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Original Article

IgE-mediated soy protein sensitization in children with cow's milk allergy

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Abstract

Background Soy-based formula as an alternative to cow's milk formula is preferable to extensively hydrolyzed protein formula because of the lower cost and more acceptable taste. However, cow's milk allergy patients can subsequently develop a sensitivity to soy protein.

Objective To compare soy protein sensitization in children with and without an allergy to cow's milk.

Methods This study was conducted in Yogyakarta from September 2007 until March 2008. Subjects were children aged below 4 years with an atopic history. Subjects were divided into 2 groups: those with a positive skin prick test to cow's milk and those with a negative skin prick test to cow's milk (control group). Both groups were given soy formula and tested at 6 weeks for sensitization to soy.

Results There were 45 children in each group. Age, sex, and atopic history were similar in both groups. We found no soy protein sensitization (negative skin prick results) in all subjects from both groups.

Conclusion Risk of immunoglobulin E-mediated sensitization to soy protein was not proven in children with cow's milk allergy. **[Paediatr Indones. 2012;52:67-71]**.

Keywords*: cow's milk allergy, immunoglobulin E-mediated sensitization to soy protein*

Allergies in children can start in infancy and continue into adulthood. An allergy is a condition characterized by the occurrence of an overreaction of the immune system to usually harmless environmental substances. Allergies may occur early in life due to children's immature immune status and high gastrointestinal mucous permeability.[1] If a child has an atopic history he may become easily sensitized, and develop allergies to allergens such as food and airborne particles.[2]

For non-breastfed infants, cow's milk formula contains the many of the first foreign proteins given to an infant. Allergy to cow's milk has become more common today, as an increasing number of parents give cow's milk formula to their infants. Allergy to cow's milk is often the first atopic disease in children.[3] The incidence of cow's milk allergy has been estimated at 2-7.5% in formula-fed infants and 0.5% in exclusively breastfed infants, generally occurring within the first six months of life.[4] A study from Cipto Mangunkusumo Hospital, showed approximately 2.4% of children were allergic to cow's milk.[5] In Yogyakarta, an estimated 30,000 children suffer from cow's milk

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allergy.[6] Management of cow's milk allergy involves substituting the formula with a non-cow's milk base until tolerance to cow's milk is developed. Substitutes for cow's milk formula include extensively hydrolyzed protein formula, amino acid formula, and soy-based formula. Soy-based formula is recommended because it is hypoallergenic, lower cost, has an acceptable taste and has adequate nutrition to meet the growth needs in children.[7]

Soybean-based foods are very popular in Indonesia, including soy milk, tempeh, tofu, and soy sauce. But some children with cow's milk allergy can be subsequently sensitized and develop a soy milk allergy. This may be caused by cross-reaction between the soy protein B3 polypeptide and 11S globulin protein casein from cow's milk.[9] Sensitization to soy and soy milk allergy in cow's milk allergy patients remain to be a health problem in various regions of the world, with a reported prevalence of 8 to 14%. However, severe anaphylactic reactions rarely occur.[10] Ahn KM *et al* reported a prevalence of 17% in Bangkok and 18.3% in Korea of soy allergy in cow's milk allergic children.[11] A study in Indonesia reported incidence of sensitization to soy milk of 17.5%.[12]

The time required for sensitization to soy milk by oral administration has not been reported in humans. However, McLaughlan *et al* reported that in guinea pigs sensitization to cow's milk protein or soy milk occurred at day 37 of feeding.[13] Similarly, a study by Villoslada *et al* showed that sensitization took six weeks of exposure to cow's or goat's milk proteins in mice.[14] According to Vandenplas, sensitization takes one to six weeks,[15] while according to Wegrzyn, sensitization occurs within one to two weeks.[16] Sensitization can also occur within a few days or even three or four weeks after consuming soy milk.[17] Inspite of varying opinions on soy milk sensitization, substitution with soy milk is still largely recommended.

The aim of this study was to determine whether cow's milk allergy is a risk factor for soy protein sensitization in children.

Methods

This study was conducted at Bhakti Ibu Hospital, Yogyakarta from September 2007 until March 2008. Subjects were children aged less than 4 years with atopic history. Inclusion criteria were children who had not consumed soy formula and had negative skin prick tests to soy milk. We excluded children with congenital abnormalities and severe allergic reactions (anaphylaxis or severe atopic dermatitis). Subjects were divided into 2 groups based on their skin prick test results to cow's milk. We calculated the need for 45 subjects per group, taking into account the relative risk,[18] and the percentage of soy-sensitive children with allergy to cow milk's (17.5%[12]) and those without allergy to cow's milk (1.1%[31]). We selected for controls with age matching within 6 months. Informed consent was obtained from parents. This study was approved by the Research Ethics Committee, Gadjah Mada University Medical School /Sardjito Hospital.

