

Soy allergy in atopic children

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Background: Although soy is considered a major food allergen (along with milk, egg, peanut, fish, and wheat), the prevalence of soy allergy in the pediatric population is not well defined.

Objective: To determine the prevalence of soy allergy in atopic children attending the Allergy Clinic at the Pediatric Department of Milan University.

Methods: Seven hundred four patients with allergic signs and symptoms, aged 1 month to 18 years, were recruited between December, 1991 and April, 1992. The subjects with positive skin prick tests to soy were tested using a DBPCFC with powdered soy formula in fruit juice, and rice or corn flour as placebo. In children who refused the liquid challenge, capsules containing dehydrated soy flour or talcum powder as placebo were administered. An age-matched and sex-matched group of subjects with negative skin prick tests to soy were tested using an open challenge with soy formula.

Results: A positive skin prick test to soy was found in 148/704 patients (21%); 131 out of 148 children with positive skin prick test (group A) and 131 out of 556 children with negative skin prick test to soy (group B) were challenged with soy: 8/131 (6%) in group A had a positive soy challenge while no clinical reactions were observed in children in group B. A younger median age, a positive past and current personal history of cow milk allergy, and a previous history of soy allergy were found most often in children with positive soy skin prick test and positive soy challenge than in children with positive skin prick test and negative soy challenge. The eight soy-allergic children reacted to the soy challenge mostly with cutaneous and gastrointestinal symptoms; symptoms were immediate in six and late in two children. The eliciting dose of soy was very small in the immediate reactions; higher and repeated doses were necessary for the onset of late reactions.

Conclusion: The prevalence of clinical soy allergy in our children with positive skin prick tests to soy is 6.1% (8/131), while none of 131 children with negative skin prick test to soy reacted to the challenge.

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INTRODUCTION

Consumption of soybean is common in children. Since the use of soy milk was suggested in 1929 by Hill and Stuart as an alternative for feeding children with cow milk protein intolerance,¹ soy protein-based infant formula has become a routinely used, safe and nutritionally adequate feeding for infants with cow milk allergy. The use of soy formulas has increased over the years and in 1991 a 6-fold increase in soy use in the United States by the year 2000 was projected.²

Gastrointestinal reactions to soy have been reported in some infants under 3 years of age with cow milk intolerance³; however, only a few cases of systemic or extraintestinal reactions to soy have been reported, all in atopic patients older than 3 years of age.⁴

Although soy is considered a major food allergen along with milk, egg, peanut, fish, and wheat,⁵ prospective controlled clinical trials that estimate the prevalence of soy allergy in children are lacking. This investigation was designed to determine the prevalence of soy allergy (as defined by positivity of soy skin prick test and soy challenge) in a group of atopic infants and children attending the Allergy

Clinic at the Pediatric Department of Milan University.

METHODS

Subjects

Patients seen at the Allergy Clinic of Pediatric Department of Milan University between December, 1991, and April, 1992, were recruited for the study.

All patients with signs and symptoms suspected to be of allergic origin were enrolled in the study after informed consent was obtained from the parents. Patients on antihistamines and/or steroids were excluded from the study. A total of 857 patients were enrolled (549 males and 308 females, aged 1 month to 18 years, median age 7 years 8 months).

Procedures

At the initial visit to the hospital clinic, the subject's allergy history was recorded on a standardized case history report. Information was collected on family history of atopic disorders in parents and siblings, personal history of allergic symptoms, past or current cow milk intolerance, previous ingestion of soy formula, and previous soy intolerance.

Laboratory studies included a battery of skin prick tests using commercially available extracts of inhalant and food allergens: pollens (grasses, ragweed, mugwort, *Parietaria judaica*, and trees), molds (*Alternaria tenuis* and *Aspergillus fumigatus*), animal dander (cat and dog), dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), milk, egg, pea, and peanut (standard glycerosaline solution, Lofarma Laboratories, Milan, Italy). Standardized soy glycerinated extract (1:20 wt/vol) was used (Greer Laboratories, Lenoir, NC).

