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REGULAR ARTICLE

Adverse reactions to milk in infants

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Abstract

Aim: To study the age when symptoms of adverse reactions to milk occur, in premature and term children, the debut of various symptoms, immunoglobulin E (IgE)- and non-IgE-mediated reactions and the frequency of tolerance at 1 year.

Methods: Six hundred and eight children, 193 premature and 416 term infants, were followed. Symptomatic children were invited to a clinical examination. The criteria for the diagnosis were: histories of suspected cow's milk allergy (CMA) and proven IgE-mediated reactions to cow's milk or positive elimination/challenge tests.

Results: Twenty-seven out of 555 (4.9%) were diagnosed with adverse reactions to cow's milk. All had symptoms before 6 months of age. The main symptoms were: pain behaviour (13), gastrointestinal symptoms (7), respiratory symptoms, (6) and atopic dermatitis (1). One child had proven IgE to cow's milk. Premature and term infants displayed the same symptoms and age of debut. Thirteen children were tolerant to cow's milk at 1 year.

Conclusion: Adverse reactions to milk start early in life, with pain behaviour, gastrointestinal, and respiratory symptoms being the most common, and rarely atopic dermatitis. Non-IgE-mediated reactions were the most frequent. Symptoms and age of debut were the same in premature and term infants. Half of the children tolerated cow's milk at age 1.

INTRODUCTION

Adverse reactions to cow's milk are frequent in the first year of life. The symptoms may start during the first weeks of life and may be cutaneous (50–60%), gastrointestinal (50–60%) or respiratory (20–30%), often with symptoms in more than one organ system (1). The reported frequency of cow's milk allergy (CMA) in the first year of life is between 2 and 7% (2,3). It is well known that most children outgrow their adverse reactions to cow's milk during the first year of life (4). According to a 2002 review that was based on 229 PUBMED articles, the frequency of tolerance at 1 year was 45–50% and at 2 years of age was 60–75% (1). The diagnosis was made on the background of reproducible adverse reactions to cow's milk proteins, confirmed by controlled elimination/challenge tests (1).

Adverse reactions to cow's milk may be either immunoglobulin (IgE) or non-IgE mediated, but there are few published reports of the relationship between the two. In the few existing reports, the frequency of IgE-mediated allergies varied from 26% to 73% of the total adverse reactions to milk (5,6).

As there are few reports in the literature on adverse reactions to milk during the first year of life, we wanted to study this in infancy. The aim of the present study was to define the age when the first symptoms of adverse reactions to milk occur, the occurrence of symptoms in multiple organ systems, the frequency of tolerance at 1 year of age, as well as to establish the incidence of IgE-mediated allergy and non-IgE-mediated adverse reactions. Furthermore, we wanted to investigate and compare possible differences in occurrence and symptomatology in premature children (whose immune system is not fully matured) and term children. Some investigators have reported fewer allergies among premature children (7–9).

PATIENTS AND METHODS

Study population

One hundred and ninety-three premature infants, gestational age (GA) 28 to 35 weeks; birth weight, mean 2224 (1214–2880) g (Table 1), born consecutively at the maternity clinic of Oestfold Hospital Trust, and the two following children born at term, birth weight, mean 3648 (2650–5050) g, total number 609. At the 1-year follow-up, 555 children (91% of the total population) participated, 166 (86%) premature and 389 (93%) term children. The mothers were asked to participate during the first 4 days after delivery. Verbal and written information were given, and a written consent was collected from those who agreed to participate. All the families were given the cell phone number of the investigator, and were instructed to call if there was any sign of illness.

Table 1 Premature children, GA and birth weight

Patient number	GA (months)	Birth weight (g)
1	33	2815
2	33	2310
3	35	2220
4	29	1232
6	34	2120
7	34	2350
8	35	2880
9	28	1241

Exclusion criteria

Families not situated in Oestfold county or the southern part of Akershus county, families unable to communicate in Norwegian, families not capable of participating for other obvious reasons and children presenting with other or serious diseases were excluded.

Questionnaires and interviews

A written questionnaire was recorded at the time of inclusion, and at the 6- and 12-month follow-up. One of the parents was interviewed by phone at 1, 4 and 12 months after inclusion, and specifically asked about abdominal and respiratory symptoms, skin rashes and pain behaviour. They were also questioned about whether or not they felt their child was healthy.

