

Cow's Milk Allergy in Thai Children

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SUMMARY Cow's milk allergy (CMA) is nowadays a common problem in Thai children. We reviewed medical records of patients with CMA from the Department of Pediatrics at King Chulalongkorn Memorial Hospital of the past 10 years, from 1998 to 2007. The criteria for the diagnosis of CMA included: elimination of cow's milk formula resulting in improvement of symptoms, and: recurrence of symptoms after reintroduction of cow's milk by oral challenge or by accidental ingestion. Of the 382 children with a diagnosis of CMA, 168 were girls and 214 were boys. The average age at the time of diagnosis was 14.8 months (7 days-13 years). The average duration of symptoms before diagnosis was 9.2 months. A family history of atopic diseases was found in 64.2% of the patients. All of the mothers reported an increased consumption of cow's milk during their pregnancy. The most common symptoms were respiratory (43.2%) followed by gastrointestinal (GI) (22.5%) and skin manifestations (20.1%). Less common symptoms included failure to thrive (10.9%), anemia (2.8%), delayed speech due to chronic serous otitis media (0.2%) and anaphylactic shock (0.2%). A prick skin test with cow milk extract was positive in 61.4%. Exclusively breast-fed was found in 13.2% of the patients. Successful treatment included elimination of cow's milk and milk products and substitution with soy formula in 42.5%, partial hydrolysate formula (pHF) in 35.7%, extensive hydrolysate formula (eHF) in 14.2%, and amino acid formula in 1.7%. Continued breast feeding was successful in 5.9% (with maternal restriction of cow's milk and milk products). Our study demonstrates the variety of clinical manifestations of CMA in Thai children especially respiratory symptoms which are usually overlooked.

The diagnosis of cow's milk allergy (CMA) is rather challenging. Because of its variety of clinical manifestations, the diagnosis is often overlooked and the prevalence of CMA therefore thought to be low. No report has been published on the prevalence of CMA in Thailand. The prevalence of atopic diseases is increasing nowadays and currently as high as 35%.¹ The risks for CMA seem to be related to genetic and environmental factors. The mechanisms of CMA are IgE mediated, non-IgE mediated, or both.² Maternal exposure to cow's milk protein in moderate amounts during the second trimester can cause the primary sensitization in the fetus.³ Subsequent exposure to cow's milk protein after birth then initiates the symptoms. Moreover, since the gastrointestinal (GI) defense mechanisms and secretory IgA are not fully developed in infants, CMA is more likely to occur in this age group. Host *et al.*⁴ reported the incidence of CMA at 1.8-7.5%, but the

definite diagnosis by a double-blind placebo-controlled food challenge (DBPCFC) test, found the incidence to be only 2-5%. Interestingly, if diagnosed using symptom criteria and the response to avoidance of cow's milk, the incidence might increase to 5-15%.⁴ The incidence of CMA in breast-fed infants in Host's study was only 0.5%.⁴ Children with CMA mostly present with more than 2 symptoms in 2 or more systems. Host found skin manifestations to be the most common presentation (50-70%), followed by GI (50-60%) and respiratory manifestations (20-30%).⁴

Prick skin tests (PST) may be beneficial in

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IgE-mediated CMA. In the non-IgE mediated group, eosinophils in secretions, the milk precipitin test, intestinal biopsy and hemosiderin pigment stains from a bronchoalveolar lavage may be helpful. However, the gold standard for the diagnosis of CMA is the DBPCFC test.

Unlike in the western world, milk is not a usual part of the Thai diet, and there is no report on the annual adult consumption of milk in Thailand. A temporary increase in milk consumption could result in the sensitization of pregnant women and young infants. Since there has been an increase in the milk consumption in Thai pregnant women, the prevalence of CMA increased among the new generation of Thai children. We report here the spectrum of clinical symptoms of CMA in Thai children.

