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Evaluation of cow milk protein sensitization in children suspected cow milk protein allergy

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Abstract

Cow milk is one of the most common cause of food allergy in children age less than 5 years. Gastrointestinal and cutaneous manifestations are the most common presenting presentations. The diagnosis of cow milk allergy (CMPA) is mainly based on history, food elimination and re-challenge of cow milk. Evaluation of sensitization to cow milk is the additional investigation for the diagnosis. This study evaluates cow milk sensitization status by prick skin test and specific IgE to cow milk in children aged less than 5 years who are suspicious of non-severe CMPA and mainly presented with gastrointestinal and cutaneous manifestations in Thammasat University Hospital. Sixty-one patients were included in the study. The mean age of onset was 5 ± 10.9 months. Gastrointestinal presentations were presented in 36 patients (60.6%), followed by the skin presentations in 17 patients (27.9%). Positive skin prick test to cow milk was found 1 patient (4.4%); positive specific IgE to cow milk (> 5 kUA/L) was found in 2 patients (4.8%). Oral challenge to cow milk protein was positive in 14.8%. Oral food challenge is very helpful in confirming the diagnosis of CMPA, particularly in the non-IgE mediated group.

Keywords: Cow's milk protein allergy, Skin prick test, Serum IgE for cow's milk, Oral food challenge test

1. Introduction

Cow's milk protein allergy (CMPA) is frequently encountered among children with prevalence and incidence reported within a range of 0.5 percent to 17 percent [1-6], depending on diagnosis methods. CMPA is currently rising due to preference in feeding modified formula milk to infants early. Other factors consist of genetic and environmental factors. Symptoms and presenting symptoms among patients with CMPA are exhibited in multiple systems such as the cutaneous, gastrointestinal and respiratory systems. Patients may have symptoms in only one system or multiple systems in some cases.

CMPA is diagnosed by background inquiries and physical examinations. Patients are asked about when symptoms occur after drinking milk and about history of cow's milk consumption among mothers during pregnancy and breastfeeding. The methods used to support diagnosis consist of the allergy skin testing, specific IgE for cow milk and gastrointestinal endoscopy. The gold standard for diagnosis is oral food challenge. In practice, diagnosis of CMPA in Thailand uses only history of suspicious presenting symptoms. If the aforementioned symptoms occur, patients will be advised to follow treatment guidelines for treating CMPA by abstaining from cow's milk and dairy products and/or changing the type of milk consumed such as extensive hydrolysate formula and testing for more allergies to support the disease. However, patients do not receive confirmation tests for diagnosis because oral food challenges require specialist doctors. Thus, few reports are offered on test results for diagnosis to be made.

Therefore, this study was aimed at studying CMPA test results among pediatric patients with history or presenting symptoms fitting CMPA for cow's milk protein allergy diagnosis by using the skin prick test, testing IgE levels specific to cow's milk and testing presenting symptoms by oral challenge test.

2. Materials and methods

2.1 Subject selection

This study is a descriptive retrospective cohort study conducted by collecting data from pediatric patients suspected of cow's milk allergy treated in the Pediatric Out-patient Examination Unit and the General and Special Pediatric Patients' Ward, Thammasat University Hospital, in 2012-2017. Data was collected from 73 patients with history of suspected allergy who were tested. Fluctuations between population ratios and sample ratios were set at no more than five percent with reliability at 95 percent. The researcher obtained a sample size of 61 pediatric patients with suspected CMPA who were treated at the Pediatric Out-patient Examination Unit and the General and Special Pediatric Patients'ward, Thammasat University Hospital. We comprehensively reviewed medical records, demographic data, and results of SPT and IgE of all subjects by using electronic and paper charts. This study was approved by the ethic committee of Thammasat University.

