We believe this discrepancy is related to our patients being initially treated at a tertiary hospital, so the diagnosis was considered earlier. Additionally, literature studies report the median age of FPIES symptom onset considering other triggering foods, and we know that cow's milk protein triggers symptoms more quickly than other foods [2,3,11]. All the children were exposed to cow's milk protein through the use of formulas, supporting the literature indicating that FPIES is rare in exclusively breastfed infants [12].

The observed results also suggest that the disease often requires multiple OFCs for evaluation and management [1,3]. Overall, it is a disease with a good prognosis, with about 50% of children acquiring tolerance by 12 months and 94% by 30 months [6,13,14].

In our population, the mean age for tolerance acquisition was later than in the literature, which we attribute to risk factors such as other atopic conditions and the presence of children with genetic syndromes.

It is known that some factors can influence tolerance acquisition. Overall, tolerance to solid foods is more delayed compared to cow's milk protein tolerance [3,15]. However, patients with other atopic conditions or atypical FPIES (with positive IgE) also acquire tolerance later [1,16,17]. In our sample, we observed an interesting finding: the two patients who took longer to acquire tolerance had genetic syndromes. This association suggests that genetic conditions may play an important role in the process of acquiring tolerance, potentially influencing immune and adaptive mechanisms [18–24].

Pecora V. *et al*. evaluated a group of 51 children with FPIES and showed that DS may be more prevalent in these patients, suggesting a possible genetic connection in the T, B, and innate cell mechanisms involved in the disease, making these children more sensitive to cow's milk protein [25]. Another subsequent retrospective study by Pecora V. et al. of 85 patients with FPIES found that 10 (11.76%) had DS. The main allergens were cow's milk, egg, fish, soy, wheat, and beef. Patients with DS had more severe FPIES reactions than others, with increased leukocytes, absolute neutrophil count, and elevated C-reactive protein levels [26]. Similarly, Okazaki F. *et al.* analyzed 43 children with DS, and 5 (11.6%) were diagnosed with FPIES, all with severe forms of the disease. The causative foods were cow's milk and wheat. A higher incidence of colostomy history was observed in FPIES children, suggesting that formula feeding after this surgery could have been a triggering factor [27].

Iguchi *et al.* reported three cases of children with DS and FPIES. All patients presented with severe manifestations of FPIES induced by cow's milk protein (hypovolemic shock, metabolic acidosis, and acute kidney injury) and required intensive care with fluid resuscitation and alternative diets [28]. Wakiguchi *et al*. evaluated two pediatric patients with Down syndrome and FPIES. Although this rare association is not yet well understood in the literature, they concluded that the condition might be more severe and require a longer duration to establish tolerance compared to patients without Down syndrome [29]. Finally, Jimbo *et al*. published a case report of a child with DS and FPIES, with severe manifestations, and suggested that in severe FPIES children, it is encouraged to introduce unconsumed high-risk foods in the hospital safely to avoid severe reactions at home and prevent unnecessary food eliminations [30]. More studies are needed to evaluate this association; however, based on the data, we believe that children with DS should receive even greater attention due to the severity of the FPIES symptoms and delayed acquisition of tolerance.

A relevant fact is that our study was conducted during the pandemic, and due to difficulties in accessing healthcare services, a significant number of patients did not undergo follow-up and performed TPO without hospital supervision. This practice, although not recommended due to the severity of the symptoms and the risks involved, occurred as a consequence of the restrictions imposed by the pandemic period.

This study has some limitations that should be considered. It is a single-center study, which may limit the generalization of the results to other populations. Additionally, the sample size is relatively small.

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5. Conclusions

FPIES is a rare disease with severe initial symptoms, often underdiagnosed. Despite its good prognosis, management is complex, often requiring multiple OFCs until food tolerance is acquired. Although tolerance to cow's milk protein is acquired earlier compared to other foods, certain factors, such as other atopic conditions and genetic syndromes, can delay this acquisition. While the data provides valuable insights into the nature and management of this condition, there is still much to learn about its pathophysiology, risk factors, and effective treatments.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

DS	Down syndrome
FPIES	Food Protein-Induced Enterocolitis Syndrome
OFC	Oral Food Challenge

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