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ORIGINAL ARTICLE

Diagnostic validity of fecal occult blood test in infants with food protein-induced allergic proctocolitis

Estudio de validez diagnóstica de la prueba de hemorragia oculta fecal en lactantes con proctocolitis alérgica inducida por proteína alimentaria

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Abstract

Introduction: Food protein-induced allergic proctocolitis (FPIAP) is the most frequent presentation of non-IgE mediated food allergy (FA). The diagnosis is made by oral food challenge, however, non-invasive diagnostic tests are not available. In Chile, the fecal occult blood test (FOBT) is frequently used to confirm FPIAP, however, there are no studies that support this practice. **Objective:** To establish the diagnostic validity of FOBT in the evaluation of infants with FPIAP. **Patients and Method:** Case-control study with prospective recruitment of infants with rectal bleeding and suspicion of FPIAP, and controls were healthy infants, in whom the FOBT was conducted. All cases underwent an elimination diet, after which the diagnosis of FPIAP was confirmed by oral food challenge. **Results:** 25 cases and 29 controls were included without significant differences in age, gender, type of delivery, feeding, and maternal age. The cases had higher rates of allergic comorbidities, medication use, and family history of allergy. The FOBT was positive in 84% of cases and in 34% of controls ($p < 0.001$). The sensitivity of the FOBT for the diagnosis of FPIAP was 84%, specificity was 66%, positive predictive value 68%, and the negative predictive value 83%. The area under the ROC curve was 0.75 (CI 95% 0.61-0.88). **Conclusions:** Although the FOBT has an adequate sensitivity to diagnose FPIAP in infants with rectal bleeding, this test had abnormal results in more than a third of healthy infants. Therefore, the routine use of FOBT is not recommended for the diagnosis of FPIAP.

Keywords:
Allergic proctocolitis;
milk allergy;
food allergy;
occult blood;
infant

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Introduction

Food allergies (FAs) are very frequent diseases in children, with a cumulative prevalence of 3-6% in the general population and possibly an increasing incidence[1]. FAs can be divided into those of immediate hypersensitivity that are mediated by specific immunoglobulin E (IgE) against food allergens and can trigger anaphylaxis, and those of delayed hypersensitivity or non-IgE-mediated that mainly affect the gastrointestinal tract. In Chile, immediate hypersensitivity FAs have been reported to affect 5.5% of schoolchildren[2]. Of the non-IgE-mediated FAs, the most common form is food protein-induced allergic proctocolitis (FPIAP), although its exact prevalence is unknown[3].

International studies show that in infants the prevalence of cow's milk protein allergy (CMPA) is about 2%[4,5]. In a recent study of infants in Santiago, Chile, the incidence of CMPA was 4.9%, mostly non-IgE-mediated. Although the authors of this study do not explicitly report the incidence of FPIAP, they do describe that at least 1.6% of infants had mucous stools and/or rectal bleeding due to CMPA, suggesting that the incidence of FPIAP in Chile may be around this figure[6].

FPIAP is characterized by stools with blood and/or mucus in infants who usually appear to be healthy. They may also have other symptoms such as colics, gastroesophageal reflux, vomiting, diarrhea, or pain on defecation. Different studies report that FPIAP causes between 18 and 64% of rectal bleeding in infants[7,8]. Although its etiology and pathogenesis are unclear, FPIAP in infants develops after exposure to food antigens, either from intake of milk formulas or from exposure through breastfeeding.

Cow's milk protein (CMP) is the food most frequently associated with non-IgE-mediated gastrointestinal FA. In exclusively breastfed infants, FPIAP has been described as usually due to CMP, soy, egg, and corn in the maternal diet. Meanwhile, in children fed with milk formula, FPIAP is usually due to CMP or soy[9]. In 60% of cases, FPIAP develops while exclusively breastfed[10]. It most often begins between the second and eighth week of life, however, disease onset has been described from the first week of life[11]. In most cases, FPIAP resolves by the age of 12 months, unlike food protein-induced enterocolitis and enteropathy syndromes that can persist into later life. However, most non-IgE-mediated gastrointestinal FAs that begin in infancy resolve before school age[3].

While IgE-mediated FAs have accurate diagnostic tests such as skin prick tests and serum-specific IgE measurement, there are no non-invasive diagnostic tests validated for the diagnosis of non-IgE-mediated FAs such as FPIAP. Therefore, in order to establish the association between gastrointestinal symptoms and non-IgE-mediated FA, it has been determined that the gold standard is, as in IgE-mediated FA, the oral food challenge (OFC) test that induces recurrence of symptoms after re-exposure to food[12,13].

