

# Clinical Analysis of Cow's Milk Allergy in Eleven Neonates

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## Abstract

**Objectives:** To analyse the clinical manifestations of neonates suffering from cow's milk allergy (CMA), and to explore the treatment of CMA in neonates, as well as to conduct a one-year follow-up study. **Study design:** To conduct a clinical chart review of a small cohort of neonates of confirmed cow's milk allergy. **Results:** Eleven neonates were diagnosed as suffering from CMA from May 2008 to May 2010, all of which also had digestive tract symptoms. Five were suffering from eczema at the same time. Five had positive sIgE. The other six got negative sIgE and diagnosed as having CMA when using milk to conduct food-avoiding challenge test. In the following one year, nine got tolerance to milk. **Conclusions:** The clinical manifestations of neonates suffering from CMA were diversified; the positive rate of sIgE is not high; food-elimination challenge test could be an alternative for diagnosing food allergy. Significant outcome can be achieved when applying food-avoiding treatments to milk-fed infants. Within one year, 9/11 (82%) of the infants suffering from CMA got tolerance to cow's milk.

## Key words

Cow's milk allergy; Diagnosis; Neonates; Therapy

## Introduction

The past several years have witnessed a significantly climbing trend of anaphylactic disease worldwide. Children have high prevalence of allergic diseases which has alarmed pediatricians all over the world.<sup>1</sup> There is a lack of exact epidemiological data about allergic gastrointestinal diseases in neonates.<sup>2</sup> Regarding children, milk is one of the most common food allergens.<sup>3-5</sup> Nevertheless, there are few reports about cow's milk allergy (CMA) in neonates. This

research illustrates a detailed clinical manifestations of 11 neonates suffering from CMA within the two-year-period from May 2008 to May 2010 using IgE and(or) other alternatives as well as an observation of diagnosis and treatment of CMA in neonates.

## Methods and Patients

### General Information

Jiaying Second Hospital is an upper first-class hospital. From May 2008 to May 2010, the newborn department and neonatal intensive care unit (NICU) admitted 11 neonates with CMA out of a total of 1632. Six were male and five were female. The mothers of five neonates had consumed cow's milk in late pregnancy. Nine were term neonates and two were premature neonates. Mean age at diagnosis was 22 days of life (13-40).

### Diagnostic Criteria

The diagnosis of food allergy was made basing on the process of (1) suffering from abdominal distension, diarrhoea, vomiting, bloody stool, food refusal, crying,

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irritation, etc. for unknown reasons (2) eliminating infection, lactose intolerance, congenital intestinal malformations, inborn metabolic error and other organic diseases (3) demonstration of presence of food specific Immunoglobulin E (IgE) by *in vivo* test or (4) a positive food challenge<sup>6</sup> if special Immunoglobulin E (sIgE) is negative, and/or (5) convincing history of immediate reaction to an isolated food item.

#### **Food-elimination Challenge Test**

If symptoms did not improve upon 2 week elimination of cow milk for infants on formula-fed or upon maternal avoidance of cow milk/dairy product while breastfeeding the infant, causes of symptoms other than cow's milk allergy should be actively sought. Open milk challenge test was conducted if the patients improved.

#### **Open Cow's Milk Challenge Test<sup>6</sup>**

Open cow's milk challenge test was usually applied for diagnosis of CMA in neonates at home. The challenge period was one week. The paediatricians and parents of neonates would acknowledge the formulation constituent. Milk intake was begun at 0.5 ml to 20 ml on the first day, and gradually increased to 90 ml on the second day and 300-600 ml per day at the end of the week. The challenge test would be re-conducted twice – at the eighth day and after four weeks. Milk tolerance was said to form if no symptoms were discovered during the challenge week and an intake of normal amount of milk can be kept for at least four weeks.

#### **IgE and sIgE**

IgE was measured by Roche E170 Electrochemiluminescence with a normal range of 0-100 IU/L.

sIgE was measured by extracting about 2 ml venous blood from the infants before isolating the serum, followed by immunity trace assay to determine specific IgE.

#### **Food Tolerance<sup>7</sup>**

If open food challenge was negative while there were no untoward effects when having previous allergenic food, food allergy was said to have resolved, or tolerance to food was formed.

#### **Treatment**

Mothers who continue feeding infants with breast milk was advised to avoid cow's milk. Others needed to adopt food-avoiding therapy. Deeply hydrolyzed milk and partially hydrolyzed milk were used for ordinary patients.

Amino acid formula milk was used for critically ill patients for 3-6 months before gradually transiting to normal milk powder. Fruit, vegetable and grain were added at the same time. Meanwhile, we suspended the introduction of eggs and seafood for critically ill neonates.

#### **Follow-up Study**

We conducted a follow-up study for each of the eleven cases in the following one year and re-measured sIgE at the end of the one-year-period. Food tolerance, other possible allergens and anaphylactic diseases in these neonates were observed.

