

## CASE REPORT

## IgE-mediated cow milk allergy and infantile colic: diagnostic and management challenges

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**SUMMARY**

Cow milk allergy (CMA) is a common problem affecting 2–3% of children and is the most prevalent food allergy in infancy. Infantile colic is also a common problem in the first year of life. A frequent practice among physicians is to recommend a dairy-free diet to breast-feeding mothers and infants in cases of infantile colic. However, recent studies suggest that late introduction of potentially allergenic foods may increase the risk of developing a life-threatening food allergy. We describe two infants managed with dairy-free diet to control symptoms of colic in whom CMA developed. It is possible that unnecessary cow milk restriction may have contributed to the development of food allergy in these infants.

**BACKGROUND**

Food allergy is a common problem faced by paediatricians and family physicians in clinic and emergency room settings.<sup>1</sup> It is an immune-mediated adverse reaction to food that can be both IgE and non-IgE mediated. IgE-mediated food allergy can present with skin, gastrointestinal, respiratory and cardiovascular symptoms, and may be life threatening. The most common food allergy in infants is cow milk allergy (CMA) and it affects 2–3% of children.<sup>2</sup>

Cow milk is an important source of nutrition and a ubiquitous ingredient in many foods. Given that allergic reactions may mimic other conditions, it is very important to accurately diagnose CMA. Furthermore, recent studies suggest that late introduction of potentially allergenic foods and elimination diets due to symptoms that are unrelated to an IgE-mediated food allergy may increase the risk of developing a life-threatening food allergy. We describe two cases of CMA in infants that developed after strict elimination diet due to infantile colic. These cases exemplify the difficulty in establishing the diagnosis of CMA in infants and highlight the potential risk of unnecessary elimination diets.

**CASE PRESENTATION****Case 1**

A 2-month-old boy was brought to the emergency department after developing generalised flushing of the skin (figure 1A). He was delivered after an uncomplicated term pregnancy and had a birth weight of 3.125 kg. He was exclusively breast-fed. At one month of age, due to symptoms of infantile colic, the primary care physician recommended a dairy-free diet for the mother. At the age of 2 months, the mother introduced a cow milk-based formula to the infant for the first time. Three hours

after feeding, when he woke up from his nap, shortly after breast feeding, the mother noticed generalised flushing of the skin. In addition, he had low-grade fever (up to 38.1°C) since the morning of the same day. He was brought to the emergency department for assessment.

The physical examination revealed a well-appearing infant, with rectal temperature of 37.9°C, heart rate of 193 beats/min, respiratory rate of 32 breaths/min, blood pressure of 103/58 mm Hg, and weight of 5.1 kg. His skin was diffusely erythematous. The remainder of his physical examination was normal.

**Case 2**

A 6-month-old boy who was referred to our allergy clinic due to suspected CMA. This infant was fed with a cow milk-based formula for the first 2 months of age. Owing to symptoms of infantile colic (episodes of crying or fussing most frequently after a feeding) he was switched to nutramigen (cow milk hydrolysate) at the age of 2 months. At the age of 5 months, he was reintroduced twice to cereals with cow milk-based formula and, within minutes, developed facial flushing, hives and angioedema of the wrists and ankles. During his current visit at the clinic, his grandfather accidentally touched his face after adding milk to his coffee and the infant presented with hives immediately afterwards (figure 2).



**Figure 1** Flushing in an infant.

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**Figure 2** Infant presenting with hives shortly after contact with cow milk.

### INVESTIGATIONS

Laboratory tests for the first case revealed a complete blood count, electrolytes and creatine level within the normal range. The urinalysis was also normal. Given his age, the erythroderma and a borderline fever of 37.9, the possibility of staphylococcal scalded skin syndrome was considered. Intravenous piperacillin-tazobactam was administered, and the infant was admitted to hospital for observation and ongoing treatment. The erythema dramatically improved 2 h after presentation to the hospital. Given the unexplained flushing and the history of a possible temporal relationship to the first formula feed, an allergy consultation was requested. Although the course of the symptoms was not obviously consistent with an allergic reaction, a skin prick test (SPT) was conducted using both an extract of cow milk protein and fresh milk. In addition, blood was drawn for measurement of milk-specific IgE levels (UniCAP, Phadia, Uppsala, Sweden). The SPT was negative and milk-specific IgE level was less than 0.1 kU/l. Therefore, an open food challenge with cow milk formula was undertaken. Within 5 min of drinking 5 ml of the formula, the infant developed generalised hives, confirming the diagnosis of CMA.