Children with symptoms consistent with possible adverse reactions to milk, as well as children whose parents did not consider them to be completely healthy, were invited to the outpatient clinic at the hospital in Fredrikstad within the following 4 to 5 days. A general clinical examination was performed, with special focus on skin, lung and abdominal conditions.

Skin prick test (SPT)

SPT were performed on both lower arms with 1-mm tip lancet (ALK-Abello, Copenhagen, Denmark) and allergen extracts from milk, egg, cod, hazel nuts, peanuts, wheat and soy (ALK-Abello). Histamine chloride 10 mg/mL (ALK-Abello) was used as a positive control, and NaCl 0.9% as a negative control. The SPT was read after 13 min. The contours of the wheals were encircled by a pen, with the two diameters perpendicular to each other, measured in millimetre, added and divided by two. The results were presented in millimetre. SPT equal to or greater than 3 mm was considered positive.

Faecal blood

The diapers of children were analyzed with hemofec A and B for the detection of blood in their stool. The test was performed on at least two different locations of the diaper, and a change in colour within 3 sec was considered positive.

Total and specific IgE

Blood was drawn to determine total and specific IgE against food and inhalant allergens (Alastat, DPC, Los Angeles, CA). The analyses were performed at the department of clinical chemistry, Oestfold Hospital Trust.

Elimination/challenge test

Immediately after their first examination, the infants were fed a diet totally free from cow's milk proteins for 14 days. As a milk substitute, an extensively hydrolyzed formula was introduced. For those who were not exclusively fed with milk, porridge was made with the same formula. In breastfed infants, the mother was given detailed dietary instructions on how to follow an elimination diet free from cow's milk proteins.

A symptom score diary card was filled out daily by one of the parents, with special focus on respiratory symptoms like apnoe or coughing, pain behaviour recorded as crying hours, gastrointestinal symptoms like vomiting or diarrhoea, as well as observed blood in the stool. Furthermore, the appearance of skin rashes and itching were noted in detail.

The challenge was performed by introducing cow's milk proteins either by formula to the infant or through the mother's milk. The reappearance of symptoms, whether in hours or days, was noted. The challenge was considered positive when symptoms reappeared with reintroduction of cow's milk proteins. The change in symptoms had to be reproducible, and thus the elimination/challenge test was repeated at least once.

Scoring atopic dermatitis (SCORAD) index

The children with atopic dermatitis were evaluated according to SCORAD index (10).

Diagnosis

The diagnosis of CMA was based on the following criteria:

(1) A history of suspected CMA, a positive SPT and an elevated specific IgE to cow's milk.
(2) A history of suspected CMA, a negative SPT, a negative specific IgE to cow's milk and an elimination/challenge test performed twice; both tests had to be positive.

At 1 year of age, all the children had an open challenge with cow's milk proteins. The children were fed their usual porridge made with cow's milk. If no adverse reactions appeared within a week, they were introduced to cow's milk to drink.

Statistical analysis

Categorical response variables were compared between groups using Pearson's Chi-square test. Changes within one group were assessed using Mc Nemars test. An unpaired *t*-test was used to compare continuous background variables. All p-values equal to or below 0.05 were considered significant. Statistical analyses were performed with SPSS software, version 14.0 (SPSS, Inc., Chicago, IL).

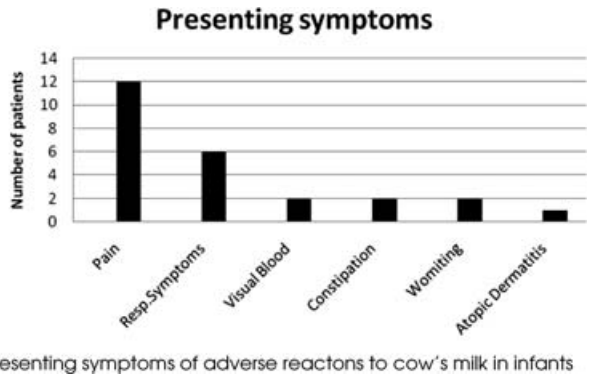

Figure 1 Presenting symptoms of adverse reactions to cow's milk in infants.