A diagnostic dilemma repeatedly faced by pediatricians and other physicians is that, in the absence of macroscopic rectal bleeding, it is often difficult to distinguish FPIAP symptoms from common and benign signs and symptoms that occur in infants such as physiological gastroesophageal reflux, watery stools, constipation, and infantile colics. For this reason, it is currently essential to perform the OFC test to avoid overdiagnosis, excessive medicalization, and dietary interventions that are often unnecessary.

In Chile, the diagnosis of FPIAP is often supported by the fecal occult blood test (FOBT), although there is no evidence in the literature for this. In a study carried out in 106 children in Santiago with suspected CMPA, it was observed that 37 of them (34%) had undergone the FOBT[14]. Out of these, 20 patients had rectal bleeding and only seven had positive FOBT. Of the remaining 17 patients who did not have rectal bleeding, five had a positive test. However, this study included forms of CMPA other than FPIAP and the diagnosis was not confirmed with OFC in all patients.

The use of FOBT is not mentioned in the CMPA clinical guidelines of the Chilean Ministry of Health[15], nor in the foreign clinical guidelines of the World Allergy Organization (DRACMA)[4], the European Society for Pediatric Gastroenterology, Hepatology and Nutrition[5] or the European Academy of Allergy and Clinical Immunology[16].

The hypothesis of this study is that FOBT does not correctly distinguish patients with FPIAP from healthy infants. The main objective is to determine the diagnostic validity of FOBT in the evaluation of infants with FPIAP. As secondary objectives, we aim to describe the clinical characteristics of infants with FPIAP.

Patients and Method

Study design and population

A case-control study with prospective recruitment was designed. The inclusion criteria of cases were age less than one year with macroscopic rectal bleeding, exclusively breastfed, receiving mixed feeding or exclusively formula-fed. The exclusion criteria were other forms of non-IgE-mediated FA (e.g. allergic enteropathy), history of necrotizing enterocolitis, inflammatory bowel disease and other chronic bowel diseases, and IgE-mediated FA (e.g. anaphylaxis to CMP).

The inclusion criteria for the controls were age under one year and healthy at the time of recruitment.

The exclusion criteria were history of FA or other allergic diseases (e.g., atopic dermatitis), chronic intestinal diseases, history of necrotizing enterocolitis, and family history of FA in first-degree relatives.

The calculated sample size was 42 patients, 21 cases and 21 controls assuming an α error of 0.05 and β of 0.20 and a conservative estimate of the prevalence of a positive FOBT in healthy infants of 15%.

This study was approved by the Scientific Ethics Committee of the Faculty of Medicine of the Pontifical Catholic University of Chile and was conducted in compliance with the regulations of good clinical practice.

Study procedure

Patients were evaluated at outpatient centers in the Christus UC Health Network or at the UC Clinical Research Center. At the time of recruitment, the study procedures were explained to parents and/or guardians and the informed consent process was conducted. Parents were then given a detailed questionnaire of their child's health history and symptoms of FA, and participants underwent a complete physical examination.

In children with rectal bleeding and suspected FPIAP, standard therapeutic management determined by national and international clinical guidelines was performed. They were asked to discontinue CMP (or other food potentially causing the bleeding) for four weeks, either in maternal diet if she was breastfeeding and/or in the infant if she/he was formula-fed. In addition, a detailed guideline for CMP-free feeding and/or other suspicious foods was provided.

Formula-fed infants were asked to avoid the suspected food and if it was CMP, were prescribed an extensively hydrolyzed milk formula. In those who did not tolerate extensively hydrolyzed formula, it was changed to an elemental amino acid-based formula. At four weeks, an OFC was performed with CMP intake in the mother if she was breastfeeding or in the child if she/he was formula fed. In those who recurred with rectal bleeding after the challenge, the diagnosis of FPIAP was confirmed and the patient was defined as a 'case'. Differential diagnosis of other causes of rectal bleeding was made by physicians who evaluated the patient, ruling out other obvious causes of rectal bleeding (e.g., anal fissure).

During this period, two stool samples were taken, the first one at the time of recruitment between 0 and 72 hours after rectal bleeding, and the second one, when healthy and without macroscopic rectal bleeding, for at least two weeks after the onset of the elimination diet to ensure that the child was healthy (i.e. without bleeding). This was done in order to compare the stools of the child when sick versus healthy.