## **Results**

#### **Clinical Manifestations**

The clinical manifestations of the 11 neonates are summarised in Table 1. All had accompanying digestive tract symptoms. Five had eczema as well. One was suffering from severe dehydration, shock and acute renal failure. One had moderate anaemia and hypoproteinaemia. One contracted pneumonia twice during neonatal period without asthma or other respiratory symptoms.

#### **Diagnosis of CMA**

Five of the eleven had positive milk sIgE, one of whom was accompanied by positive fish, shrimp and crab sIgE, and another had positive egg white and yolk sIgE. The other six had negative milk sIgE and was diagnosed to be suffering from CMA by milk challenge test, as shown in Table 2.

#### **Feeding Conditions**

As shown in Table 3, at the time of diagnosis, one infant was exclusively breast-fed; four were formula fed; and one were on mixed feeding. Five mothers frequently consumed milk in their late pregnancy.

#### **Other Clinical Manifestations**

Out of the eleven, four had allergic family history and three had blood eosinophilia  $\geq 4\%$ .

#### **Results of the One-year Follow-up Study**

Nine infants acquired tolerance to milk, as shown in Table 4. One of the other two was a mixed-fed boy, who had a total IgE up to 569 IU/L and positive cow's milk sIgE as well as positive dermatophagoides pteronyssinus and dermatophagoides farinae IgE when tested at the end of

**Table 1** Clinical characteristics of the paediatric patients

| #  | Abdominal distension | Diarrhoea | Vomiting | Bloody stool | Refuse food | Irritation | Eczema | Shock | Renal failure | Hypo-proteinaemia | Others |
|----|----------------------|-----------|----------|--------------|-------------|------------|--------|-------|---------------|-------------------|--------|
| 1  | √                    | √         | √        | –            | √           | –          | –      | √     | √             | –                 | –      |
| 2  | –                    | √         | √        | –            | –           | –          | –      | –     | –             | √                 | √      |
| 3  | √                    | –         | –        | –            | –           | –          | √      | –     | –             | –                 | –      |
| 4  | –                    | –         | –        | –            | √           | √          | √      | –     | –             | –                 | –      |
| 5  | –                    | √         | –        | √            | –           | –          | –      | –     | –             | –                 | –      |
| 6  | √                    | –         | –        | –            | √           | √          | –      | –     | –             | –                 | √      |
| 7  | –                    | √         | √        | –            | –           | –          | √      | –     | –             | –                 | –      |
| 8  | √                    | –         | √        | –            | –           | –          | –      | –     | –             | –                 | –      |
| 9  | √                    | –         | –        | √            | –           | –          | –      | –     | –             | –                 | –      |
| 10 | –                    | √         | –        | –            | –           | –          | √      | –     | –             | –                 | –      |
| 11 | –                    | √         | –        | –            | –           | √          | √      | –     | –             | –                 | –      |

Others: moderate anemia and/or pneumonia

**Table 2** Positive sIgE and positive food challenge test distribution

|                 | Milk | Milk and fish, shrimp, crab | Milk and egg white, yolk | Positive food challenge test | Total |
|-----------------|------|-----------------------------|--------------------------|------------------------------|-------|
| Number of cases | 3    | 1                           | 1                        | 6                            | 11    |

**Table 3** Feeding conditions and whether mothers had milk in late pregnancy

|                 | Breast feeding | Artificial feeding | Mixed feeding | Mothers had milk in late pregnancy |
|-----------------|----------------|--------------------|---------------|------------------------------------|
| Number of cases | 1              | 4                  | 6             | 5                                  |

**Table 4** Tolerance to milk and time taken

|                 | 4-6 months | 7-9 months | 10-12 months | Total |
|-----------------|------------|------------|--------------|-------|
| Number of cases | 2          | 4          | 3            | 9     |

the one-year period. He had suffered from wheezy illness for four times. The other patient was an artificial-fed boy with negative milk sIgE and poor weight gain. His erythrocyte sedimentation rate was stable at 50 mm/h and he was diagnosed as having allergic proctocolitis with repeated bloody stools by colonoscopy. We then treated him with prednisone.

## Discussion

### *Clinical Manifestations of Neonates Suffering from CMA*

The clinical manifestations of neonates suffering from CMA appeared to be differentiated, including allergic

eosinophilic gastroenteritis (AEGE), food protein-induced enterocolitis syndrome (FPIES), allergic proctocolitis (AP) etc. Critically ill patients even suffered from dehydration, shock, acute renal failure, anemia, hypo-proteinaemia and oedema which place great threat upon infants' health. A mother of one of the eleven infants was a Hepatitis B Virus (HBV) carrier. The patient, after being fed with breast milk, contracted diarrhoea. After seven days, severe dehydration, shock, acute renal failure developed since his parents underestimated the early symptoms. The infant's diarrhoea recurred following intake of ordinary milk. He did not improve after being fed with lactose-excluded milk. His blood eosinophilia rose up to 7.8% and his father once contracted nettle-rash. Despite negative milk allergen sIgE

and total IgE, we considered him to be allergic to cow's milk. Amino acid formula milk was used instead of ordinary milk. Diarrhoea disappeared on that very day. The infant left hospital after 16 days. On the day he left, his parents did not follow the doctor's advice and fed the infant with ordinary milk, before diarrhoea appeared again that night. Consequently, we diagnosed it as CMA and decided to feed him with amino acid formula milk for 3 months, then deeply hydrolyzed milk for 3 months, followed by ordinary milk, with addition of fruits and vegetables. After 9 months, deeply hydrolyzed milk powder was discontinued. The infant could tolerate ordinary milk. During follow-up when he was one-year-old, he was in favourable condition in terms of nutrition and growth status.