All subjects were given soy protein isolate milk for 6 weeks, after which we conducted blinded soy protein skin prick tests. Soy protein skin prick tests were performed using reagents from Alyostal prick test (Stallergenes SA-France) 1000 IC/mL. Test reagents, positive control and negative control were placed on the volar forearm area 2 cm away from the elbow fold or wrist. Care was taken to use area without skin rash. Liquids were pricked into the skin using lancets/needles at an angle of 30 - 45° to the skin surface. After 15 minutes, liquid residue was removed with tissue paper, and results of the examination were read. All data was processed by SPSS for Windows. We calculated relative risk (RR) to compare skin prick results between groups.

Table 1. Basic characteristics of subjects

	Allergy to cow's milk (n=45)	No allergy to cow's milk (n=45)
Age, months		
≤12	21	22
>12-24	14	17
>24-36	5	3
>36-48	5	3
Mean age, months (SD)	18.0 (11.3)	16.7 (10.1)
Sex (male)	18	25
Atopic history	45	45
Mother	16	19
Father	12	13
Father and mother	1	0
Sibling	16	13

Results

There were 90 subjects enrolled in this study, divided into two groups. Age, sex, and atopic history were similar in the two groups (**Table 1**).

Figure 1 shows that allergic reactions to cow's milk were mostly manifested as dermatitis (21 subjects), rhinitis (9 subjects) and constipation (6 subjects).

After 6 weeks follow-up, we found no cases of soy protein sensitization (all negative skin prick results) in all subjects from both groups.

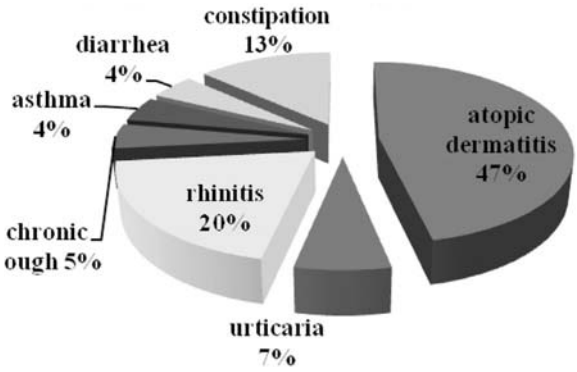

Figure 1. Clinical manifestations of cow's milk allergy

Discussion

In this study, cow's milk allergy occurred mostly in children aged less than 12 months (18.0 SD 11.3). This finding is in agreement with other studies that reported cow's milk allergy occurred in under four year-olds, particularly in the first 12 months of life and decreasing with age.[19-21] A study by Zeiger *et al* found that of subjects with cow's milk allergy, 20.4% were aged 0-12 months and 58.4% were aged 12-24 months, with a mean age of 19.1 months.[10] Allergy to cow's milk may be related to the immaturity of the gastrointestinal barrier and immune system in infants and children.[19-21] In early life, the mucosal epithelial layer has low levels of mucin and sIgA, thus resulting in reduced gastrointestinal tract barrier function, in terms of ability to prevent attachment of antigen to mucosal surfaces and antigen clearing. Production of gastric acid and protease enzymes may also decrease. This condition may be accompanied by high permeability of gastrointestinal mucosa resulting in a high incidence of allergic reactions.[20,22]

Clinical manifestations of cow's milk allergy mostly occurred in the integumentary system (53.4%), followed by respiratory (28.8%) and gastrointestinal (17.7%) systems. Our findings were similar to those of Zeiger *et al*,[10] Muktiarti *et al*,[12] and Host *et al*[23] In contrast, Hill *et al* reported gastrointestinal symptoms to be the most common clinical manifestation.[24]

We found no sensitization to soy protein in any of our subjects, possibly due to earlier tolerance to soybean protein if the subjects had consumed soy protein-based foods (such as tempeh, tofu, soy sauce, *oncom*, and *tauco*). Indonesians consume many forms of soy protein-based foods at levels of 18.6 kg/capita/year in cities, and 13.9 kg/capita/year in villages.[25,26] Tempeh is often used as nutritional therapy for acute diarrhea treatment in children. Darwin[27] and Mien[28] showed that soybean protein formula can shorten hospitalization duration for diarrhea compared to rice formula. It can also improve weight gain in children with chronic diarrhea. Soenarto *et al* showed that acute diarrhea in children improved with soy formula, with shorter duration of illness and increased weight gain.[29]

Another possible explanation for our results is our use soy protein isolate, which is less allergenic. Tsumura *et al* reported allergenicity to soy milk protein isolates (β-conglycinin which is a fraction of the 7s globulin and P34) was diminished by the presence of enzymes hydrolyzing *Proleather FG-F,* an alkaline protease from *B. subtilis*.[30] These allergens are different from those reported to cause cross-reactions in cow's milk allergy patients, namely the B3 polypeptide, a fraction of the 11S globulin.[9] The allergens we used for skin prick test were in accordance with Tsumura's research. A study by Ragno *et al* of 20 cow's milk allergy patients used soy milk as a placebo.[32] None of those patients developed sensitization to soy protein.

In conclusion, cow's milk allergy does not increase the risk of immunoglobulin E-mediated sensitization to soy protein in children.

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