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Cow Milk Protein Allergy During the First Year of Life : A 12 Year Experience at the Children's Hospital, Bangkok

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SUMMARY **CMA should be suspected for patients aged less than one year who had persistent diarrhea and/or hematemesis with no enteric pathogen found. Confirmed diagnosis could be made by Goldman challenge test. Patients with confirmed CMA should be treated by changing the cow milk feeding to soy milk feeding. However, in our study, 17% of CMA patients were also allergic to soy protein. Thus the soy milk was replaced by the elemental formula for successful treatment of this group of patients.**

Beside persistent diarrhea, hematemesis, anemia and hypoalbuminemia were other possible findings among patients with CMA with or without soy protein allergy.

Incidence of cow milk allergy (CMA) has been reported to be 0.3-7.5 percent.[1-3] In Thailand the incidence of CMA is not known. Recently, Thailand has diverted her economic development from agriculture to industry which results in the movement of a large proportion of agricultural labour to urban industries. Breast feeding mothers can nurse their infants at the rice field sites or come home at nursing times on their will. However, working mothers at factories could not do so, thus cow milk formula is inevitable to substitute the mother milk for feeding infants at large of the latter group. This practice, not only caused diarrheal diseases due to deficiencies of passive immunity and unhygienic preparation of infant formula, but chronic diarrhea due to CMA was also observed. In this study, children who were diagnosed to have CMA by challenge test using Goldman criteria[4] with modifications were studied to verify the prevalence, clinical manifestations and the outcome of treatments.

PATIENTS AND METHODS

Patients

A total of 4,557 patients age less than one year who were admitted to Children's Hospital, Bangkok with symptoms of gastrointestinal tract disorder during a twelve year period (1982-1993) were included in the study. These were 4,548 patients with diarrhea (acute, ie the course of diarrhea was shorter than 2 weeks; and chronic, ie the course of diarrhea was longer than two weeks) (group 1), 7 patients with hematemesis (group 2) and 2 patients with both diarrhea and hematemesis (group 3).

Upon arrival at the hospital, information was recorded on history of illness, immediate complaints, feeding practices (breast feeding vs bottle feeding, milk formulation, milk preparation, methods used in cleaning the feeding utensils, etc.), conditions at birth (natural vs caesarean, parturition, birth weights, complications, eg cyanosis, jaundice, anemia), histories of growth and development, immunization programs, parent occupations and levels of education, familial linked genetic disorders/diseases, infec-

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tions (eg tuberculosis) in the families and other attributes of the patients.

Physical examinations were then performed on each patient. These included checking the body weight, body temperature, pulse rate, respiratory rate, blood pressure nutritional status (weight by age; according to Gomez classification), degree of dehydration, heart and lung signs, abdominal distension condition, condition of anemia, neurological responses, edema and others. Laboratory examinations included complete blood count, urine analysis and stool examination. Patients of the first and third groups were subjected to additional examinations, stool cultures for bacterial pathogens,[5] appearance of stool (watery, mucous, mucous-bloody), stool for reducing substance,[6] degrees of dehydration assessed by clinical appearance and laboratory data on serum electrolyte levels, BUN, creatinine and uric acid. The patients of groups 2 and 3 were subjected to blood examination, coagulograms and platelet counts. One of the patients of group 2 received upper gastro-intestinal tract examination, ie barium single meal. It was found that most of the patients of groups 2 and 3 came to the hospital immediately after the hematemesis was found at home, thus most of them did not show any sign of severe anemia and blood transfusion was not required.

Criteria for patients suspected to have CMA.

Patients with diarrhea (groups 1 and 3) were suspected to have CMA when the diarrhea persisted after either (1) no pathogens were found (2) specific pathogens were recovered from stools which, subsequently eliminated by chemotherapy or (3) when condition of stool reducing substance was found and changing of the normal cow milk formula to low lactose cow milk (Almiron) or free lactose cow milk (Olac) formula had been done. The patients of groups 2 and 3 were suspected to have CMA when their blood coagulograms and platelet counts were normal and no other etiology of gastrointestinal tract disorders was found. Histories of patients suspected to have CMA were reviewed in more detail including history of allergic conditions in the family, eg allergic rhinitis, recurrent urticaria, food allergy and others.