For the second infant, SPT with milk extract was positive (8 mm wheal size compared with control) establishing the diagnosis of CMA. Hence, the mothers in both cases were advised to avoid milk and dairy products and continue breast-feeding or use cow milk hydrolysate. An epinephrine autoinjector was prescribed for both infants.

### DIFFERENTIAL DIAGNOSIS

Differential diagnosis of generalised flushing and/or hives includes infectious, malignant and allergic conditions.<sup>1</sup> In these cases, the development of cutaneous symptoms within a few minutes after exposure to cow milk is highly suggestive of CMA.

### TREATMENT

Treatment of CMA relies on avoidance of cow milk and dairy products as well as self-carry of epinephrine autoinjector. Desensitisation protocols show good results. However, these are

currently under research and no desensitisation guidelines have been established at this point.

### OUTCOME AND FOLLOW-UP

Follow-up at 6 months later for our cases revealed healthy infants that grow well. They are still avoiding cow milk. Given the natural history of CMA, an oral challenge to cow milk will be considered at the age of 1 year if skin test will be negative.

### DISCUSSION

'Adverse food reaction' is an umbrella term used to describe clinically abnormal responses that occur after the ingestion of food or food additives. These responses can be further classified into those that do not involve the immune system (food intolerance) and those that are mediated by the immune system (food allergy or hypersensitivity).<sup>3</sup> Food allergy can be mediated by immunoglobulins, immune cells (T cells) or a mixture of these.<sup>3</sup> Allergic reactions mediated by IgE occur when antigens bind to IgE antibodies attached to mast cells. Cross-linking of two IgE antibodies by an antigen causes degranulation of mast cells and releases potent inflammatory mediators, resulting in an immediate allergic reaction.<sup>3</sup>

CMA is the most common food allergy in infancy and may result in a life-threatening allergic reaction, that is, anaphylaxis.<sup>2</sup> IgE-mediated reactions occur within 2 h after ingestion, and include cutaneous symptoms such as angioedema, urticaria and pruritus, gastrointestinal symptoms such as vomiting and abdominal pain, respiratory symptoms such as wheeze and cough, and/or cardiovascular symptoms such as hypotension or shock.<sup>2</sup> In contrast, CMA symptoms attributed to non-IgE-mediated or mixed reactions present with less acute gastrointestinal, respiratory, cutaneous and nutritional manifestations and are usually not life threatening.<sup>3</sup> The latter may include gastroesophageal reflux, oesophagitis, enteropathy, colitis, failure to thrive, constipation and colic.<sup>2</sup> The diagnosis of an IgE-mediated CMA is based on the combination of clinical history and confirmatory tests including SPT and specific IgE levels. The food challenge is considered to be the gold standard.<sup>2</sup> In the two cases described, the positive food challenges (the first graded and supervised, and the second unintentionally provoked by contact) establish the diagnosis of an IgE-mediated CMA. It is possible that flushing in the first case developed within the first 2 h following the feed, while the baby was asleep, but was only noticed after the infant awoke from his sleep. In contrast to the expected course of allergic reactions that requires prior sensitisation, the reaction in the first case described occurred at first exposure to cow milk. However, it was reported that food-related allergic reactions may occur at first exposure potentially due to sensitisation in utero or during lactation.<sup>4</sup> The negative SPT for case 1 is not an unexpected finding given that neonates with food allergies are reported to have low levels of specific IgEs.<sup>2</sup>

