Clinical practice. Diagnosis and treatment of cow’s milk allergy

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Received: 10 February 2009 /Accepted: 18 February 2009 /Published online: 7 March 2009
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Abstract

Introduction Cow’s milk allergy (CMA) is thought to affect 2–3% of infants. The signs and symptoms are nonspecific and may be difficult to objectify, and as the diagnosis requires cow’s milk elimination followed by challenge, often, children are considered cow’s milk allergic without proven diagnosis. Diagnosis Because of the consequences, a correct diagnosis of CMA is pivotal. Open challenges tend to overestimate the number of children with CMA. The only reliable way to diagnose CMA is by double-blind, placebo-controlled challenge (DBPCFC).

Therapy At present, the only proven treatment consists of elimination of cow’s milk protein from the child’s diet and the introduction of formulas based on extensively hydrolysed whey protein or casein; amino acid-based formula is rarely indicated. The majority of children will regain tolerance to cow’s milk within the first 5 years of life.

Conclusions Open challenges can be used to reject CMA, but for adequate diagnosis, DBPCFC is mandatory. In most children, CMA can be adequately treated with extensively hydrolysed whey protein or casein formulas.

Keywords Cow’s milk allergy · Double-blind placebo-controlled food challenge · DBPCFC · Hypoallergenic formula

Introduction

The prevalence of cow’s milk allergy (CMA) is estimated to be between 2% and 3% in infants and marginally lower in older children [1, 2]. The percentage of parents that believe their child has CMA (or any other food allergy), however, amounts to between 5% and 20% [2–4]. Signs and symptoms of CMA are nonspecific and often difficult to objectify. Due to diagnostic burdens, the number of children treated for CMA is probably two to three times higher than justified [5]. A wrong diagnosis of CMA may not only result in somatisation but also in insufficient topical treatment of eczema, fear for or problems with the introduction of solids, and dietary deficiencies. Moreover, the long-term elimination of cow’s milk protein (CMP) in a sensitised child without CMA may elicit severe adverse reactions when cow’s milk is reintroduced [6]. Careful diagnosis of CMA, therefore, is of utmost importance.

Definitions

Adverse reactions to CMP can be present from birth, even in exclusively breast-fed infants. Not all reactions are of allergic nature. In 2001, the EAACI published a report on the terminology of adverse reactions [7]. The umbrella phrase, food hypersensitivity, covers non-allergic food hypersensitivity (traditionally named ‘food intolerance’) and allergic food hypersensitivity (food allergy). The latter requires an underlying immune mechanism. Most children with CMA have immunoglobulin E (IgE)-mediated allergy as a manifestation of their atopic constitution, with or without atopic eczema, asthma, or allergic rhinitis. A small group have cell-mediated allergy with gastro-intestinal symptoms [8].
History and physical investigation

Although signs and symptoms themselves (Table 1) cannot be used to diagnose CMA, history may be helpful as it can give clues to other diagnoses. Symptoms may start after the substitution of breast-feeding with formula feeding. The repeated occurrence of urticaria or rash shortly after CMP ingestion is suggestive of CMA. In general, signs and symptoms occurring late (>2 h) after the consumption of CMP are not caused by CMA [9]. Also, inconsistent signs and symptoms and those that do not emerge after every feeding must have a different aetiology.

The concurrent presence of other signs of atopy, such as eczema, wheezing, and asthma, increases the likelihood of CMA but cannot be used as a diagnostic proof. Especially the relation between CMA and eczema is difficult to assess. Although they can be present simultaneously and although CMP challenge may aggravate moderate to severe eczema in about 30% of cases [10–12], there is no proven relationship with mild eczema; moreover, there is no solid evidence that eczema can be expected to improve significantly on a CMP elimination diet [13]. Atopic eczema should be treated adequately with topical medication before CMA is considered [12]. Generally, other physical signs are lacking or nonspecific. Growth should be monitored closely.