Histamine (1%) was used as a positive control and human serum albumin as a negative control. The degree of

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skin prick test positivity was graded using the test wheal size/histamine wheal size according to the recommendations of the Societa' Italiana di Allergologia e Immunologia Clinica (SIAIC)⁶:

- 1+ = from 1/4 to 1/2 histamine wheal size
- 2+ from 1/2 to 1 x histamine wheal size
- 3+ from 1 to 2 x histamine wheal size
- 4+ > 2X histamine wheal size.

Total serum IgE concentration was measured by Phadebas PRIST (Pharmacia Diagnostic, Uppsala, Sweden). Serum IgE values more than two standard deviations (SD) above the geometric mean for age were considered abnormal.⁷

The subjects with positive skin prick tests to soy were further tested using a DBPCFC to soy. Challenges were performed in the hospital clinic during a 1-day admission. An age-matched and sex-matched group of subjects with negative skin prick tests to soy was tested using an open challenge according to Leinhos et al.⁸ Patients were asked to stop taking any antihistamine ten days before the challenges. All soy foods were strictly eliminated from the diet during the 2 weeks preceding the day of the challenge. At the end of the 2 weeks of soy-free diet, a fecal occult blood test was performed in all patients. On the day of the challenge all patients were symptom-free, and a repeat skin prick test to soy was done to confirm the earlier skin prick test results. The DBPCFC was conducted on two non-consecutive days and the soy and placebo challenges were separated by at least 48 hours. Randomization was done by a department nurse not involved in the administration of the challenge.

Up to 200 mL of powdered soy formula (Isomil, Abbott Laboratories, Ross Products Division, Columbus, Ohio) made up in fruit juice and water at the concentration typically fed to infants (13%, 1.8 g soy protein/100 mL), and rice or corn flour as placebo (13% solution) made up using the same diluent, were administered in the

fasting state during a 2-hour period. Gradually increasing doses were given every 20 minutes starting with one drop on the inner lower lip (one drop, 1 mL, 5 mL, 10 mL, 50 mL, and 134 mL). In older children who refused the challenge with soy milk (n = 38), up to 40 capsules (white opaque gelatin tinted with titanium oxide, Lofarma Laboratories, Milan, Italy) containing dehydrated soy flour (88 mg soy protein/capsule) or talcum powder (placebo) were administered in a graded fashion every 20 minutes, starting with one capsule (cps) and followed by 2 cps, 3 cps, 5 cps, 10 cps, and 19 cps. The capsules were opened and the powder dissolved in a minimal amount of fruit juice and water. Open challenge was performed with 200 mL of 13% soy formula (Isomil powder reconstituted in water or fruit juice) administered in a graded fashion with increasing doses every twenty minutes. No food or drink was allowed during the challenge. Meals were deferred until 1/2 hour after the completion of the challenge to avoid food delaying absorption of the test item and also to avoid introducing other possible allergens.

When clinical reactions occurred, the challenge was immediately stopped and the appropriate treatment given. The type, severity, and time of onset of the reaction, the amount of food eliciting the symptoms, and the duration of symptoms were all recorded during the challenge.

All the children were carefully observed during each challenge and for at least four hours after the challenge prior to discharge from the hospital clinic. If no symptoms appeared in the following 24 hours, parents were instructed to feed their children soy in the diet on a daily basis for at least 1 week at home. Children were given 200 mL/day (3.6 g protein) of soy formula (Isomil powder, reconstituted as directed by the manufacturer) or other soy products (yogurt, bread, pasta, or cookies) in quantities that would provide approximately 3.6 g protein/day.

At the end of the week a fecal occult blood test was performed (OC-Hemodia, Eiken, Tokyo, Japan).

Statistical Analysis

Data from patients with positive and negative skin prick tests to soy were compared using the chi square test.

The Fisher's exact test was used to compare data from patients with positive soy skin prick test/positive soy challenges and patients with positive soy skin prick test/negative soy challenges.

RESULTS

A total of 704 of the 857 infants and children enrolled in the study had one or more positive skin prick tests to inhalants and/or food allergens and were classified as atopic. A positive skin prick test to soy was found in 148 (21%) of the atopic infants and children (group A), a negative skin prick test to soy was found in 556 (79%) (group B). The degree of soy skin prick test positivity was 1+ in 63 subjects, 2+ in 73 subjects, 3+ in 11 subjects and 4+ in 1 subject.