SUBJECTS AND METHODS

We reviewed the data of 382 children with the diagnosis of CMA at King Chulalongkorn Memorial Hospital in the past 10 years (1998 -2007). The criteria for this diagnosis were: a significant clinical improvement after elimination of cow's milk and: a recurrence of symptoms after re-introduction of cow's milk. Laboratory parameters such as PST or serum cow milk specific IgE antibody were only supportive. DBPCFC is the gold standard but not practical in all patients.

All 382 cases of CMA were diagnosed by pediatric allergists. Most were out-patients that either came by themselves or were referred to the allergy clinic because of chronic symptoms. Some of the patients were admitted because of critical problems such as anaphylaxis, GI bleeding, or recurrent respiratory or GI problems. Infections and lactose intolerance were excluded. The study was approved by the Research Ethics Committee of the Faculty of Medicine, Chulalongkorn University.

RESULTS

There were 214 males and 168 females. The mean age at diagnosis was 14.8 months (7 days to 13 years). The mean duration of symptoms before diagnosis was 9.2 months (2 minutes to 12 years: 2 minutes in case of anaphylaxis and 12 years in case of AD, severe AR and failure to thrive since the age

of one year). A family history of allergic diseases was present in 64.2%. All of the patients had a history of increased maternal consumption of cow's milk during pregnancy. All cases had two or more chronic and recurrent symptoms. The clinical manifestations are presented in Table 1. We found that respiratory symptoms were the most common presenting symptoms (43.2%), varying from chronic rhinitis to pulmonary hemosiderosis. Gastrointestinal (GI) symptoms were the second most common (22.5%), varying from diarrhea to gastroparesis. Skin manifestations were the third most common (20.1%), consisting of atopic dermatitis and urticaria. The other manifestations were failure to thrive (10.9%), anemia (2.8%), delayed speech due to chronic serous otitis media (0.2%), and anaphylaxis (0.2%). All admitted cases were fully investigated to exclude other causes.

In most cases, the parents refused an oral challenge by physicians but more than once reactions occurred after accidental ingestion. Ten percent of the patients had a positive oral challenge by physicians because they were admitted with critical problems. Other types of food allergies, particularly egg and seafood allergy co-existed in this group of patients with 11% and 5.4%, respectively. A prick skin test (PST) with cow's milk protein extract was positive in 97 of 158 case tested (61.4%). Fiocchi *et al.*⁵ reported the positive predictive value of PST to be 20-86%.

We compared the PST using pHF and regular cow's milk formula and found that pHF was negative in all patients who were positive to regular cow's milk formula. pHF was used as treatment of CMA in selected patients younger than 2 years old who had a negative PST to pHF and no urticaria, anaphylaxis or serious GI or pulmonary manifestations. The patients treated with pHF had a good clinical response and in almost 90% all symptoms disappeared within 2 weeks. The 10% who did not respond and continued to be symptomatic despite switching to pHF for at least 2 weeks, were prescribed extensive hydrolysate formula (eHF). Some children older than 2 years were switched to soy formula with a good clinical response. For children who had urticaria, anaphylaxis, serious GI or pulmonary manifestations and for those who failed to improve with pHF or soy formula, eHF was recom-

Table 1 The clinical manifestations of cow's milk allergy in Thai children

Clinical manifestations	Number of symptoms (%) (N = 825)
Respiratory	356 (43.2)
Chronic rhinorrhea	132 (37.1)
Nose block	117 (32.9)
Recurrent wheeze	76 (21.3)
Secretory rhonchi	30 (8.4)
Pulmonary hemosiderosis	1 (0.3)
GI	186 (22.5)
Diarrhea	62 (33.3)
Vomiting	41 (22.0)
GI bleeding	28 (15.1)
Enterocolitis	17 (9.1)
Gastroesophageal reflux	15 (8.0)
Colic	13 (7.0)
Constipation	5 (2.7)
Protein losing enteropathy (PLE)	2 (1.1)
Steatorrhea	2 (1.1)
Gastroparesis	1 (0.5)
Skin	166 (20.1)
Atopic dermatitis	120 (72.3)
Urticaria	46 (27.7)
Others	
Failure to thrive (FTT)	90 (10.9%)
Anemia	23 (2.8%)
Delayed speech	2 (0.2%)
Anaphylactic shock	2 (0.2%)

mended. For children who failed to improve with eHF, amino acid formula (Neocate®) was used.