RESULTS

Of the 555 children in 1-year follow-up, 87 reported symptoms and were examined at the hospital. According to the diagnostic criteria, 27 of 555 children (4.9%) were diagnosed with adverse reactions to milk. Twenty-six children were diagnosed by elimination/challenge tests; all but one of these was exclusively fed with milk. Seventeen of the 27 children presented with symptoms within the first 4 weeks of life. All but one had debut of symptoms before 3 months of age.

The main symptom at presentation was pain behaviour/abdominal colic in 13 of 27 children. Seven of these children had additional symptoms. Four had excessive vomiting, one had atopic dermatitis, one had constipation and one had coughing and wheezing.

Of the seven children, who presented with gastrointestinal symptoms other than pain behaviour, two had excessive vomiting as the main symptom. Both these children had diarrhoea and one had coughing and wheezing. Two other children presented with constipation as the main symptom. They also had pain behaviour and vomiting, and one a history of apnoe. Two of these seven children had visual blood in the stool. One child presented with diarrhoea.

Six out of 27 presented with respiratory symptoms, wheezing and coughing (4) and apnoe (2), but careful questioning of the parents, as well as clinical examination, revealed that all these six children had additional symptoms. All had excessive vomiting, two also had pain behaviour and one child had atopic dermatitis.

One child presented with atopic dermatitis (Fig. 1).

During the first year of life, 10 children developed atopic dermatitis. The one child with atopic dermatitis as the presenting symptom was reported during interview. Two other children were diagnosed with eczema at the first clinical examination, although their parents had reported pain behaviour and respiratory symptoms, respectively, as the only symptoms. Later during the first year of life, additionally seven children developed atopic dermatitis, several months after the diagnosis of cow's milk protein intolerance (CMPI).

IgE-mediated allergy to eggs was found in two children. The one child with atopic dermatitis as the presenting symptom of CMA also had an allergy to eggs. The second child developed allergy to eggs and atopic dermatitis at 7 months of age, 6 months after debut of symptoms of adverse reactions to milk.

Just one child, the one with atopic dermatitis as the presenting symptom, had a positive SPT, as well as elevated IgE level to cow's milk proteins.

Eleven children had a positive hemofec test at the first visit to the hospital. All these children had negative hemofec tests when tested during the elimination diet, with reappearance of detectable blood in the stool on challenge.

Sixteen children were exclusively breastfed at symptom debut, and thus had developed adverse reactions to cow's milk proteins in their mother's milk.

At 1 year of age, 14 of 27 children were tolerant to cow's milk, with no reaction to an open challenge test. Nine of the 13 nontolerant children presented with the same symptoms on challenge as their presenting symptoms, mainly pain behaviour. At challenge, four of these children presented additional gastrointestinal symptoms, diarrhoea or vomiting. The four children with change in symptoms, all presented on challenge with gastrointestinal symptoms, one with diarrhoea and the other three with vomiting. Initially, two of these had respiratory symptoms, and the other two had pain behaviour.

Nine out of 27 children were premature. They presented with the same mixture of symptoms as the term children, and they all had debut of symptoms before 3 months of age. No statistically significant difference was found between the occurrences of cow's milk reactions in the first year of life among premature infants (9/166 premature infants) compared to the term infants (18 of 389 term infants), with Chi-square value = 0.033, odds ratio (OR) = 0.85.

Six out of 13 nontolerant children at 1 year were premature.

DISCUSSION

In this study, we have found that adverse reactions to milk start early in life. All but one in our cohort presented symptoms before 3 months of age. Symptoms appeared mainly in the gastrointestinal and respiratory organs. The majority of the children had symptoms in more than one organ. We found just one child with IgE-mediated allergy to cow's milk. Half of the children were tolerant to milk at 1 year of age. The premature children had debut of symptoms at the same age as the term children, and they also had the same mixture of symptoms.

In this birth cohort of 555 children, we have found the frequency of adverse reaction to milk to be 4.9%, which is in accordance with Moneret-Vautrin, reporting between 2 and 5%, but somewhat more than Host and Martorell, reporting 2–3% (1,2,11). We found that 17 of 27 (63%) children presented with symptoms during the first month of life. That most of the children had debut of symptoms before 3 months of age is in accordance with earlier studies by Host (1).

In our population, the frequency of atopic dermatitis in children with adverse reactions to milk was 37% during the first year of life. We found gastrointestinal symptoms in 66%

of the children and respiratory symptoms in 37%. This is all in accordance with other investigators (1,12).

