Rectal bleeding and cow's milk protein-induced allergic proctocolitis: A prospective study

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Key messages:

- Only 1/3 of rectal bleeding before 4 months of age was an allergic proctocolitis (FPIAP).
- Median age of resolution of FPIAP induced by cow's milk (FPIAP-CMP) was 6.8 months.
- Acquisition of tolerance in FPIAP-CMP should be tested before the age of 9 months.

To the editor,

Food protein-induced allergic proctocolitis (FPIAP) is a non IgE-mediated allergy, usually occurring in infants under six months of age, whose symptoms are rectal bleeding (RB) as well as diarrhoea in 1/3 of cases, with normal growth. Cow's milk protein (CMP) allergy (CMPA) is the first diagnosis evoked by the majority of practitioners when RB occurs in a CMP-fed infant,[1] while some studies suggest that CMPA is not involved in the majority of cases.[1–3] The only diagnostic test involves eliminating-reintroducing the culprit food. RB usually disappears within 72 hours after starting the elimination diet and reappears after a challenge. When the diagnosis is confirmed, management consists in excluding the culprit food, which is usually CMP.[4,5] In CMPA, it is recommended to test the acquisition of tolerance from the age of 12 months.[6] Although non IgE-mediated digestive allergies such as FPIAP resolve earlier than IgE-mediated allergies,[6] it is not yet recommended to perform these challenges before the age of 9-12 months.[7] However, tolerance in FPIAP induced by CMP (FPIAP-CMP) may occur even earlier than in other non-IgE-mediated CMPA.

To confirm this postulate, we first assessed the incidence of FPIAP-CMP in a cohort of newborns and infants with RB, and then determined the age at tolerance acquisition in confirmed FPIAP-CMP patients (ClinicalTrials.gov ID: NCT04651829; ethic approval from

the French-speaking Paediatric Hepatology, Gastroenterology and Nutrition Group (GFHGNP) (#2020-017); parents received oral and written information about the protocol according to the Helsinki declaration). All infants under 4 months of age who were referred for visible RB (from repeated bloody spots to more abundant fresh blood in or around stools) in our Paediatric Gastroenterology Department, through the Emergency department, the Neonatology or the Maternity ward, were prospectively approached between May 2014 and December 2017. Only children whose RB disappeared after a CMP elimination diet were selected for the study. An oral food challenge (OFC) for diagnostic purposes (OFC-D) was carried out after 2-8 weeks of a CMP elimination diet, at home, with a simple gradual cow's milk reintroduction protocol over several days. Diagnosis of FPIAP-CMP was confirmed when the parents reported reappearance of RB, diarrhoea, vomiting, worsening of pre-existing regurgitation, weight stagnation, and/or significant change in behaviour such as food refusal, sleep disorder, excessive crying within the following two weeks. When FPIAP-CMP was confirmed, an open OFC was proposed every two months from the age of four months to determine the acquisition of tolerance (OFC-T). Skin prick test and/or specific IgE were assessed regularly. Tolerance to CMP was confirmed when the infant consumed CMP daily without any recurring symptoms (similar to those mentioned before). Exclusion criteria were RB due to another cause – gastrointestinal infection, surgical aetiologies (volvulus, acute intestinal intussusception, Hirschsprung disease), ulcerative necrotizing enterocolitis, local causes (anal fissures, perianal erosions), coagulopathy; exclusive breastfeeding; infants who did not have OFC-D within three months after the start of elimination diet.

Seventy-six patients consulted for RB before the age of 4 months over the study period. Reasons for exclusion (n=15 patients) are presented in Figure 1. Amongst the remaining 61 patients, the RB disappeared after the exclusion of CMP for 58, who therefore constituted our study cohort. The median age at onset of RB was 21 days (range=0-120), or two days after the first introduction of CMP (range=0-84, mean: 11 days). No infants were receiving

complementary feeding at the time of onset of RB. The age at the time of starting the CMP elimination diet was 23 days (range=2-141), with a median of two days after the onset of symptoms (range=0-34, mean: 5 days). Due to persistence of RB, 10 patients required an AAF, within a median time of 8 days (range=2-26). Four patients received AAF as the first-line treatment after the onset of RB.