Fifty-one CMA cases who were exclusively breast-fed (13.2%) developed symptoms. For these cases we encouraged to continue breast feeding but to exclude cow's milk and milk products from the maternal diet, which was successful in only 5.9%. Most of the patients (42.5%) were switched to soy formula, 35.7% to pHF, 14.2% to eHF, and 1.7% to Neocate.

DISCUSSION

In our study, the diagnostic criteria for CMA were based on a significant clinical improvement in response to the elimination of cow's milk and on the recurrence of symptoms within 2 weeks after re-

introduction of cow's milk. We did not investigate whether clinical manifestations were IgE mediated or non-IgE mediated, because there was no laboratory that could make such a diagnosis for all clinical symptoms and some symptoms will be mediated by both, IgE and non-IgE anyway. Although DBPCFC was not used as diagnostic criterion, we think that our definition is practical and applicable for physicians in clinical practice.

Our study is the largest such study in Thailand to date. There were 3 previous studies regarding prevalence and presentation of CMA in Thailand. A retrospective study at a Children's hospital done between 1983-1994⁶ addressing CMA in 4,557 children with persistent diarrhea with or without GI bleeding found the prevalence to be 0.63%. In that study clinical improvement occurred in 82.7% of pa-

tients treated with soy milk and in 17.3% treated with eHF.

In a case series of 10 cow's milk protein sensitive enteropathy (CMPSE) patients in Chulalongkorn Hospital,⁷ the mean age was 3.5 month. The presenting GI symptoms were hematemesis ($n = 6$), mucous bloody diarrhea ($n = 3$), and chronic watery diarrhea ($n = 2$). The endoscopic findings were acute and chronic gastritis.

In a retrospective study of 23 children who presented with hematemesis at Siriraj Hospital,⁸ 20 were diagnosed as CMA based on an improvement after avoiding cow's milk. The other 3 cases were diagnosed with gastroesophageal reflux disease (GERD). The patients were treated with eHF ($n = 2$), soy milk ($n = 4$), and pHF ($n = 4$) and all had clinical improvement within 2-3 days.

Gastrointestinal manifestations are well known to be associated with CMA. In a recent international study,⁹ GI manifestations were found less commonly than skin manifestations. In another study,¹⁰ 16-42% of GERD patients possibly had primary CMA and usually presented with other symptoms. The incidence of infantile colic in CMA patients was reported as high as 44%.¹¹ Moreover, CMA was reported to be a possible cause of chronic constipation in older infants and toddlers.¹²

Respiratory symptoms of CMA are very difficult to distinguish from respiratory infection. Respiratory tissue diagnosis is not readily available. However, respiratory manifestations were recently reported more often¹³ and were the most common presentation in our study. Rhinitis was the most common symptom (70%), followed by recurrent wheeze (24%). Nasal congestion and serous otitis media were not uncommon. Moissidis *et al.*¹⁴ reported 8 cases of milk-induced pulmonary disease in infants (Heiner syndrome).

CMA presents with a broad range of clinical symptoms and syndromes.^{15,16} In this study we found almost every symptom that had been reported, including uncommon symptoms such as serous otitis media, and steatorrhea. Auricchio *et al.*¹⁷ reported a case of intolerance to cow milk proteins and steatorrhea induced by beta-lactoglobulin. None of the pa-

tients in this report had isolated symptoms. All patients were recruited from Chulalongkorn Hospital which is a teaching hospital and a primary, secondary and tertiary medical center, and therefore the manifestations and findings documented in this study may not be representative for the general population with cow's milk allergy in the community.