| Table 1 Signs and symptoms of CMA (those printed in italics are suggestive of severe allergy) |
|---------------------------------|---------------------------------|
| Gastrointestinal                | Vomiting, regurgitation         |
|                                 | Abdominal pain                  |
|                                 | Colic                           |
|                                 | Diarrhoea                       |
|                                 | Constipation                    |
|                                 | Haemochezia                     |
| Skin                            | Rash                            |
|                                 | Atopic eczema                   |
|                                 | Urticaria                       |
|                                 | Swollen lips                    |
|                                 | Angio-oedema                    |
|                                 | Pruritus                        |
| Respiratory                     | Rhinitis                        |
|                                 | Conjunctivitis                  |
|                                 | Hoarseness, dysphagia           |
|                                 | Wheezing, asthma                |
| General                         | Food refusal                    |
|                                 | Growth retardation              |
|                                 | Iron-deficient anaemia          |
|                                 | Irritability, disturbed sleep   |
|                                 | Apnoea, apparent life-threatening events |
|                                 | Anaphylaxis                     |

Laboratory investigation

The role of laboratory tests in CMA diagnosis is debatable. The tests used in clinical practice only reveal sensitisation to CMP, which is not necessarily followed by clinically relevant allergy. Over 50% of sensitised children do not have food allergy [14–16]. In our experience, positive skin prick tests and allergen-specific IgE tests tend to be falsely interpreted as proof of CMA. This is not at all innocuous [6].

Although there is a strong positive correlation between the level of allergen-specific IgE and the chance of having CMA, unequivocally high specific IgE titres are rare and may occur in non-allergic children [17–19]. In general practice, therefore, laboratory tests are seldom helpful. The only way to prove CMA is through elimination and challenge.

Cow’s milk challenge

After the elimination of CMP from the child’s or the mother’s diet, signs and symptoms should disappear within a few days. Atopic eczema, when caused by CMA, may take 4 weeks to improve sufficiently. Upon challenge, renewed confrontation with CMP results in recurrence of the presenting signs and symptoms.

Challenges may be performed either open or double-blindly. With open challenges, both the staff performing the test and the parents know that the child is given CMP and in what amount. Double-blind placebo-controlled food challenges (DBPCFC) are designed to withhold this information both to the parents and the staff until afterwards. They are performed with placebo and verum in random order. CMP is concealed in a way that both test feedings look and taste similarly. DBPCFCs are superior to open challenges, but they are difficult to perform, require extensive preparation and are relatively expensive [9].

Open challenge

Open challenges can be used as the first diagnostic step. Challenges should follow an approved protocol, suited for the circumstances. In 1995, a national protocol for CMA diagnosis and treatment was introduced in Dutch well-baby clinics, including a simple open challenge, which is still in use [20]. After 2 weeks of elimination diet, the child ingests 10 ml of original formula while being supervised for 1 h; on the three following days, the formula is given in increasing amounts [20]. While originally, the protocol was developed to avoid inappropriate CMA diagnoses, presently, it is thought that it contrarily may induce falsely positive results and should
be followed by DBPCFC. Preset conviction, subjective symptom appreciation and random symptom fluctuation increase the risk of falsely positive results. Between 27% and 70% of open-challenge CMA diagnoses are rejected after DBPCFC [21, 22].

Apart from this, a generally accepted open challenge procedure has only been published in 2007, when a European working group formulated a protocol for CMA diagnosis in general practice meant for children with relatively mild signs and symptoms [23]. The child’s own formula is given in increasing amounts over 3 h (Table 2). In our opinion, however, open challenges should only be used to reject CMA [1, 10, 12].

**DBPCFC**

Double-blind challenges are the gold standard. In 2007 as well, the Health Council of the Netherlands issued a report asking for the general introduction of DBPCFCs [1]. Dutch paediatric allergy centres and many hospitals already practice DBPCFCs [24–26]. They can be performed in well-baby clinics and general practices as well, as long as basic precautions have been met, including thorough knowledge of the procedure, careful patient selection and the equipment to block adverse reactions. The importance of DBPCFCs is underscored by the fact that between 13% and 30% of placebo tests are eliciting adverse reactions [24, 27]. There is no generally accepted protocol for DBPCFC. The protocol presented here is used in the Wilhelmina Children’s Hospital [25].