The fresh stool samples were obtained from the diaper and stored in 3 mL of RNAlater® solution (Ambion®, New York, USA) which were refrigerated at 4ºC and then sent to the Translational Allergy and Immunology Laboratory of the Pontifical Catholic University of Chile. All samples were then stored at -80ºC and analyzed at the end of the study.

After thawing, each sample was homogenized in the RNAlater® stabilizing solution and the fecal blood was then determined using the one-step fecal occult blood test kit (ABON® FOB, Hangzhou, China). For this, 10 µL of the homogeneous solution was added to the kit's collecting tube, vigorously shaken by inversion and two drops were added to the test device. After five minutes, the results were read. The presence of two colored lines indicated a positive result for the presence of blood in the stool sample.

Statistical analysis

Statistical analyses were performed using IBM® SPSS® software version 25.0 (IBM Corp., Armonk, NY). Statistical comparison between cases and controls was performed through Student T-test for numerical independent variables or Chi-square test for categorical variables. A ROC (receiver operating characteristic) curve was then performed and the sensitivity, specificity, positive and negative predictive value were determined. All values are expressed as an average ± standard deviation unless otherwise specified. A bidirectional P-value less than 0.05 was considered statistically significant.

Results

Clinical characteristics

25 cases with rectal bleeding and 29 healthy controls were included, with no significant differences between them in age, gender, type of delivery, feeding, maternal age, and average number of children. Table 1 shows the clinical and demographic characteristics of the patients. The average age of onset of FPIAP symptoms in cases was 2 ± 1.5 months and the average age of the first sample collection was 3.8 ± 2.6 months. 48% of the cases were delivered by c-section and 72% of them were exclusively breastfed at the time of their first rectal bleeding episode. In patients fed either mixed or exclusive formula, the average time between the start of formula feeding and rectal bleeding was 11 ± 12.8 days.

As comorbidity of FPIAP, 56% of the cases presented seborrheic dermatitis, 20% atopic dermatitis, 12% bronchiolitis, and 8% allergic rhinitis. In contrast, only one of the controls presented comorbidity which was bronchiolitis. A 48%[12] of the cases used some medi-

cation, most often probiotics and proton pump inhibitors. Twenty-two cases (88%) had family history of allergy and nine cases (36%) had history of a sibling with FA. The symptoms most frequently associated with rectal bleeding were colics (92%), gastroesophageal reflux (52%), atopic/seborrheic dermatitis (56%), diaper rash (48%), sleep disturbance (40%), poor weight gain (20%), and food rejection (4%) (Figure 1).

Fecal occult blood test

The FOBT was positive in 84% of cases (first sample) and in 34% of controls ($P < 0.001$) (Figure 2). The sensitivity of the FOBT for the diagnosis of FPIAP was 84% (95% CI: 64-95%), specificity 66% (95% CI: 46-82%), positive predictive value 68% (95% CI: 55-78%), and negative predictive value 83% (95% CI: 65-92%) (Table 2). The analysis of the ROC curve showed an area under the curve of 0.75 (95% CI 0.61-0.88).

In the second sample of FOBT taken from the cases, being healthy and without macroscopic rectal bleeding, the test was positive in 16%.

Discussion

This study assesses the diagnostic validity of FOBT in infants with rectal bleeding secondary to FPIAP compared to healthy infants. The results of this study show that, although FOBT has adequate sensitivity to diagnose FPIAP in infants with macroscopic rectal bleeding, it has inadequate specificity since more than one-third of healthy infants had positive FOBT.

Previous studies in healthy infants or with non-allergic diseases have shown a high prevalence of positive FOBT. Gralton KS, et al. observed that in a group of 180 children under one year of age hospitalized due to non-gastrointestinal diseases, 22.8% had positive FOBT[17]. Another study of 31 healthy 9-month-old infants fed with cow's milk formula showed that 29% of them had occult blood in their stools[18]. This study showed 34% positivity of FOBT in healthy infants, a figure even higher than that of previous studies, reaffirming the inapplicability of using this test to diagnose gastrointestinal pathologies in infants given the high number of false positives. The causes of the high prevalence of altered FOBT in healthy infants are not clear. The digestive mucosa from the oral to the perianal zone is exposed to multiple lesions of different kinds and any minor mucosal damage that allows the escape of red blood cells to the lumen will be evidenced by the occult blood test, hence the low specificity that it has in the diagnosis of specific digestive disorders.