These two cases draw attention to potential problematic aspects related to the management of infantile colic. Infantile colic is common in infancy, and while its pathogenesis remains unclear, food allergy/intolerance has been suggested to play a role in its development. However, colic and fussiness are not likely to be isolated manifestations of CMA.<sup>2</sup> Further, although infantile colic is challenging to manage, it has a benign clinical course and usually resolves by 3 months of age.<sup>5</sup> In contrast, IgE-mediated CMA is reported to be a major cause of anaphylaxis and mortality in children, and requires compliance with a strict dairy-free diet and carrying an epinephrine autoinjector at all times.<sup>2</sup>

Many lactation consultants, paediatricians and family physicians nowadays advocate maternal elimination diets to maintain the benefits of breastfeeding in infants who present with colic.<sup>6</sup> This approach is supported by a few studies suggesting a significant difference between cry and fuss time at baseline versus during exclusive neocate or nutramigen use.<sup>7, 8</sup> However, these studies are limited by the small sample size (6 and 17 patients, respectively) and lack of control group.<sup>7, 8</sup> Further, one of these studies reports that although in some instances, colic improves with elimination of cow milk formula, the effect diminishes with time, and only infrequently is the effect reproducible.<sup>8</sup> However, recent studies suggest that food elimination may increase the risk of IgE-mediated food allergy. Katz *et al* conducted a prospective cohort study to determine the risk factors for the development of CMA. In their study, IgE-mediated CMA was significantly higher in infants started on formula beyond 15 days of life, with an odds ratio of 19.3 (95% CI 6.0 to 62.1). They concluded that early exposure to cow milk protein might promote tolerance.<sup>9</sup> Similarly, Flinterman *et al*<sup>10</sup> described 11 children who were on a cow milk-free diet for a prolonged period (median 2.3 years) because of atopic dermatitis and sensitisation to cow milk. More than 70% of those children developed symptoms consistent with an IgE-mediated milk allergy after accidental ingestion of cow milk and almost 100% developed acute allergic reactions during double-blind placebo control food challenge (DBPCFC) with cow milk. The study suggests that acute allergic reactions might result from prolonged avoidance of allergen exposure. This corresponds with the clinical course of CMA in case two. Case 2 developed CMA after 3 months of strict avoidance of dairy products although he did not have IgE-mediated allergy to cow milk protein in the first few months of life. Du Toit *et al* drew a similar conclusion regarding peanuts<sup>11</sup> and a recent series of cases exemplifies transition between food protein-induced enterocolitis syndrome and IgE-mediated milk allergy after avoidance of cow milk formula and reintroduction.<sup>12</sup> Accordingly, the AAP (American Academy of Pediatrics) recently retracted previous recommendations related to the introduction of potentially allergenic foods. The new recommendations state that delaying the introduction of solids past 6 months shows no evidence of a protective benefit (including solids that are thought to be highly allergenic).<sup>13</sup>

The optimal timing of food introduction that would contribute to the development of cow milk tolerance rather than allergy is currently unknown. In a recent study, it was reported that only 0.05% of the infants who were started on regular cow milk-based formula within the first 14 days versus 1.75% who were started on formula between the ages of 105 and 194 days had IgE-mediated CMA ( $p < 0.001$ ).<sup>9</sup> Alternatively, given that in case 1, the mother had been drinking milk and then stopped, and that in the second case, dairy products were removed completely from the infant's diet, it is possible that interruption of exposure to cow milk protein<sup>10</sup> might have contributed to the

development of allergy in these infants. Randomised controlled trials controlling for potential confounders are required to establish the optimal age of milk protein introduction for induction of tolerance and the role of elimination diets.

### Learning points

- ▶ Physicians should be aware of the possibility of cow milk allergy (CMA) presenting in this uncharacteristic manner, and investigate, manage and refer patients as indicated.
- ▶ CMA allergy can present in infancy with a negative skin test.
- ▶ These cases highlight the potential risk of developing an IgE-mediated food allergy possibly as a result of an unnecessarily restricted maternal and/or infant's diet.

**Competing interests** None.

**Patient consent** Obtained.

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