**Preparation** The diet should be CMP free for at least 2 weeks. The patient’s condition should be stable, especially concerning skin symptoms. Topical corticosteroids may be continued, but antihistamines should be discontinued at least one week in advance. Preparation includes a thorough history for previous adverse reactions.

**Safety** Tests should be performed in a day-care setting or during admission. Depending on the severity of previous signs and symptoms, a monitoring device and intravenous access may be needed. Clemastine and epinephrin for parenteral use must be at hand. The personnel should be well trained, also regarding the management of (rare) severe acute reactions.

**Test material** The child is given his/her own hypoallergenic formula or expressed breast milk. The research kitchen prepares coded bottles with (verum) or without (placebo) 5 g Protifar® powder (Nutricia/SHS), containing 4.4 g CMP, per 250 ml formula.

**Procedure** Placebo and verum are administered on separate days, preferably 1 week apart. The test formula is given in increasing dosages at fixed intervals (Table 2) [26]. Adverse reactions are recorded. After a negative test, the child remains under supervision for 2 h, after a positive test for 4 h. The parents are asked to report late reactions. After the second test, a follow-up period of at least 48 h is observed before the seal is broken [26].

**Evaluation** The test is discontinued when the child experiences objective adverse reactions, subjective reactions that persist for 30 min or longer or repeated short-lived subjective reactions [9]. Allergic and non-allergic reactions are assessed separately and in the light of the child’s history (Fig. 1). The final interpretation of the tests is given in Table 3. The DBPCFC is considered negative when verum did not elicit adverse reactions or when reactions following verum are not worse than following placebo. Even

| Table 2  | CMP administration schedules during challenge |
|----------|-----------------------------------------------|
| **Step** | **Open challenge; child’s own formula (Ref 34)** | **DBPCFC; hypoallergenic formula, with 5g of Protifar® (Ref 28)** |
|          | T (min) | Dose (ml) | CMP (mg)* | T (min) | Dose (ml) | CMP (mg) |
| 1        | 0       | Drop on lips | – | 0 | 0.1 | 2 |
| 2        | 15      | 0.5 | 8 | 15 | 1 | 18 |
| 3        | 45      | 1.0 | 15 | 30 | 10 | 176 |
| 4        | 75      | 3.0 | 45 | 45 | 20 | 352 |
| 5        | 105     | 10 | 150 | 60 | 30 | 528 |
| 6        | 135     | 30 | 450 | 80 | 40 | 704 |
| 7        | 165     | 50 | 750 | 110 | 60 | 1,056 |
| 8        | 195     | 100 | 1,500 | 150 | 90 | 1,584 |
| Total    | 195     | 2,925 | | 250 | | 4,400 |

*Based on a mean protein content of 1.5 g/100 ml; depending on brand, the protein content of infant formula is between 1.3 and 1.6 g/100 ml; of follow-on formula, 1.7 and 1.9 g/100 ml
DBPCFCs, however, may not provide unequivocal results [27, 28].

Risk assessment

Although it is impossible to predict reaction severity during food challenges [29], some rules apply. Severe adverse reactions are more likely with previous severe reactions, with previous reactions on very low CMP doses, in older children, in children suffering from asthma and after prolonged exclusion of cow’s milk [6, 30, 31].

Severe reactions with CMP challenges, however, are rare. During over 12 years of open challenges in Dutch well-baby clinics [20], no severe adverse events have been reported to the supervising committee (K.I. van Drongelen, Netherlands Nutrition Centre, personal communication) [20]. With the DBPCFC protocol presented here, over 500 challenges have been performed without any severe adverse events. Hence, CMP challenges can be safely performed in general practices, provided basic safety precautions are met. High-risk challenges should be performed in the hospital.