Modified Goldman test for confirmation of CMA.

Patients suspected to have CMA were studied in detail by performing modified Goldman challenge tests to confirm the diagnosis by the clinician criteria. Each patient was challenge with 30-60 ml of cow milk orally twice at 3-4 week interval. Clinical manifestations were recorded in details after each challenge. Positive modified Goldman test refered to the patient who developed consistent and similar symptoms as the original symptoms when they arrived at the hospital for the first time within 48 hours after the cow milk challenge, ie diarrhea for group 1, hematemesis for group 2 and both symptoms for group 3, respectively.

RESULTS

Twenty-nine patients of the 4,557 infants (0.63%) were suspected by the clinician criteria to have CMA. These cases were then studied in details for CMA confirmation. Cow milk formula was replaced by soy milk formula for feeding all of the patients. It was found that 24 patients (82.7%) recovered quickly from the illness (diarrhea and/or hematemesis) while 5 patients (17.3%) remained ill. Thus, the soy milk formula was replaced by the casein hydrolysate formula and the 5 patients recovered thereafter. Thus, these 5 patients were assumed to be allergic also to soy proteins. All patients became healthy while they were maintained on the above appropriate practices for 3-4 weeks when the first modified Goldman challenge test was initiated by feeding 30-60 ml of cow's milk to each of them. Twenty-four cases developed challenge reactions in the form signs and symptoms similar to their respective original complaints (diarrhea and/or hematemesis) within 24 hours after the challenge, while the remaining 5 cases developed symptoms latter but within 48 hours. The patients were then changed to their suitable milk formulas until they were recovered and returned homes. Appointments were made with the parents to bring their children back at 3-4 weeks later when the second modified Goldman test was repeated at the hospital. Similar results to those in the first challenge test were obtained after the second test. However, all patients were well tolerated and no anaphylactic reaction was found. It was concluded that all of the 29 patients had CMA.

Among the 29 CMA patients, there were 17 males and 12 females (sex ratio = 1.4:1). There were two pairs of twins and one male and one female siblings. The age range of the allergy onset was 0.5-6 months with the mean of 2.5 ± 1.4 months. The age range when diagnosis could be made was 1.5-6 months with the mean of 3.5 ± 1.3 months. It was found that 13 from 29 infants (44.8%) who received breast milk feeding for 1-4 months followed by cow milk had a delayed onset of the symptoms to 3.3 ± 1.6 months as compared to 2.5 ± 1.4 months of 16 from 29 infants (55.2%) who were fed exclusively with cow milk. However, the figures were not statistically significant ($p > 0.05$). Thirty one percent (9/29) of the cases had a history of allergy in the families (5 allergic rhinitis, 3 bronchial asthma and one urticaria).

Medical records of these 29 CMA cases revealed that upon hos-

Table 1. Information and clinical findings of two pairs of twins and sibling who had CMA.

Case	Age in month(s) when onset of symptoms was found	Age in months when diagnosis was made	Allergen	Symptoms and findings
First pair of twins				
- Older male	2	3	Cow milk and	Diarrhea
- Younger male	2	2.5	soy proteins	Diarrhea
Second pair of twins				
- Older female	4	5	Cow milk	Diarrhea
- Younger female	3	5	Cow milk	Diarrhea and hematemesis
Siblings				
- Older brother	1	3	Cow milk and	- Persistent diarrhea with NEC*
- Younger sister	1	3	soy proteins	- Persistent diarrhea and *Salmonella* and *Aeromonas* were isolated from stool

*NEC = Necrotizing enterocolitis

pital arrival 17.3% had fever, 37.9% had abdominal distension, 55.2% had dehydration and 51.7% had pallor. The nutritional status was normal in 11 patients (38%) while first, and second degrees of protein energy malnutrition were observed in 8 (27.6%), and 10 (34.4%) patients, respectively. No third degree of protein energy malnutrition was observed among the patients.

