

Multiple food allergy: a possible diagnosis in breastfed infants

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Six infants suspected of food allergy during breastfeeding were evaluated using prick tests, total IgE, RASTs and intestinal permeability measurements during fast and provocation with mother's milk. An elimination diet was undertaken in mothers, removing first cow's milk protein (CMP), then, when inefficient, all foods suspected on the clinical history or a positive prick test in the child, followed by oral challenges in mother's diet with the corresponding food. The sole CMP-free diet in mothers always proved insufficient. In four, an additional diet excluding two to three other foods cleared the symptoms. Oral provocations in mother's diet with those foods were positive in all. In two, mothers turned down a diet excluding more than four foods, symptoms cleared while feeding the child with an extensively hydrolysed formula, whereas challenges with mother's milk induced immediate reactions. Intestinal permeability was altered during provocation tests with mother's milk sampled before maternal diet. Food allergy during breastfeeding may be due to multiple foods and the inefficacy of the sole CMP elimination in mothers does not rule out food sensitization.

□ Allergy, breast-milk, infant

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β -Lactoglobulin (1, 2) and other dietary proteins, such as ovalbumin, ovomucoid (3) and gliadin (4) have been detected in mother's milk, indicating that food antigens can pass from mother to infant via breast-milk. This probably reflects a naturally occurring phenomenon (5), which could also be responsible for sensitization and development of food allergy in some infants with an allergic predisposition. They react to dietary proteins during breastfeeding with eczema (6, 7), colic (8), colitis (9, 10) and even anaphylactic shock (11). The most often incriminated food is cow's milk and the frequency of cow's milk protein (CMP) allergy (CMPA) during exclusive breastfeeding amounts to 0.4% in Swedish infants (12). Egg and soy may also be involved and their elimination by the mother has been recommended when CMP avoidance is inefficient (13). However, infants can tolerate milk and react to other food proteins (14, 15), the responsibility of which remains overlooked for most of the time (8, 11). The purpose of this paper is to stress the benefit that breastfed infants with symptoms possibly relevant to allergy may gain from being managed by taking into account the role of multiple food allergy.

Subjects and methods

Subjects

Patients were six breastfed infants (4M and 2F), suspected of being allergic to breast-milk components because of suggestive symptoms, such as vomiting, colic and diarrhoea and/or eczema (Table 1). Five infants presented with digestive symptoms that appeared during the first month of life.

They were receiving medical treatment for protracted regurgitation and/or vomiting, without any benefit. Two of them also suffered from apparent life-threatening events with bradycardia and hypotonia, occurring after breastfeeding. The sixth infant exhibited eczema alone at age 2 months.

Three infants had never received CMP (case nos. 1–3) and one lactating mother (case no. 1) had adhered to a CMP-exclusion diet since delivery because of CMPA in the previous infant. A partially hydrolysed formula (Nestlé, Diepal NSA) had been given during the first 3 days of life in case nos 4 and 5 and was given at an amount of about 1 bottle per day since the age of 3 weeks in case no. 6. In the latter case, mother stopped giving the partially hydrolysed formula at age 5 weeks, but symptoms did not improve under exclusive breastfeeding. All but one had first degree relatives with atopic disease (Table 1).

Methods

Skin prick tests. Standard glycerinated extracts (Stallergènes, France) were applied by the prick technique in the child's back, using Stallerpoint® lancets (Stallergènes, France). Prick tests with mother's milk were performed by the prick technique using a drop of mother's milk obtained at the time of the test. Histamine dihydrochloride, 10 mg/ml, was used as a positive control, and 50% glycerol as a negative one. Wheal reactions 3 mm greater than the negative control were considered positive (16).

Intestinal permeability tests. Intestinal permeability tests (IPT) were carried out according to the method previously

Table 1. Clinical data of patients and previous history of atopic disease in mother and first degree relatives.