Interestingly, we found just one child with IgE-mediated CMA that is 3.7% of children with adverse reactions to milk. This is much less than that reported by Moneret-Vautrin and Kamelmaz, who reported 14% and 73%, respectively, with IgE-mediated allergy (2,3).

It may be argued that we might have overlooked some children with IgE-mediated allergy to cow's milk. We consider this unlikely, because of the very close follow-up with personal interviews by phone at 1, 4 and 12 months, and also written questionnaires at 6 and 12 months. All children with any symptom, even vague, were invited to an examination, and no one failed to appear. Therefore, we are quite certain that in this birth cohort the frequency of IgE-mediated CMA before 1 year of age is low, that is, 0.2%.

The apparent discrepancy between IgE- and non-IgE-mediated adverse reactions to milk might be explained by an over-diagnosing of non-IgE-mediated reactions. We find this unlikely as the diagnosis was based on convincing results of the elimination/challenge test, with close follow-up in a hospital setting during the procedure. In cases where the result of the challenges was inconclusive, we did not consider this to be an adverse reaction to cow's milk, even though these children might possibly have had an early development of tolerance.

Most of our children were diagnosed between 1 and 4 months of age. In cases of early development of tolerance, we might have lost the diagnosis if the interviews or questionnaires had been postponed until later in the first year of life, as half of the group were tolerant at 1 year. This might explain the large number of non-IgE-mediated adverse reactions.

Another explanation of the apparent discrepancy between IgE- and non-IgE-mediated adverse reactions is the rather surprising finding of respiratory symptoms as the main complaint. In these cases, one could easily overlook the diagnosis by examining the child with regard to respiratory infections or an early debut of asthma.

At 1 year of age, all the children had a planned open provocation at the hospital. Half of the children in our study, 14 of 27, showed no adverse reactions to milk at that age. This is in accordance with earlier studies by Host and Martorell (1,11). We find a planned challenge, especially important for an early diagnosis, based on elimination/challenge tests. In the lack of objective criteria, one has to keep in mind that the diagnosis might be wrong, as well as the fact that early tolerance is usual, and therefore, an early challenge is reasonable.

The child with IgE-mediated CMA was not tolerant at 1 year of age.

We find the same frequency and the same symptoms and age of debut in premature and term children. To our knowledge, there is no report in the literature on these topics. At 1 year, 6 out of 13 nontolerant children were premature. More term children than premature children had become tolerant. The difference is not significant; however, the groups may be too small for evaluation. Theoretically, premature children may have a tendency to become tolerant later than term children, due to delayed development of their immune system.

We are aware of the fact that the gold standard for diagnosing food allergy is double-blind, placebo-controlled (DBPC) challenge (13). In the literature, however, there is support for open elimination/challenge test below the age of 1 (1). For practical and clinical reasons, we found it impossible to do DBPC challenges in the age group of 1–6 months, when most Norwegian infants are mainly breastfed. It is difficult, for practical reasons, to carry out the DBPC challenge through the mother.

Another possibility for an exact diagnosis is to do the DBPC challenge when the infant is around 1 year of age, and is having it's own meals. We intended to do so, to verify the diagnosis. We did DBPC challenge in eight children, finding that seven had no adverse reactions to milk at that time. Thus, the diagnosis was not confirmed in 1-year-old children. This is not surprising, however, as about 50% of children are tolerant at 1 year of age (1,4,11).

Consequently, in our opinion, DBPC challenge is not suitable for diagnosing adverse reactions to cow's milk in early infancy.

In conclusions, in our study, we found that adverse reactions to milk are common in infants and occur in 4.9%, regardless of GA at birth. The symptoms often appear during the first month or months of life, even in exclusively breastfed children.

The diagnosis should be considered in infants with gastrointestinal, respiratory and cutaneous symptoms.

If no IgE-mediated allergy is verified, an elimination/challenge test should be carried out. In our study, non-IgE-mediated adverse reactions seemed to be much more common than IgE-mediated reactions in the first year of life.

About half of the children who demonstrated adverse reactions to milk in the first months of life did not show any adverse reactions at 1 year of age. This demonstrates the importance of performing an open challenge at that time.

Children with prevailing allergies might either maintain their symptoms or acquire new or additional symptoms.

For practical, economical and social reasons, it is important to establish when the age of tolerance occurs in a child diagnosed with adverse reactions to milk.

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