2.1.1 Inclusion criteria

The subjects had to meet all of the following criteria: children aged less than or equal to five years with suspected presenting cutaneous and/or gastrointestinal symptoms of cow's milk allergy with the following information: cutaneous symptoms consisting of atopic dermatitis based on Hanifin-Rajka's diagnosis criteria, gastrointestinal symptoms such as vomiting, diarrhea, stomachache and bloody stool and suspected cow's milk allergy symptoms improved after abstaining from cow's milk. Patients came to be tested for allergies and to be diagnosed at the Allergy Clinic and/or the Gastrointestinal System Clinic.

2.1.2 Exclusion criteria

Patients with chronic diseases such as heart disease, chronic lung disease, immunodeficiency, chronic gastrointestinal diseases, diseases with digestion and absorption deficiency or chronic diseases requiring patients to receive an immunosuppressant for a long period of time.

2.2 Oral food challenges (OFC)

OFC were performed by experienced physicians in a proper environment equipped for emergency. Patients were examined prior to starting feeding, as well as before each dose was administered. Any signs or symptoms that occurred during the OFC were also recorded. Clinical observations continued for at least 4 h after the last food dose. The initial dose for the OFC was 3 mg, as recommended by the European Academy of Allergy and Clinical Immunology food allergy and anaphylaxis guidelines [7], and a total of nine doses were given to patients that showed no reactions to the logarithmic dose increments. The maximum dose included 3 g of the protein. A total of 4.5 gr milk protein was applied. The starting dose should always be lower than the one which triggered the allergic reaction. Emergency resuscitation equipment and drugs were available in case of emergency.

2.3 Statistical analysis

Descriptive statistics were calculated for all variables. Frequencies were calculated for categorical variables and presented as percentages. Mean and standard deviation was calculated for continuous variables. All statistical analyses were conducted using STATA version 15.1.

Definitions of SPT positive: aged less than two years and wheal > 6 mm, aged more than two years and wheal > 8 mm [8].

IgE positive: age less than one year and IgE 5 kU/L, aged more than one year and IgE 15 kU/L. [9].

3. Results and discussion

According to data collection from 61 pediatric patients with suspected symptoms of CMPA who came to be treated in the Pediatrics Department, Thammasat University Hospital, when all patients received confirmation by oral food challenge, the prevalence of CMPA was found at 14.8 percent. The patients consisted of 29 male patients (47.5%) and 32 female patients (52.5%). Most of the patients had no family history of allergies and

smoking (86.9% and 88.5%, respectively). The mean age when symptoms began to appear was 5.02 ± 10.98 months. The mean weight and height were within in a normal growth range.

Patients had only the following gastrointestinal symptoms (60.6%): allergic proctocolitis (22 patients), protein-induced enteropathy (4 patients), food protein-induced enterocolitis (4 patients), gastroesophageal reflux disease (GRED) (1 patient), constipation (4 patients), eosinophilic esophagitis/gastritis (2 patients) and bloating (1 patient). This was followed by only cutaneous symptoms consisting of atopic dermatitis (17 patients) (27.9%) and seven patients had both gastrointestinal and cutaneous symptoms (11.5%) (as shown in Table 2).

Table 1 Demographic Data of Patients with History of Suspected CMPA.

Basic Data	No. (N = 61)
Gender	
Male	29 (47.5%)
Female	32 (52.5%)
Gestational Age at Birth	
Full-term (≥ 37 Weeks)	48 (78.7%)
Premature (< 37 Weeks)	13 (21.3%)
Birth Weight	
< 2,500 Grams	11 (18%)
≥ 2,500 Grams	50 (82%)
Mean Weight (Grams)	2,978.5
Family History of Allergy	
Present	8 (13.1%)
Family History of Contact with Cigarettes	
Present	7 (11.5%)
Age When Symptoms Occurred (Months)	
Mean ± Standard Deviation	5.02 ± 10.98
Age at First Doctor's Visit (Months)	
Mean ± Standard Deviation	6.43 ± 11.77
Weight by Age Criteria (%)	
Mean ± SD	98.44 ± 20.62
Height by Age Criteria (%)	
Mean ± SD	100.23 ± 8.84

Table 2 Clinical manifestations in patients with history of suspected CMPA.