Case	Age at onset of symptoms	Diet	Symptoms	Atopic disease in mother	Atopic disease in father and siblings
1	2 months	BF*	eczema	Quincke oedema (kiwi), eczema	sister: multiple food allergy
2	first week 2 months 3 months	BF	regurgitation, crying ALTE after feeding gastritis	rhinitis	brother: CMPA
3	first week 2 months	BF	diarrhoea, failure to thrive crying, ALTE after feeding, regurgitation	urticaria (strawberry), eczema, rhinitis	sister: asthma brother: asthma
4	15 days 2 months	BF	colic, regurgitation refusal to eat, gastritis	urticaria Quincke oedema (paracetamol)	none
5	20 days 3 months	BF	colic, constipation eczema, regurgitation	none	none
6	3 weeks 1 month 1/2	BF + PHF BF	regurgitation, colic regurgitation, colic	angioedema (peach)	sister: asthma

BF, breast feeding, PHF, partially hydrolysed CMP formula, ALTE, apparent life threatening event.

Mother undertaking CMP exclusion diet, children who received partially hydrolysed CMP formula 1–3 times during the first 3 days of life.

described (17). Briefly, urine was collected during the 5 h following the ingestion of a mannitol/lactitol aqueous solution (0.1 g/kg of body weight for each sugar, 1.001 mOsm/l). During the fasting IPT, markers were given alone. The next day, a provocation IPT was performed in similar conditions, markers being given mixed with 100 ml of breast-milk. Analysis was performed by gas–liquid chromatography. Results were expressed as the proportion of oral mannitol and lactitol excreted and as the ratio of these values (L/M ratio, percentage). For the provocation IPT, the L/M ratio was expressed by comparison with that of the fasting IPT: provocation L/M ratio/fasting L/M ratio (P/F). A provocation IPT was considered to be abnormal with $P/F > 1.10$, i.e. the mean + 2 SD of P/F in a control population of non-allergic infants tested with various foods (17).

Diagnosis of allergy to breast-milk-borne antigens

The allergic evaluation started with prick tests, carried out with mother's milk and with cow's milk, soy, egg, fish and peanut (16, 18), together with the foods suggested by the clinical history. A blood sample was performed in order to determine total IgE, RASTs (Pharmacia SA, France), and absolute eosinophil counts. The investigation was completed in all patients by IPTs, during both fast and provocation with mother's milk.

Owing to the frequency of CMPA during breastfeeding (8–10), a CMP elimination diet was systematically undertaken in mothers. In the absence of a total disappearance of symptoms, mothers were prescribed a diet excluding, in addition to CMP, all foods suspected on the clinical history or a positive prick test in the infant (RASTs appeared not to be contributive). If this diet was efficient, challenges with the excluded foods were performed in the hospital ward at

1-week intervals. The mother ingested a normal amount of the food to be tested, breastfed within 12 h and the infant was clinically monitored by the medical staff during the 5 following h. The challenge was considered positive if the medical staff observed vomiting, colic, diarrhoea and/or urticaria in the infant, less than 2 h after breastfeeding. Each time, a previous breastfeeding in the hospital ward before any ingestion by mother of the eliminated food served as a negative control.

In all cases, elimination diets were explained to mothers by a dietician, the compliance checked and adequacy of the nutrients intake supervised.

The diagnosis of allergy to antigens contained in breast-milk was settled on both (i) the disappearance of the child's symptoms either during breastfeeding, with a corresponding elimination diet in mother, or exclusive extensively hydrolysed formula feeding; and (ii) the triggering of clinical symptoms in the infant during provocation by breastfeeding, with ingestion of the incriminated food by mother for those undertaking the elimination diet.

Results

Routine allergy testing

Prick tests were not contributive in case no. 5, characterized by complete skin reactivity and positive with various foods in all other cases (Table 3). Total eosinophil counts were always $< 450/\text{mm}^3$, except in case no. 2. No infant had high total IgE levels (range 1–3 KU/l) or detectable RASTs to any food.

Efficacy of CMP elimination in mothers

CMP elimination in mother's diet was partially effective in

Table 2. Results of the challenges with mother's milk, mother undertaking elimination diet and eating normal amounts of the incriminated food up to 12 h before breastfeeding.

