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Prevalence of Soy Protein Hypersensitivity in Cow's Milk Protein-Sensitive Children in Korea

This study was aimed to evaluate the prevalence of soy protein hypersensitivity in cow's milk protein-sensitive children in Korea. A total of 1,363 patients with atopic dermatitis, urticaria, enterocolitis syndrome, bronchial asthma or allergic rhinitis were recruited. First, we estimated the prevalence of sensitization to soy in children sensitized to cow's milk. Specific IgE levels > 0.7 kU/L by CAP assay were considered positive. Next, the prevalence of soy allergy in cow's milk allergy (CMA) patients was investigated. Those children whose parents agreed to participate the open challenge test with soy had a convincing history of allergic reactions elicited by cow's milk and these symptoms were relieved by elimination. All of them had negative soy-specific IgE. Patients with positive soy-specific IgE accounted for 18.3% of 224 children sensitized to cow's milk protein. The prevalence of sensitization to soy decreased with age (36.8% in the first year of life, 16.4% in the second year, and 13.7% in the third year). Of 21 CMA patients, 42.9% (n=9) were determined to have soy allergy (mean age 10.3 months). Our results suggest that soy protein formula should be carefully used as a substitute for cow's milk in CMA patients, especially during infancy.

Key Words : *Hypersensitivity; Soybeans; Milk Hypersensitivity; Child; Korea; Prevalence*

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INTRODUCTION

Cow's milk allergy (CMA) is one of the most common adverse reactions to foods in infancy and early childhood. It manifests various symptoms in the skin (atopic dermatitis, urticaria, and angioedema), gastrointestinal tract (vomiting, diarrhea, colics, and gastroesophageal reflux), or respiratory tract (rhinitis, wheezing, dyspnea, and cough). Treatment of CMA is based on the elimination of cow's milk protein from the diet. For this purpose hypoallergic formula or soy protein-based formula has been used in infants with CMA (1, 2).

Soy protein formula is similar to cow's milk protein in the distribution of nutrients, and thus provides normal growth and immunologic status (3, 4). It has been widely used especially for infants with CMA as a substitute, because of its low allergenicity (5), low cost, good palatability, nutritional adequacy, and no cross reactivity to cow's milk protein. However, soy protein formula has been in limited use, because some of the CMA patients are allergic to soy protein as well (6-13).

Soy-based foods are popular in Korea, and thus Korean infants and children have been frequently fed with soy-containing foods, such as soymilk, soybean curd (tofu), soy-based soup, soy sauce, and so on. In particular, soy protein formula has been commonly used for either normal healthy infants or those who are allergic to cow's milk protein. Based on the concept that food allergy is given rise to by various factors including the nature of allergen, dose and frequency of antigen exposure, etc. (14), the prevalence of food allergy to various offending allergens partly depends on the regional differences of dietary habits during infancy. For that reason, one can speculate that soy protein formula is not an appropriate diet for CMA patients in some areas where soy protein allergy is highly prevalent.

In this study, we evaluated the prevalence of soy protein hypersensitivity in cow's milk protein-sensitive children in Korea, where children are exposed to soy-based food from a very young age.

MATERIALS AND METHODS

Study population

A total of 1,363 children and adolescents referred to the Allergy Clinic of Samsung Medical Center for atopic disease were enrolled in this study. Atopic disease included atopic dermatitis, urticaria, enterocolitis syndrome, bronchial asthma, and allergic rhinitis. IgE- and non-IgE-associated soy protein hypersensitivity was evaluated to determine the prevalence of soy allergy in cow's milk-sensitive children.

First, the prevalence of IgE-associated soy hypersensitivity in cow's milk-sensitive atopic patients was evaluated. The presence of specific IgE against both cow's milk and soy was checked by either the Pharmacia CAP assay (Pharmacia and Upjohn, Uppsala, Sweden) or skin prick test. Those who performed CAP assay had atopic dermatitis, urticaria or enterocolitis symdrome, while skin prick test was done in children over the age of 5 yr with bronchial asthma or allergic rhinitis, either alone or in combination. Of 1,363 patients, 224 children with positive cow's milk-specific IgE were investigated to determine whether they were sensitized to soy protein as well. The prevalence according to the age was also analyzed. The mean age of these patients sensitized to cow's milk protein was 2.5 yr (range 3-141 months).