OFC-D was performed 36 days (range=13-80) after the start of CMP exclusion at a median age of 68 days (range=24-195). Eighteen (31.0%) patients experienced objective and/or subjective significant and persistent symptoms during OFC-D and were therefore considered to have FPIAP-CMP. The observed clinical manifestations leading to the diagnosis of FPIAP-CMP during OFC-D were as follows: relapse of RB in 38.9% of cases (n=7), significant behavioural change in 33.3% (n=6), diarrhoea in 22.2% (n=4), and vomiting in 5.6% (n=1). The clinical characteristics of the patients did not differ between the groups of patients (FPIAP-CMP with or without RB at OFC-D and non FPIAP-CMP, Table 1).

The median age at acquisition of tolerance was 6.8 months (range=3.5-24; n=16). Survival analyses showed that 75.0% of the cohort were tolerant before the age of 10 months. This corresponded to a median period of 6.2 months (range=2.7-24) between the first symptoms and resolution of the allergy. Two patients were lost to follow-up, so not included in analyses.

Infants with a first-degree family history of atopic disease (reported past or current asthma, food allergy, rhinoconjunctivitis, eczema in parents or siblings) (n=9) acquired tolerance to CMP later, *i.e.* at the age of 8.9 months (range=6.4-24), versus 5.1 months (range=3.5-10.0) when there was no family history of atopic disease (n=7) (p=0.016). Neither breastfeeding at the time of the symptom onset (p=0.7), nor age at the time of symptom onset (p=0.9) were associated with the age of tolerance.

Serological tests for allergy were performed in 34 patients (58.6%) during the first consultation (n=10, 55.6% in the FPIAP-CMP group; n=24, 60.0% in the non FPIAP-CMP group). At diagnosis, all the tested patients had CMP-specific IgE below 0.35 kU/L, except one who had a betalactoglobulin-specific IgE of 0.54 kU/L in the non FPIAP-CMP group, without IgE-mediated clinical manifestations. During follow-up, only one out of 18 patients had IgE seroconversion with CMP-specific IgE of 8.69 kU/L at 15 months of age. For this patient, the acquisition of tolerance was slower, with a change in symptoms over time suggesting an atypical food protein-induced enterocolitis syndrome (FPIES), with no cutaneous or respiratory manifestations, and without history of atopic dermatitis. In this case, tolerance to CMP was acquired at the age of two years.

We confirmed here that more than two-thirds of infants whose RB disappeared after exclusion of CMP did not relapse during OFC-D performed several weeks later. The recurrence of objective digestive symptoms was 20.7% (n=12/58). This result is close to that found in other studies undertaken with smaller populations than ours. Indeed, Arvola *et al.* attributed RB to CMP in only seven of 40 infants (17.5%).[2] No specific cause could be identified for the majority of the other patients.[2] In the birth cohort of Elizur *et al.*, RB relapsed in 21.4% of infants (3/14) during OFC-D.[3] In Korea, two of 16 infants with low-abundance RB had confirmed FPIAP.[8] Our overall frequency of FPIAP-CMP (31.0%) was possibly over-estimated in our cohort than in other published studies, because we considered non-specific subjective symptoms such as significant persistent behavioural change (*e.g.* excessive crying), which could be attributed to the change of infant formula. Since most RB is not due to CMP and some disappear spontaneously, a period of four days before starting a CMP-free diet is recommended by some authors in the absence of signs of severity.[9] We share this position.