(A) Mothers adhering to an exclusion diet

Case	Foods excluded from mother's diet	Challenge		Time at onset of reaction
		Food	Result	
1	CMP and egg	CMP Egg	ND erythema, pruritus	20 min
2	CMP and fish	CMP Fish	vomiting vomiting	1 h 30 1 h
5	CMP and fish	CMP Fish	colic, vomiting colic, vomiting	30 min 40 min
6	CMP, cocoa apple and egg	CMP Cacao Apple Egg	none colic, vomiting colic, vomiting vomiting	/ 1 h 30 1 h 20 min

(B) Mothers refusing the elimination diet

Case	Infant diet	Result of the challenge with mother's milk (mother undertaking CMP elimination diet)	
3	Alfaré®	diarrhoea, colic	1 h 30
4	Alfaré®	urticaria	30 min

ND, not done; CMP, cpw's milk protein.

cases no. 2 and 5, mothers reporting the total disappearance of symptoms for several days and their occasional reappearance during 24-h periods. In others, the diet did not improve any of the child's symptoms.

Determination of the foods responsible for the adverse effect of breast-milk

In four cases, mothers accepted the exclusion diet based on the clinical history and/or the positive prick tests. In case

nos 1, 2 and 6, all foods yielding a positive SPT in the infant were excluded from the mother's diet, leading to a total disappearance of symptoms. In case no. 5, with negative prick tests, the elimination of CMP in the mother was partially effective (see before) and a thorough clinical history led to suspect fish. Additional fish elimination led to total disappearance of symptoms. The results of food challenges are reported in Table 2.

In case nos 3 and 4, prick tests were positive for, respectively, four and five foods, and mothers were not

Table 3. Result of prick tests, IPTs and efficiency of CMP elimination diet in mothers.

Case	Age (months)	Histamine prick control (wheat diameter, mm)	Positive prick tests (wheat diameter, mm)	Food excluded from mother's diet during IPT and prick tests	Prick test with mother's milk	Fasting IPT (L/M, %)	P/F	Efficacy on the child's symptoms of CMP elimination diet in mothers
1	4	6	egg (6)	CMP	negative	5.2	2.1	Nil
2	3 3.5	4.2	CMP/fish (4, 2)	none CMP	positive negative	3.4	1.15	improvement
3	2.5	4.2	wheat/soy (4, 2) peanut (3), tomato (8)	none	ND	10.2	1.25	nil
4	3 2	8	CMP/fish/celery (6), egg (6), apple (4, 2)	CMP	positive	2.5	1.52	nil
5	3	0	none	CMP	positive	5.4	0.85	improvement
6	2 2.5	6	cocoa/apple (6) egg (4, 2)	none CMP	negative	7.5 12.3	1.45 1.39	nil

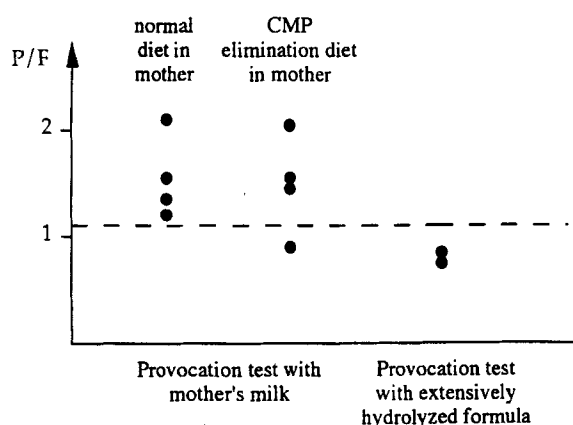


Fig. 1. IPTs are expressed as the ratio of L/M during provocation test (P) and during fast (F). First column: results of the provocation test with mother's milk, mother undertaking a normal diet; second column: results of provocation test with mother's milk, mother undertaking a CMP elimination diet; third column: results of provocation test with extensively hydrolysed CMP formula.

willing to carry out the corresponding exclusion diets. Infants were therefore fed with an extensively hydrolysed formula (Alfaré®, Nestlé) for 1 week and 3 days, respectively, this diet leading to the disappearance of symptoms. A challenge with mother's milk under the CMP elimination diet was performed, leading to immediate reaction (Table 2). In those infants, the incriminated foods remained unknown.