Presenting Symptoms	No. of Patients (N = 61)	Serum IgE/SPT positive (N=61)
Cutaneous Symptoms	17 (27.9%)	2 (3.2%)
Gastrointestinal Symptoms	37 (60.6%)	1 (1.6%)
Cutaneous and Gastrointestinal Symptoms	7 (11.5%)	NA

Of 61 patients, 23 patients received the skin prick test and 42 patients were tested for IgE levels specific to cow's milk as shown in Table 3. Laboratory results showed one positive skin prick test result (4.4%) and two positive test results for IgE levels specific to cow's milk (4.8%). All 61 patients were tested again with food challenges with 31 patients who were tested by oral food challenges at the hospital and 30 patients who were tested by accidental challenges. According to test results, 8 of 31 patients (25.8%) tested by oral food challenges at the hospital had positive results while 1 of 30 patients (3.3%) tested by accidental challenges had positive results. Repeat oral challenges yielded positive results for 9 out of 61 patients (14.8%).

According to the oral food challenge testing with 61 patients who had a mean age of 18.6 months, the oral food challenges were conducted with 37 of 61 patients aged more than or equal to 12 months, and 24 of 61 patients aged less than 12 months. Patients aged less than 12 months had more positive test results (25%). This helped confirm diagnoses better than patients aged more than one year who were tested by oral food challenge. The mean age of patients who received skin prick testing was 10.9 ± 6.1 months, and the mean age of patients tested for IgE levels specific to cow's milk was 10.8 ± 14.4 while the mean age of patients tested by oral food challenge was 18.6 ± 16.2 months as shown in Table 4.

Table 3 Allergy testing among patients with history of suspected CMPA.

Tests	No.	Positive results	Negative results
Skin prick test	23	1 (4.4%)	22 (95.6%)
Specific IgE for cow milk	42	2 (4.8%)	40 (95.2%)
Oral food challenge	61		
- Accidental challenge	30	1 (3.3%)	29 (96.7%)
- Hospital challenge	31	8 (25.8%)	23 (74.2%)

Table 4 Mean age in allergy tests and oral food challenges among patients with history of suspected CMPA.

Allergy test	Mean and standard deviation (months)
Skin prick test	10.9 ± 6.1
Specific IgE for cow milk	10.8 ± 14.4
Oral food challenge (hospital)	18.6 ± 16.2

Repeat oral challenge test results for 61 patients showed positive results for 9 patients and 5 out of 9 patients had gastrointestinal presenting symptoms (55.6%). One patient was found to have positive results for IgE levels specific to cow's milk and 4 out of 9 patients (44.4%) were found to have presenting cutaneous symptoms. One patient was out to have positive results for IgE levels specific to cow's milk. Out of 9 patients, 6 patients were tested at ages less than 12 months while 3 patients were tested after the age of 12 months and found to have positive results, which indicated predictions of slower improvement of the disease.

Table 5 Basic characteristics, condition and presenting symptoms and repeat positive oral challenge test results in the experimental group.

Case	Gender	1st Age visit (months)	Age onset (months)	Symptom	Formula used	Skin prick test	Serum IgE	Age of OFC (months)
1	M	3	3	Diarrhea	eHF	None	Negative	6
2	F	2	2	Atopic dermatitis	Breast milk	None	Positive	17
3	F	3	1	Atopic dermatitis /bloody diarrhea	eHF	None	None	24
4	M	2	1	Bloody diarrhea	eHF	Negative	None	7
5	F	4	3	Bloody diarrhea	eHF	Negative	Negative	8
6	M	2	2	Diarrhea	eHF	None	Positive	6
7	F	8	8	GERDs	eHF	Negative	Negative	11
8	F	60	60	Atopic dermatitis	eHF	None	Negative	65
9	M	3	3	Atopic dermatitis	eHF	Negative	Negative	8

Note: GERD; gastroesophageal reflux disease, eHF; extensively hydrolasated formula.