Next, the prevalence of non-IgE-associated soy hypersensitivity in cow's milk-sensitive children was evaluated. Of 1,363 patients, children with a convincing history of allergic reaction elicited by cow's milk were recruited. Among these patients with convincing history, 21 children were diagnosed as having cow's milk allergy (CMA) by relief of clinical symptoms with elimination of cow's milk protein from the diet. These patients had atopic dermatitis (n=13), urticaria (n=5), or enterocolitis syndrome (n=3), and no patients had a history of anaphylaxis by cow's milk ingestion. Nine patients showed positive cow's milk-specific IgE, while 12 of them did not. After the informed consent was obtained from their parents, open food challenge test was performed with soy. All of the patients had negative CAP value of soy-specific IgE. The serum total IgE level was 59.2 kU/L on average (range 3.3-270 kU/L), and the mean age was 12.8 months (range 2-35 months).

Serum specific IgE

Sera from children with atopic disease were analysed for specific IgE antibodies to cow's milk and soy by the CAP system (Pharmacia-Upjohn) according to the manufacturer's instructions. Briefly, patients' sera were obtained at their first visit. Fifty microliters of sera were added to Immuno CAP and incubated for 30 min. After washing, 50 μL of enzyme-anti-IgE were added. After incubation for 150 min, each sample was washed, and 50 μL of development solution was added. Incubation for 10 min was followed by the addition of stop solution. Fluorescent eluate from Immuno CAP was measured in FluoroCount 96 and was determined by comparing with the values from the standard curve. Concentrations above 0.7 kU/L were regarded as positive. The level of specific IgE was expressed as mean $\pm$ standard deviation (SD).

Skin prick test

Skin prick test was performed with cow's milk and soy (Torii, Japan). Briefly, allergen extracts were applied by means of the prick technique. Histamine and saline were used as positive and negative control, respectively. Skin prick test results were considered positive when the wheal size elicited by food allergens was equal to or greater than that produced by the positive control.

Food challenges

Food challenge test was performed in CMA patients with no specific IgE antibody to soy protein. They were fed with soy protein formula for 2 weeks with 2.1 g of protein/kg of body weight/day. In those who manifested aggravating symptoms (eczema, urticaria, diarrhea) from soy protein formula, an extensively hydrolyzed formula (HA®, Maeil, Korea) was given for 2 weeks to eliminate soy protein from their diet. Their symptoms were monitored by a physician at the Allergy Clinic. They were also fed with weaning diet except allergenic foods such as egg, soy, wheat, and peanut. During the study period, no additional weaning diet was offered. Diagnosis of soy allergy was established when the soy protein formula elicited atopic symptoms which were relieved by subsequent elimination.

Statistics

Statistical analysis was performed using SPSS 10.0 program. The Fisher's exact test and Mann-Whitney test were used to compare data from patients with positive soy challenges and those with negative soy challenges. A p value <0.05 was considered significant.

RESULTS

Prevalence of soy protein sensitization in atopic patients sensitized to cow's milk protein

Two hundred and twenty four (16.4%) of 1,363 patients

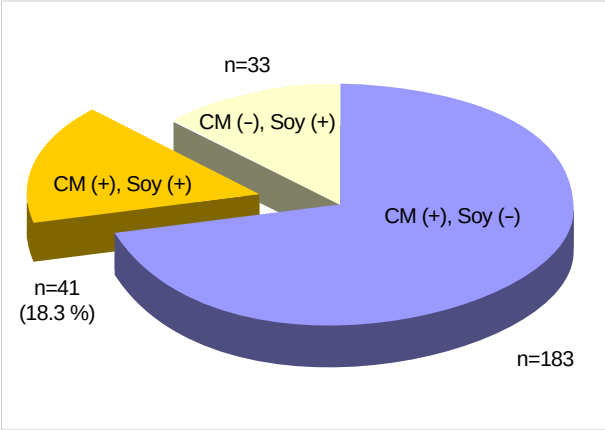

Fig. 1. Prevalence of soy protein sensitization in children who were sensitized to cow's milk protein. The mean age of patients sensitized to both cow's milk (CM) and soy protein was 2.5 yr. Most of them (n=34) had atopic dermatitis. Prevalence was written in the parentheses.