#### ***Complicated Mechanisms of Food Allergy in Neonates***

The mechanisms of food allergy are complicated. They might be IgE mediated or non-IgE mediated. Some are possibly related to food specific IgE.<sup>8</sup> Therefore, the IgE test may be positive or negative. Skin prick test (SPT) and colonoscopy are not commonly applied for newborns, while the double-blind placebo-controlled food challenge is difficult to implement,<sup>9,10</sup> bringing great difficulty in diagnosis. We consider the diagnosis of CMA confirmed if a neonate suffers from abdominal distension, diarrhoea, vomiting, bloody stool, food refusal, irritation, etc.; and has any one of the following: allergic family history, atopic dermatitis and blood eosinophilia  $\geq 4\%$  after eliminating other organic diseases; and has positive milk allergen specific IgE. If milk sIgE is negative, a milk-avoiding challenge test needs to be conducted to confirm diagnosis.

#### ***Therapy***

We would recommend patients with AEGE, FPIES and AP to limit allergic food. Once diagnosed, the infants should be fed with breast milk for 5-6 months while mothers need to avoid risky foods. Hydrolyzed formula milk would be used in newborns not able to be breast fed, to ensure adequate nutrition and to help create immune tolerance. Amino acid formula milk will be used for critically ill infants for 3-6 months before changing to hydrolyzed formula milk, then gradually transit to ordinary milk.<sup>11,12</sup> For the 11 neonates, breast feeding mothers needed to avoid milk. Hydrolyzed formula milk was used instead of ordinary milk for artificial feeding and mixed feeding infants. Four were fed with amino acid formula milk 3-6 months before transiting to hydrolyzed formula milk. All newborns'

digestive tract symptoms disappeared except one with bloody stools who was diagnosed as allergic proctocolitis by colonoscopy. He was given prednisone therapy and was still being followed-up. He is currently on complementary feeding with exclusion of cow's milk. Further investigations are required to delineate if his allergic proctocolitis is related to CMA.

#### ***Immune Tolerance***

Immune tolerance is believed to be created in more than 75% of food allergy within three years of appearance, and nearly 100% within four years. Time needed will be extended for patients allergic to differentiated foods.<sup>13,14</sup> Nine of the eleven in this series (82%) could tolerate milk within one year - within six months for two and after half year for the other seven. Pure CMA may require less time for the development of tolerance. We need to take food allergy seriously, since it is likely for infants suffering from allergy to be exposed to inhaled allergens, which is one of predictors of childhood asthma.<sup>15,16</sup>

#### ***Intrauterine Sensitisation***

One infant in our series was exclusively breast fed by his mother who had drunk milk during pregnancy. He appeared to have symptoms of allergy including abdominal distension, emesis, and bloody stools. Feiterna-Sperling and others reported a case of CMA in a newborn who had never had milk,<sup>17</sup> suggesting the theory of intrauterine sensitisation. It was the earliest time for a foetus to be exposed to food antigens from amniotic fluid through deglutition or touch. Placental insufficiency might also cause food antigens and immune factors to be transmitted to the foetus via the placenta, thus producing immune responses and causing intrauterine sensitisation. Moreover, the literature generally believed that several food proteins could be passed to infants through breast milk, thus causing allergy in the newborns. Thus, it is possible for purely-breast-fed newborns to have CMA and other food protein allergies.<sup>18,19</sup>

#### ***Other Manifestations***

No respiratory symptoms were discovered during the neonatal period in our 11 cases. We considered that wheezing and other respiratory symptoms were mostly caused by aeroallergens, whereas infants in the neonatal period were more likely to contact food allergens, hence chronic inflammation of the respiratory tract had not developed.<sup>20</sup> We would need to gather more information before being able to analyse this in greater details.

## Summary

In conclusion, it is necessary to consider food allergy in the differential diagnoses and to start dietary intervention for critical ill infants. This article also reported the appropriate early intervention of neonatal diet, which was worth further studies. We considered that, in neonates who were likely to have CMA but had negative serum total IgE and food-specific IgE, food-elimination challenge tests could be applied to confirm the diagnosis of allergy and food-avoiding therapy could be used early, in order to control the disease and to help infants to develop tolerance to the food allergens.

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