IPTs

Provocation IPTs with mother's milk, mother undertaking a normal diet, were performed in all cases, except for case no. 1, whose mother previously undertook the CMP elimination diet, and for case no. 4. Breast-milk always induced alterations of intestinal permeability with $P/F = 1.50 \pm 0.43$ (mean $\pm$ SD, range 1.15–2.16). These modifications remained while mother was prescribed a CMP elimination diet with an abnormal P/F value in 3/4 cases (Fig. 1). In case nos 3 and 4, a provocation IPT with an extensively hydrolysed formula exhibited a normal P/F, 0.82 and 0.71, respectively (Table 3).

Discussion

We report six breastfed infants with clinical symptoms possibly relevant to allergy, in which CMP elimination in mothers was inefficient. In three cases of this study (case nos 2, 5 and 6), the diet eliminating CMP, egg and soy, as proposed by some authors (10, 13) would have proven inefficient. Such a result does not rule out allergy to other foods. Indeed, many have been incriminated in sensitization of breastfed infants, such as orange, apple, banana, cocoa and pork (14, 15), even in the absence of sensitization to CMP. Our data indicate that one has first to prove

food allergy in the child and then search for the food allergens before starting any dietary manipulations in the mother. The main purpose of such a process is to help encourage breastfeeding.

As a first step, a positive prick test in the child with mother's milk strongly suggests food allergy (19) but does not prove it. IPTs have been shown to be a good tool for the diagnosis of food allergy when studied in basal conditions and after ingestion of the offending food (15, 17). In the present report, provocation IPT with mother's milk, mother undertaking a normal diet, always showed alterations of intestinal permeability. If IPTs are not available, it is possible to feed the infant with a CMP hydrolysate for a couple of days, then to perform an open challenge with mother's milk (10, 11, 13), as in two cases of this study.

When food sensitization in a breastfed infant becomes obvious, the search for the food responsible is the second step. Positive prick tests to different foods never ingested by the infant seem very suggestive of food sensitization (14, 20). In the present report, the diet relying on the positive prick tests was effective, suggesting, if not proving, an acceptable reliability. RASTs to foods were always negative, in contrast with previous reports in whom infants were older (14, 20), or presenting atopic dermatitis (7) or anaphylactic shock (11), the two latter conditions being associated with high IgE levels. In the absence of positive prick tests or RASTs, a careful survey of the clinical history may lead to the discovery of the offending food.

At the end of these investigations, the specific elimination diet must lead, if appropriate, to a rapid disappearance of the child's symptoms. It appeared that the elimination diet was accepted when foods to be excluded numbered less than three. Challenges through the mother's diet must then be performed with all the suspected foods to confirm sensitization in the child. In the absence of double-blind, placebo-controlled, food challenges, almost unfeasible in these particular cases, only immediate reactions controlled by the medical staff were retained for diagnosis. All challenges performed with foods yielding a positive prick test in the infants were clinically positive. Such a diagnosis of food allergy during breastfeeding and of the allergens involved may be important to prevent severe immediate reactions at weaning. Van Asperen et al. (21) reported, in a prospective study, that 6% of breastfed infants of atopic parents presented immediate reactions to foods occurring at the first-known exposure.

In conclusion, food allergy in breastfed infants may be due to multiple foods and the inefficacy of a CMP elimination diet in mothers does not rule out food sensitization. In this difficult condition, our data suggest first to prove food allergy in the breastfed infant and secondly to search for the possible food allergens before dietary manipulations in mothers. Such a process is probably important in preventing severe immediate reactions at weaning. In our experience, multiple food sensitization can occur and the diagnosis procedure may at least partially rely on prick tests and IPTs.

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