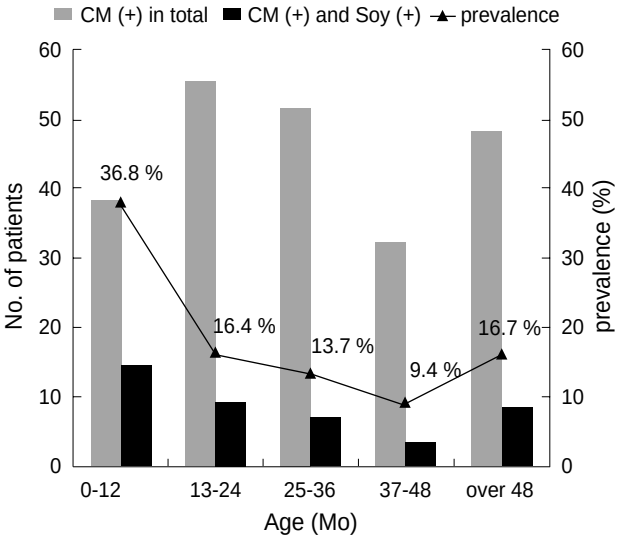

Fig. 2. Prevalences of soy protein sensitization in children who were sensitized to cow's milk protein according to the age. Prevalence in each age group is written above each bar. CM, cow's milk.

with atopic disease were sensitized to cow's milk protein, while 74 (5.4%) of them were sensitized to soy protein. Among 224 atopic children who were sensitized to cow's milk protein, 41 patients were sensitized to soy protein as well (Fig. 1). The prevalence was 18.3% (95% CI=13.2-23.4%). The male-to-female ratio was 30:11, and most of them (n=34) had atopic dermatitis. The level of specific IgE against cow's milk protein was 15.9±29.0 kU/L (range 0.89-101 kU/L), and that against soy protein was 12.4±20.6 kU/L (range 0.83-101 kU/L).

The prevalence of soy protein sensitization in cow's milk-sensitive children was analysed by age. As shown in Fig. 2, the prevalence of soy protein sensitization in infants less than one year who were sensitized to cow's milk protein was 36.8%, and it was shown to decrease with age. The prevalences during the second, third, and fourth year of their lives were 16.4%, 13.7%, and 9.4%, respectively.

Prevalence of non-IgE-associated soy hypersensitivity in cow's milk allergy patients

Children with CMA, established by a convincing history and elimination, were challenged with soy protein formula. Their CAP values of soy-specific IgE were negative. Among 21 children with CMA, 9 were allergic to soy protein as well, while 12 were not (Table 1); 5/9 patients had atopic dermatitis, 3/9 had enterocolitis syndrome, and 1/9 had urticaria. The prevalence of non-IgE-associated soy protein hypersensitivity in CMA patients was 42.9% (95% CI = 21.7-64.1%). The mean ages of the positive and negative response groups to soy challenge were 10.3 and 13.3 months, respectively. However, there was no statistically significant difference between the two groups in terms of sex, age, diagnosis, total IgE, and specific IgE against cow's milk protein (p>0.05).

Table 1. Clinical data of patients with cow's milk allergy who performed the open food challenge test with soy

	Challenge test with soy (+)	Challenge test with soy (-)	p value
Number of patients (%)	9 (42.9%)	12 (57.1%)	
Sex ratio (male/female)	6/3	5/7	0.387
Mean age (months)	10.3	13.3	0.651
Total IgE (kU/L)	42.0	72.1	0.554
Cow's milk protein-specific IgE (kU/L)	0.51±0.66*	0.96±1.32*	0.651
Soy protein-specific IgE (kU/L)	0	0	
Diagnosis			0.136
Atopic dermatitis	5	8	
Urticaria	1	4	
Enterocolitis	3	0	

* mean±standard deviation.

DISCUSSION

Food allergy is an adverse reaction after ingestion of food, which is caused by either IgE-mediated or non-IgE-mediated immune mechanism. In food allergy patients skin prick tests for foods and tests for detecting circulating specific IgE antibodies against food allergen have a good negative predictive value but a rather poor positive predictive value (15). This is because in some children specific IgE to foods may occur as a transient phenomenon regardless of the presence of atopy (16). For the diagnosis of food allergy, double-blind, placebo-controlled, food challenge test (DBPCFC) is considered as the gold standard method. Ideally DBPCFC should be used for the evaluation of either IgE- or non-IgE-mediated food allergy. However, DBPCFC is time-consuming and complicated. Besides it sometimes triggers severe adverse reaction such as anaphylaxis and thus some parents refuse to perform challenge test to their children, especially when the patients are infants. Therefore DBPCFC is difficult to perform in clinical practice for the diagnosis of food allergy.