Allergic sensitization can occur as early as in the fetal period.^{18,19} Multiple food sensitization has been described in breast-fed infants.²⁰ There is increasing evidence that ingested cow's milk and other food antigens are secreted into human milk and can potentially sensitize the breast-fed infants.²¹⁻²⁴ In this study 13.2% of exclusively breast-fed infants had CMA which was higher than in other reports. Hill *et al.*²⁵ reported 60 infants who were allergic to cow's milk, soy and the extensively hydrolysed formula, as well as several protein-containing foods including egg, wheat, peanut and fish, which was called "multiple food protein intolerance of infancy" (MFPI). Other studies confirmed these observations.²⁶⁻²⁸ It has been estimated that approximately 10% of infants with CMA are intolerant to the extensively hydrolysed milk protein formula.²⁹ In this study we found 6 cases of severe multiple food allergy who reacted to eHF but tolerated the amino acid formula. One of the patients was allergic to multiple foods including rice.³⁰

From our observations in this study we conclude that clinical clues which suggest CMA are: 1) a positive family history for allergic diseases, especially in first-degree relatives, 2) symptoms occurring after exposure to cow's milk, 3) the presenting symptoms are chronic and recurrent, involving more than 2 symptoms and systems, 4) a history of increased maternal consumption of cow's milk during pregnancy, and 5) for exclusively breast-fed babies, a history of increased maternal consumption of cow's milk during lactation.

The best treatment of CMA is to discontinue cow's milk and milk products. In breast-fed babies, the mother must also discontinue cow's milk and milk products. eHF can be used as breast milk substitute. Anyhow, in practice, eHF was often not successful due to its unacceptable taste and significantly higher cost. In the past, we treated CMA with soy formula and had a good clinical response in the ma-

jority of cases (80%). But the problem with soy milk was that in the public opinion the quality of soy milk protein is inferior to cow milk protein and more expensive too. When pHF became commercially available in Thailand in 1999, and after CMA patients with mild symptoms such as atopic dermatitis, nasal congestion, chronic rhinorrhea, coughing, wheezing, colic, diarrhea and vomiting tested negative to PST of this formula, we recommended it with satisfactory results. The compliance with pHF was superior to that of soy formula or eHF because it tasted better and was cheaper.

In Thailand, the prevalence of CMA has increased during the past 10 years after launching milk products for pregnant women. Unlike in the western world, cow's milk is not a part of the regular Thai diet. Many Thai women who do not usually drink milk will start consuming milk daily in the second trimester of their pregnancy with an average of 2 glasses per day, but in some case already one glass per day can cause cow's milk allergy in infants via intrauterine sensitization. The prognosis of CMA in our study was good.³¹ The rate of outgrowing the disease was 45-56% after 1 year, 60-77% after 2 years, 84-87% after 3 years, and 90-95% after 5 years. Anyhow, 31-75% of CMA patients had co-existing food allergies and 50-80% of CMA of patients will develop an air-borne allergy. Patients with non-IgE mediated CMA may have a higher healing rate and a shorter duration of their symptoms than the IgE mediated group.³²

Breast milk can prevent food allergies because it delays exposure to foreign protein and contains secretory IgA. Soluble factors in the breast milk stimulate the development of the gut barrier and the immune response. There was no difference between eHF and pHF regarding the prevention of allergic disease.³³ pHF may theoretically induce a better oral tolerance to food antigen than eHF.

To prevent food allergy, it is recommended that infants are exclusively breast-fed during the first 6 months of life. Although in western countries no dietary restrictions are recommended for pregnant women³⁴, our study suggests that increased cow's milk consumption during pregnancy should not be advised to Thai mothers. A prospective study should be conducted to confirm this hypothesis.

We conclude that CMA is a common and often overlooked problem of Thai children. Respiratory symptoms are the most common presentation. CMA should be suspected in young infants with chronic respiratory, gastrointestinal, and atopic skin symptoms. Increasing cow's milk consumption should not be advised to pregnant and lactating Thai women because of the possible intrauterine sensitization and subsequent development of cow's milk allergy in newborns. If breast-feeding is not adequate during the first 6 months of life, hypoallergenic (HA) formulas, either pHF or eHF should be used in high risk infants to reduce their risk of CMA.

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