Laboratory findings revealed that 11 of the 29 cases (42.3%) had hematocrits below 30%. Eight of the 11 patients were from group 1 while the other 3 patients belonged to group 2. Peripheral eosinophilia (>250 cells/mm^3) was found in 5 cases. The presence of occult blood in stools was found in 15 patients. Four patients had serum albumin less than 2.5 g/dl.

Background informations and clinical findings of the two pairs of twins and siblings who had CMA are shown in Table 1. The first pair of the twins were boys who had CMA and soy protein allergy. They were presented with diarrhea. The second pair of twins were girls. Both of them were allergic to cow's milk protein; one of them had diarrhea while another had both diarrhea and hematemesis.Both siblings had CMA and soy protein allergy. The older brother was presented with persistent diarrhea and later necrotizing enterocolitis (NEC). The younger sister had persistent diarrhea alone and *Salmonella* and *Aeromonas* were isolated from her stool.

After the confirmed diagnosis of CMA and soy protein allergy, the suitable milk formulations were prescribed for the patients to avoid their respective allergens. All cases were recovered and gained weights thereafter.

DISCUSSION

In this study defined diagnosis of CMA by challenging with cow's milk twice to clinically suspected cases of CMA at 3-4 weeks apart was performed. The prevalence rate of CMA was 0.63 percents; the rate which was similar to those reported by Goldman,[4] Freier[7] and Lebenthal[8] which were 0.5-1 percent. Higher prevalence in males than in females with the ratio of 1.4:1 was similar to other reports.[2,3,9]

The mean age of CMA onset was 2.5 ± 1.4 months which was similar to those reported in the series of Gerrard[2] which were at the age of 2-3 months. The infants who received breast feeding seem to have delayed onset of symptoms than those received only cow's milk feeding but the difference was not statistically significant ($p > 0.05$). Probably the duration of breast feeding was too short and the numbers of patients of the two criteria were too small to see any impact.

Clinical manifestations in this study were interesting in that beside diarrhea and occult blood loss in stool, hematemesis was found to be the second major presenting symptom (31%) which was high and had not been reported eleswhere except

in the presence of hematochezia.[10-12] However, because the mothers of the patients with hematemesis seeked medical help shortly after the infants developed the illness and early diagnosis and prompt treatment were made by the experienced clinicians, thus, anemia was less pronounced in this group.

Peripheral eosinophilia (>250 cells/mm^3) was found in 19 percent of CMA cases which was slightly higher than the report of Savilahti[13] which was 16 percent of cases.

The findings of CMA in identical twins and siblings are interesting as there has never been this kind of evidence. Moreover, the percent of positive history of allergy, ie the patients' families reported herein (31%) is similar to the figures reported elsewhere by Hide and Guyer[14] and Jacobson and Lindberg[15] who found that 35% of their patients had allergic evidence in the family members. The older brother sibling in our series had persistent diarrhea with necrotizing enterocolitis (NEC) while the younger sister had the diarrhea with the presence of *Salmonella* and *Aeromonas* organisms. These findings indicate that the features were due to post infectious protein intolerance as described previously by Walker-Smith[19] which in the infectious diarrhea, proteins could be absorbed as macromolecules through the damaged intestinal mucosa which eventually may induce host hypersensitivity.[17-19]

Treatment of most patients with CMA who were presented with persistent diarrhea was successful by changing the cow milk to soy milk formulation in this study. However, five cases of the 29 CMA patients (17.1%) were also allergic to soy milk. These findings were similar to those of the previous reports which association of soy protein allergy among CMA patients was in the range of 17-40%.[15,20-24] The patients with soy protein allergy recovered after changing the soy milk to elemental formula which contained casein hydrolysate.

In our study, 82% of the CMA patients developed recurrence symptoms within 24 hours after the milk challenge test. The figure is slightly higher than those reported by Goldman[4] and the Italian Collaborative Study in 1988[20] which was in the range of 50-74%. The disputation might be due to the fact that, in our study the challenge amount of milk was higher.

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