CMPA is a more frequently encountered problem because parents and doctors have awareness and monitoring; furthermore, more formula milk is used with infants. However, because this disease has symptoms and presenting symptoms in various systems such as the gastrointestinal, cutaneous and respiratory systems, there is a need for additional allergy tests to diagnose, categorize and confirm diagnoses, because the aforementioned symptoms are not specific to only cow's milk protein allergy. Ordinarily, parents tend to think of this disease among infants with the aforementioned symptoms more than definite diagnoses by oral food challenges. As parents gained more suspicion of this disease, excessive treatment has been pursued. In this study, the prevalence of cow's milk protein allergy in first-year infants was found to be as high as 14.8 percent when diagnoses were confirmed by oral food challenges. This finding was high when compared to previous studies discovering different prevalence rates with the following diagnoses: Self-reported diagnoses by caregivers found prevalence at 1.2-17 percent, skin prick tests found prevalence at 0.2-5.2 percent, skin prick test with specific IgE found prevalence at 0-2 percent and diagnoses by oral food challenge found prevalence at 0.6-3 [4-6]. When compared to a study conducted by Venter et al., the prevalence of cow's milk protein allergy

from oral food challenges among patients with parents who reported symptoms fitting the disease was 2.3 percent. However, when double-blinded, placebo-controlled food challenge (DBPCFC) was used, the prevalence was one percent [10]. The age group most frequently found to have cow's milk protein allergy was in the first year [11-12]. The prevalence of the disease in this study was higher than previous studies. This can be explained in that the patients in the present study, most of whom came from specialist clinics such as the Gastrointestinal Disease Clinic and the Allergy Clinic. Patients, were assessed and diagnosed in physical documents by specialty clinics. Patients were found to have higher trends of CMPA than parents who reported or suspected symptoms, thereby causing confirmation by oral food challenge to show higher prevalence of the disease and detailed inquiry of clinical symptoms to have contributed to diagnoses. However, patients should be confirmed by oral food challenge according to treatment guidelines in order for patients to receive suitable treatment and limited cow's milk among patients who have the disease along with reducing the cost of unnecessary treatments in this group of children.

Regarding presenting symptoms, this study found most patients to have symptoms and presenting symptoms in the gastrointestinal system, followed by the cutaneous system. All patients had symptoms fitting atopic dermatitis. Patients with symptoms in both symptoms were found at only 11.5 percent. Most gastrointestinal symptoms found in this study were not severe such as diarrhea, vomiting, bloating and constipation. Food protein induced allergic proctocolitis was found most in 36 percent of all patients (22 out of 61 patients). Data was slightly different from previous studies [1,3]. When compared to previous studies, Host A was found to have cutaneous symptoms the most (50-70%), gastrointestinal symptoms (50-60%) and respiratory symptoms (20-30%). In the present study, gastrointestinal symptoms were found more frequently than cutaneous symptoms. The most encountered gastrointestinal symptoms found among the non-IgE mediated group was food protein induced allergic proctocolitis. All infants had symptoms in the first six months and this symptom was found among breastfeeding infants and infants who consumed modified formula milk for infants. Infants in this group became cured of the disease at the age of one year. Concerning cutaneous symptoms, atopic dermatitis was the most encountered symptom and hives was not found. Respiratory symptoms were not found in this study because allergies occurred as an atopic march, meaning many patients were found with AD in the first part of life while symptoms of respiratory allergies followed later. In the present study, the patients had a mean age of $5.02 + 10.98$ months, causing no presenting symptoms of the respiratory system to be found. Current reports on respiratory symptoms found mucus, recurrent respiratory tract infections and recurrent wheezes more frequently at 70 percent, 54.6 percent and 24 percent, respectively [13,14].