This work also highlighted that FPIAP-CMP resolved in half of cases before the age of 7 months and in three-quarters of cases before the age of 10 months. Age at FPIAP-CMP

resolution is still imperfectly known and there are no specific guidelines, neither regarding the age from which a first OFC-D can be offered, nor for the recommended interval between each OFC-T. Few authors therefore propose OFC-T before the age of nine months.[4,5] A very few research studies suggest, however, that some FPIAP cases resolve before the age of 9-12 months. It therefore seems reasonable to start OFC-T from the age of 4-6 months and repeat it every two months to prevent many infants from unnecessary CMP free-diet. Although seroconversion in IgE-mediated forms is rare since it affected only one of our patients, OFC-T should be preceded by a specific IgE assay or a skin prick test (unlike OFC-D[7]), and OFC-T may be performed at home only in the event of negative results. Note that patients with FPIAP and specific positive IgE become tolerant later on,[5] as was the case for our patient.

The main limitation of our study was that we did not perform double-blind reintroduction tests. However, the open OFC at home is the first choice to evaluate the tolerance to milk in mild to moderate non IgE-CMPA,[7] with a known risk of the parents over-interpreting the subjective symptoms. In these situations, we tried to support parents, and to convince them to continue reintroduction by slowing down reintroduction, but there was still a risk of over-diagnosing the FPIAP-CMP.

In conclusion, this work confirmed that the RB of newborns and infants fed CMP is due to an allergy to CMP in less than one-third of cases. For confirmed forms of FPIAP-CMP, it also underlined the need to test the acquisition of tolerance before the age of 9 months, which is currently the recommended age, since the majority of cases resolve before this age. These results should help to modify the recommendations for these forms of non-IgE-mediated allergy.

Author contribution: JA, JL and PT involved in project concept and study design. AL and JA contributed to data acquisition. AL involved in analysis and interpretation of data, and wrote the first draft of the manuscript. All authors contributed to manuscript editing, reviewed and approved the final version of the manuscript.

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

Tables

Table 1: Patients' characteristics

	FPIAP-CMP n=18		Non FPIAP-CMP n=40	p
	Rectal bleeding at OFC-D n=7	Other symptoms at OFC-D n=11		
Boys (n; %)	5 (71.4%)	6 (54.5%)	22 (55.0%)	0.8
Age at first symptoms (days) (min-max)	30 (6-47)	12 (1-49)	21 (0-120)	0.2
Time period after first exposure to cow's milk (days) (min-max)	20 (5-31)	5 (0-17)	2 (0-84)	0.8
Age at cow's milk elimination diet (days) (min-max)	27 (9-31)	20 (3-63)	28 (2-141)	0.2
Time period between elimination diet and OFC-D (days) (min-max)	36 (15-61)	44 (13-78)	34.5 (18-80)	0.5
Age at OFC-D (days) (min-max)	67 (31-85)	68 (24-101)	69 (31-195)	0.7
Breastfeeding at the time of symptoms (n; %)	2 (28.6%)	7 (63.6%)	19 (48%)	0.4
Age of tolerance (months) (min-max)	7.2 (3.5-24)	6.1 (4.0-12.8)	-	0.7
Prematurity (< 37 weeks of amenorrhea)	2 (28.6%)	2 (18.2%)	13 (32%)	0.8
Term if prematurity (weeks of amenorrhea) (min-max)	35.3 (33.7-36.9)	33.6 (33.3-34.0)	33.7 (31.7-36.6)	0.5
Bronchiolitis or childhood asthma (n; %)	0	0	0	-
Other food allergy (n; %)	0	0	0	-
Atopic dermatitis (n; %)	1 (14.3%)	1 (9.1%)	5 (12.5%)	1.0
Family history of atopy (n; %)	5 (71.4%)	6 (54.5%)	25 (62.5%)	0.8

FPIAP-CMP: food protein-induced proctocolitis induced by cow's milk proteins; OFC-D: oral food challenge for diagnosis purposes

Figure legends

Figure 1: Flow chart

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