The diagnosis of non-IgE-mediated FA is still a major clinical challenge. Unlike IgE-mediated FAs where the pathogenesis of the disease is very well defined, the absence of a clear etiopathogenesis for non-IgE-mediated FAs makes it difficult to develop valid and accurate diagnostic tests.

It has been proposed that delayed maturation of the gastrointestinal immune system leads to the food hypersensitivity that characterizes FPIAP[19]. Therefore, histopathological alterations in the rectosigmoid colon of affected infants are generally sought.

Rectosigmoid biopsy studies of infants with FPIAP have shown eosinophilic and T-lymphocyte infiltrates in the lamina propria[20,21]. A meta-analysis showed eosinophilic infiltration in colonic or rectal biopsies in 89.3% of patients, although there may have been a bias in including biopsy confirmed patients in the studies analyzed[22]. Since obtaining these biopsies requires endoscopic studies, it is usually preferred not to perform them when FPIAP is suspected due to its invasive nature for infants, and it is reserved for infants with massive bleeding or as part of a differential diagnosis of hematochezia. In addition, the variability between biopsy samples from the same patient is wide. In a clinicopathological study of FPIAP conducted by Odze et al., 40% of patients had one or more normal biopsy samples[11].

Other researchers have looked for non-invasive serum and fecal biomarkers for the diagnosis of FPIAP, but have failed to find tests with adequate sensitivity and specificity. The meta-analysis by Lozinsky et al. showed that 48.3% of 263 infants with FPIAP had eosinophilia in blood[22]. In addition, a decreased ratio of interferon-γ/IL-4, an increase in Th2 lymphocytes, and a decrease in regulatory T lymphocytes have been observed[23]. However, none of these findings are specific to FPIAP, but rather demonstrate an atopic state or other allergic diseases.

For diagnostic tests of FPIAP in stools, stool smear samples typically do not show eosinophils[11]. More promising reports have shown proteins derived from eosinophilic granules in stools of children with FPIAP or with food protein-induced enterocolitis syndrome[24,25]. Saarinen KM, et al. showed elevated concentrations of eosinophilic cationic protein in stools of children with FA with late gastrointestinal symptoms, however, this study included patients with IgE-mediated and non-IgE-mediated CMPA[24]. Finally, it should be noted that serum-specific IgE measurements, as well as skin prick and patch tests, are not recommended for the diagnosis of FPIAP or other non-IgE-mediated gastrointestinal allergies[3,26]. Other markers of inflammation such as fecal calprotectin do not differentiate between colonic inflammation of different origins (infectious, allergic, etc.), in addition to their physiological elevation during the first year of life[27].

Considering the above background, and as recom-

Table 1. Clinical and demographic characteristics of patients

Characteristic	Cases (n = 25)	Controls (n = 29)	P-value
First stool sample age, months (mean ± SD)	3.8 ± 2.6	3.3 ± 1.9	0.41
Symptom onset age, months (mean ± SD)	2 ± 1.5	-	-
Gender, n (%)			0.79
Male	13 (52%)	14 (48%)	
Female	12 (48%)	15 (52%)	
Type of delivery, n (%)			0.46
C-section	12 (48%)	11 (38%)	
Vaginal	13 (52%)	18 (62%)	
Exclusive breastfeeding, n (%)	18 (72 %)	18 (62%)	0.44
Time between start of formula feeding and symptoms, days (mean ± SD)	11 ± 12.8	-	-
Maternal age, years (mean ± SD)	31 ± 4	32 ± 4	0.56
Child number, (mean ± SD)	2.2 ± 1.0	2.1 ± 1.5	0.97
Comorbidity, n (%)			
Seborrheic dermatitis	14 (56%)	0	< 0.001
Atopic dermatitis	5 (20%)	0	< 0.001
Bronchiolitis	3 (12%)	1 (4%)	0.23
Allergic rhinitis	2 (8%)	0	0.12
Medications, n (%)			
Probiotics (Lactobacillus reuteri)	8 (32%)	4 (14%)	0.11
Proton pump inhibitors	5 (20%)	0	0.01
Levocetirizine	2 (8%)	0	0.12
Zinc	2 (8%)	0	0.12
Family history, n (%)			
Cow's milk protein allergy	9 (36%)	0	< 0.001
Atopic dermatitis	5 (20%)	0	0.01
Asthma	10 (40%)	2 (7%)	0.004
Allergic rhinitis	13 (52%)	2 (7%)	< 0.001