Recently in the pediatric population quantification of food-specific IgE was reported to be useful for diagnosing IgE-associated symptomatic allergy to egg, milk, peanut, and fish instead of DBPCFC (17). In that report, diagnostic decision points that are 90% to 100% predictive of clinical reactivity to each allergen was established. For the patients with food-specific IgE below the decision points DBPCFC is required to confirm the diagnosis. When only the patients with specific IgE above the decision point were studied without DBPCFC, the prevalence of food allergy to each allergen would be underestimated. On the other hand, the prevalence of sensitization might be higher than that of food allergy confirmed by DBPCFC. Nevertheless we estimated the prevalence of sensitization for the IgE-mediated hypersensitivity in the symptomatic atopic children, based on the fact that sensitization to food allergen is often the first evidence of development of IgE-mediated ato-

pic disease in genetically predisposed subjects. In the present study the prevalence of sensitization to soy protein in atopic children was observed as 5.4%. This figure is similar to those reported from previous studies (18-21), which varied from 4% to 22%. This variability is probably due to the differences in methodology to identify specific IgE to soy protein, either in vitro or in vivo and in patient selection such as disease entity, age distribution, specialty referral, involved area with different dietary habits, etc. The prevalence of sensitization to cow's milk protein in our study was 16.4%, and among them 18.3% of children was sensitized to soy protein as well. In particular, the prevalence of soy protein sensitization in patients sensitized to cow's milk protein during infancy was as high as 36.8%, suggesting that this period is critical in sensitization to food allergen.

For diagnosing non-IgE-mediated soy allergy open challenge test was undertaken only in selected children whose parents agreed to participate. All of them are symptomatic CMA patients and showed negative soy-specific IgE. They were challenged with soy protein formula on the basis of the report that both skin prick test and RAST have a good negative predictive value (22). Our data showed that the prevalence of non-IgE-associated soy protein allergy in CMA children was 42.9%. Bock et al. reported that only 6.9% of the children with CMA showed soy protein allergy, which was evidenced by either DBPCFC or open challenge test (6). Of a 93 IgE-associated CMA cohort (age range 3 to 41 months), 14% were determined to have soy allergy according to Zeiger et al. (7). On the contrary, some authors demonstrated a higher prevalence of soy allergy in CMA patients, varying from 30% to 100% (8-13). This difference is related to the number of study population, patients' age, diagnostic method, and so on. In other words, those studies involved a small number of patients, a young age group of less than 12 months, and history-based diagnosis of soy allergy demonstrated a high prevalence, while IgE-associated CMA children were likely to demonstrate a low prevalence. In the present study, the small size of study population (n=21) and mixed type of CMA children might have influenced the 42.9% prevalence of soy allergy. In addition, soy allergy was diagnosed by open food challenge test, although ideally negative responses to open food challenge should be confirmed by DBPCFC. The mechanism of non-IgE-mediated food allergy still remains unclear, although food antigen-specific IgG might be involved. These antigen-specific IgG (IgG_4) antibodies are known to reflect the type of foods ingested and not indicative of specific food-related pathogenesis (23). In the present study the role of food-specific IgG was not evaluated.

Treatment of food allergy is to avoid offending food allergens. In 1983, the Committee on Nutrition of the American Academy of Pediatrics recommended that soy protein formula should not be used in the dietary management of documented clinical allergic reactions to cow's milk protein (24). However, Businco et al. (25) claimed that no references were provided showing that protein hydrolyzed formulas are superior to soy protein formula in children with CMA. Zeiger et al. (7) suggested that soy protein formula is generally a safe formula for IgE-associated CMA children, which was consistent with the recommendations of the same committee in 1998 (1). Recently, 30 kDa of a soy protein component was identified as a molecule to cross-react with caseins from cow's milk (26). This result suggests that in vitro cross-reactivity should be considered when CMA patients are treated with soy-derivatives. Controversies still remain whether soy protein formula can be used as a preferred alternative in CMA children, especially during infancy.

In conclusion, the prevalence of sensitization to soy protein in Korean atopic children sensitized to cow's milk protein was estimated at 18.3%, while the prevalence of non-IgE-associated soy allergy in CMA children was revealed to be 42.9%. DBPCFC studies in larger cohorts of babies may provide more reliable data on the prevalence of soy allergy in Korea. Our results suggest that soy protein-based formula should be carefully used as a substitute for cow's milk in CMA patients, especially in the first year of life.

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