With regard to laboratory tests such as allergic skin tests and tests for IgE specific to cow's milk protein, patients in this study were found to have received tests for IgE levels specific to cow's milk more than allergic skin test. Most test results were negative because most of the patients had non-IgE mediated allergy and some patients had mixed type allergy. In addition, most of the clinical symptoms were gastrointestinal symptoms with non-IgE allergy mechanisms, causing results from tests of IgE levels specific to cow's milk and allergic skin tests to be negative. However, consideration should be given to allergic skin test results in children aged less than one year who have IgE food allergies, which may be false negative test results. Of the patients with mixed type allergy, two patients were found to have positive test results. The patients had symptoms of atopic dermatitis and one patient had diarrhea. This case may have had mechanisms of mixed type allergy. Therefore, this patient should be monitored and the patient may have other subsequent symptoms. For these two patients with positive test results for IgE levels specific to cow's milk, predictions of the disease and duration of the disease were found to be longer than patients with negative test results. Regarding allergy tests among patients with symptoms of suspected cow's milk protein allergy, particularly non-IgE mediated symptoms, the aforementioned negative test results were unable to diagnose the disease. Therefore, there is need for proof with oral food challenges to further confirm diagnosis.

Oral food challenges are considered a confirmation test for diagnosis and many methods may be used. In this study, oral challenges were used with 24 patients who were tested before the age of 12 months and had positive results (25%). In this group of patients, test results indicated disease prevalence with more accuracy than test results from patients who were tested at the age of one year or more because patients with trends of being cured were found to be at 50- 60 percent when patients were aged more than one year. Therefore, oral food challenge used with patients aged more than one year can be used to indicate prevalence less than patients aged less than one year. However, oral food challenge can be applied more to identify patients who outgrew the disease. In this study, nine patients were found to have positive results (14.8%). One patient had positive results from accidental consumption at home. However, because this case had low to medium allergy severity, the patient had little chance of having complications. In practice, however, patients were not advised to take cow's milk at home. Furthermore, the nine patients who were tested by oral food challenge had abstained from cow's milk for at least three months and the longest case abstained for 15 months. Six patients were tested before the age of 12 months and three patients were tested at the age of more than 12 months. These three patients had atopic dermatitis, which has mechanisms of occurrence from mixed type allergy. However, one patient had positive test results for IgE levels specific to cow's milk. Disease predictions for this type of allergy mechanism showed a slower

improvement than non-IgE mediated allergy. This was consistent with positive oral food challenge test results despite being aged more than one year.

The oral food challenge test was used to confirm diagnosis. When patients' symptoms improved following 2-4 weeks of abstaining from foods with cow's milk protein, patients received appointments to follow-up on symptoms and be tested by eating foods with protein [15]. Most parents did not ask to do oral challenges because children were improved and parents did not want to risk triggering allergic reactions. Thus, diagnosis could not be confirmed. In these cases, further special testing may be considered such as allergic skin tests, tests for IgE specific to cow's milk and gastroesophageal intestinal endoscopy if there are indications. However, after detailed background inquiries and symptoms and presenting symptoms fitting Non-IgE mediated or IgE mediated allergy occur among patients aged less than one year who may have false negative skin test results, there was need for proof with oral challenges to confirm diagnosis.

4. Conclusion

CMPA is a common problem among pediatric patients. Symptoms can be present in multiple organ systems and may not be specific to cow's milk protein allergy. The presenting symptoms found in diagnoses depend on detailed background inquiries, physical examinations, inquiries for history of milk consumption and further allergy tests to provide data supporting the disease. However, the best method for confirming diagnosis is the oral food challenge test, particularly among non-IgE mediated and mixed type groups.

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6. Ethic approval

This study was approved by the human research ethics committee of Thammasat University (MTU-EC-PE-0-103/59).

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