Cow’s milk reintroduction

When CMA is refuted, standard formula and dairy products can safely be reintroduced in the diet of the child or the breast-feeding mother. Sometimes the child’s illness has put so much strain on the parents that the help of a dietician is required to complete the transition to a normal diet. When, nevertheless, adverse reactions develop after reintroduction, this may be due to the natural course of the underlying condition (eczema), but often expresses the preset conviction of the parents that notwithstanding the test outcome, their child is suffering from CMA. These signs or symptoms are likely to disappear when the introduction is continued.

Therapy

Elimination of CMP from the diet is at present the only proven therapy.

**Breast-fed infants** Breast-feeding mothers need to eliminate all dairy products from their diets. There is controversy about other measures; as the child is at increased risk of other food allergies, it could be wise for her to eliminate allergens such as soy, egg and beef as well [8]. This increases the burden for the mother, however, and may provoke the failure of breast-feeding. A practical approach would be to start with CMP elimination and to eliminate other products only when the child remains symptomatic.

**Bottle-fed infants** Formula is replaced by hypoallergenic formula based on extensively hydrolysed CMP [32]. There is limited experience with hydrolysates from other sources, such as soy and collagen. The use of soy formula in infants <6 months is discouraged [23, 33]. The only formulas suitable for treatment are those that meet the criterium of being tolerated (with 95% confidence interval) by at least 90% of patients with proven CMA [34]. The protein source may be based on extensively hydrolysed whey protein (eHW) or casein (eHC). Children that do not tolerate eHW may be able to tolerate eHC, and the other way round; despite differences in production and in vitro test results, there is no proven difference in clinical efficacy between both groups of formulas.

Some subgroups, including children with non-IgE-mediated gastrointestinal CMA and severe atopic eczema, may show better results with amino-acid-based formulas as opposed to eHC or eHW [35]. Amino-acid-based formulas

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**Table 3** Interpretation of DBPCFCs

| Verum challenge | Placebo challenge | Test outcome |
|-----------------|------------------|-------------|
| Positive        | Negative         | Positive    |
| Strongly positive| Positive         | Positive    |
| Positive        | Positive         | Negative    |
| Negative        | Negative         | Negative    |
| Positive        | Strongly positive| Negative    |

Adapted from 26.
should be restricted to children who fail to tolerate extensively hydrolysed formulas.

**Solids** There is no need to postpone the introduction of solid foods or to follow a detailed introduction schedule. Most children can tolerate other (non-dairy) foods when introduced after the age of 4 months. In highly allergic children, solids are best introduced stepwise: only one or two new foods every 3 days. Because many parents are anxious to proceed with solid food introduction, dietary advice and guidance may be necessary.

**Counselling** The diagnosis of CMA has a great impact on the family. Proper education of parents and caretakers is essential. They need not only to learn avoidance strategies, such as reading food labels and avoiding high-risk situations, but also to recognise early signs and symptoms and to treat acute reactions. Antihistamines are prescribed for mild dermal conditions but will not suffice for severe systemic reactions. Anaphylactic reactions to CMP are rare; the parents of children with a history of anaphylaxis should be provided an epinephrine auto-injector and a written individualised treatment plan [36].

**Tolerance induction**

In the past decade, there is increasing interest in specific oral or sublingual immune therapy as a treatment option for CMA in older children [37, 38]. Immune therapy may lead to an increased tolerance threshold for CMP with persisting CMA [39] and may even induce permanent tolerance to CMP [37]. More research needs to be done before immune therapy can be offered as a competing therapeutic option.

**Prognosis**

CMA usually is a temporary condition. It is suggested that by the age of 3 years, 85% of children have regained tolerance to CMP [40]. More recent studies, however, are less optimistic; persisting IgE-mediated CMA is reported to persist up to the age of 8 years in 15% [41] to even 58% of children [42]. It is advisable to repeat challenges at regular intervals in order to keep the child on an elimination diet no longer than strictly necessary. There is no reason for DBPCFCs unless the diagnosis never has been made properly. Challenges can be scheduled at the ages of 12, 18 and 24 months and yearly thereafter.

**Conflict of interest** The authors declare that they do have no conflict of interest and no financial relationships that might have influenced the present work.

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