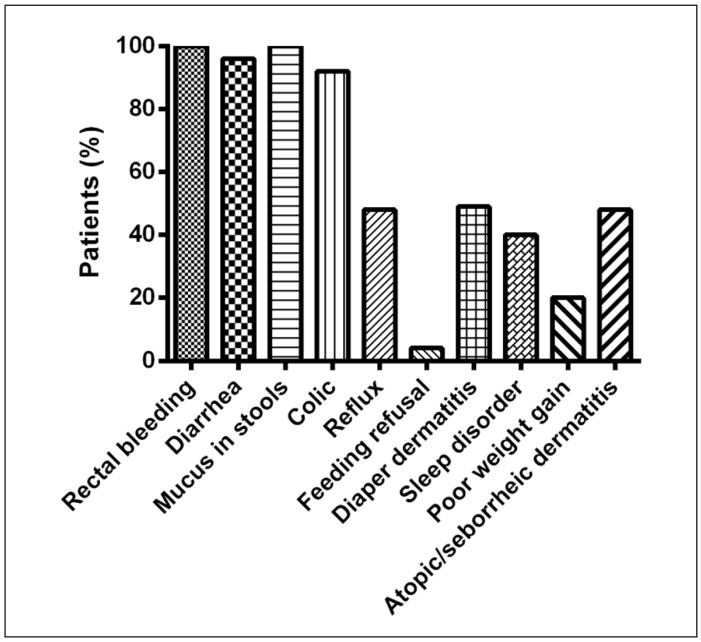

Figure 1. Symptoms of patients with food protein-induced allergic proctocolitis (n = 25).

mended by national and international guidelines, in the absence of objective diagnostic tests, the correct way to make the diagnosis of FPIAP is through a 2-4 week elimination diet and then an oral food challenge test[4,5,15]. The latter can be performed at home for infants with FPIAP, unlike IgE-mediated FA or food protein-induced enterocolitis syndrome[19].

As this study addresses the diagnostic validity of FOBT, only infants with rectal bleeding and high suspicion of FPIAP were recruited, excluding infants with possible FPIAP who did not have macroscopic gastrointestinal bleeding. This was done with the intention of recruiting really sick patients, avoiding including infants with doubtful diagnosis or gastrointestinal symptoms of another cause, and thus being able to contrast the results of the diagnostic test in patients with the disease versus healthy patients.

In conclusion, altered FOBT is not specific for determining or confirming the diagnosis of FPIAP in infants with rectal bleeding as this test is altered in more than one-third of healthy infants. Therefore, it should

not be used routinely in patients suspected of having this disease. In the future, new diagnostic tests are needed to make a correct and accurate diagnosis of FPIAP and other non-IgE-mediated FAs.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

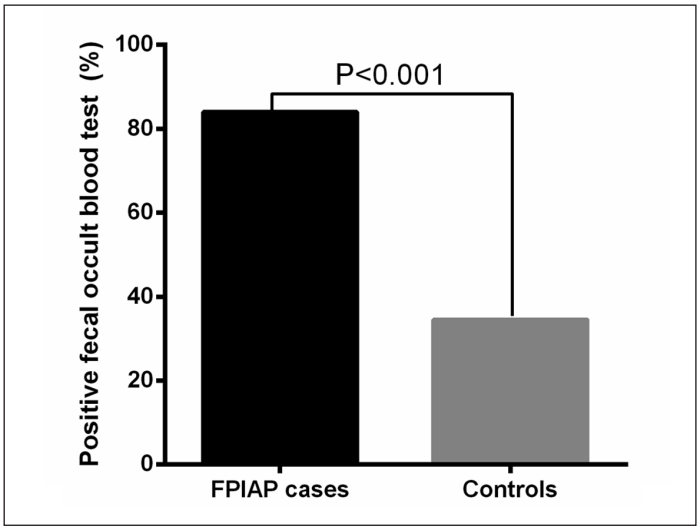

Figure 2. Fecal occult blood test in infants with food protein-induced allergic proctocolitis and healthy controls.

Table 2. Sensitivity and specificity of the fecal occult blood test in the diagnosis of food protein-induced allergic proctocolitis in infants

		FPIAP		
		+	-	
FOBT	+	21	10	31
	-	4	19	23
		25	29	

Sensitivity = 84% (IC 95% 64% - 95%)
Specificity = 66% (IC 95% 46% - 82%)
Positive predictive value = 68% (IC 95% 55% - 78%)
Negative predictive value = 83% (IC 95% 65% - 92%)

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