There were no statistically significant differences between the two groups of children when compared for age, distribution of males and females, family history of atopy, of cow milk intolerance, and soy allergy. The two groups were similar for personal history of asthma, atopic dermatitis, and past and current cow milk intolerance.

Positive personal history of pollinosis occurred in a greater percentage of subjects in group A than in group B (69/148 = 47% versus 132/556 = 24%, $P < .001$); similarly, a positive history of gastrointestinal symptoms was more prevalent in group A versus group B (29/148 = 20% versus 71/556 = 13%, $P < .05$). No significant differences between the two groups were found as far as elevation (> 2 SD) of serum IgE and skin prick test positivity for dust mite and cow milk; skin prick test positivity was significantly more prevalent in group A versus group B for pollens (137/147 = 93% versus 350/530 = 66%, $P < .001$), molds (61/144 = 42% versus

100/516 = 19%, $P < .001$), animal dander (89/143 = 62% versus 228/514 = 44%, $P < .001$), egg (44/131 = 34% versus 111/475 = 23%, $P < .05$), pea (92/148 = 62% versus 25/556 = 4%, $P < .001$), and peanut (41/148 = 28% versus 15/556 = 3%, $P < .001$).

There was no statistical difference between group A and group B in the previous use of soy formula: 30% of patients (45/148) in group A and 27% (152/556) in group B were soy formula fed in the first year of life. A history of soy intolerance was reported in 26 subjects, 10/45 (22%) from group A and 16/152 (10%) from group B ($P < .07$).

Challenges

DBPCFC to soy was conducted in 131/148 subjects of group A (92 males and 39 females, median age 10.6 years); 17 children refused to undergo the challenge. In group B 131/556 subjects (92 males and 39 females, median age 10.1 years) were challenged. Eight children in group A (8/131 = 6%) reacted positively to soy challenge, while none of the children in group B reacted to the challenge.

Characteristics of the eight patients that reacted to soy including age, clinical diagnoses, and history of soy and cow milk allergy are presented in Table 1. All the children had a history of food allergy, seven had a history of oral allergy syndrome (OAS), and five had a history of cow milk allergy. Four of the children were fed soy milk in the past. All four reported a history of soy intolerance with atopic dermatitis worsening in all cases and vomiting and sleepiness occurring in one case.

At the time of the soy feeding, three of the four children were also cow milk intolerant. The skin prick test positivity for specific allergens in the eight subjects reacting to DBPCFC to soy was as follows: birch pollen, 7; grass and animal dander, 6; molds, 5; *Compositae* and dust mite, 4; pea, 5; egg and milk, 4; and peanut, 3.

Seven of eight subjects had serum total IgE levels >2 SD above the geometric mean for age.

At the challenge 6/8 subjects had immediate clinical reactions beginning within 5 to 15 minutes from the ingestion of the eliciting dose in five children and at four hours in one child (no. 4) (Table 2). Late reactions occurred in one child after three days of the soy diet and in one child after seven days of the soy diet. The immediate reactions were itching, erythema, urticaria, or systemic anaphylaxis whereas the late reactions were gastrointestinal. In one patient (no. 8) with a late reaction the clinical symptoms occurred after seven days of soy feeding and the colonic and rectal biopsy showed an allergic proctocolitis with a marked infiltration of eosinophils in the lamina propria. Abnormal stools with presence of gross blood lasted for 3 months after the elimination of soy from the diet. After 4 months of the soy-free diet, the gastrointestinal symptoms had disappeared and the occult blood test was negative. A colonic and rectal biopsy after 11 months of a soy-free diet showed mucosal edema only in the distal colon and rectum. The occult blood test was positive for one other

patient (no. 7) with immediate onset symptoms in response to the challenge; the test was negative one week after the challenge on a soy elimination diet.

Demographic and allergy history data (gender, family history of atopy, cow milk and soy allergy, personal history of asthma, pollinosis, atopic dermatitis, urticaria, and gastrointestinal symptoms) were similar in the soy-allergic (eight patients) and soy-tolerant children (123 patients). Prevalence of previous ingestion of soy milk was also similar in soy-allergic (4/8 = 50%) and soy-tolerant (39/123 = 31%) children.

Patients in the soy-allergic group were also similar to those in the soy-tolerant group in total serum IgE >2 SD and in skin prick test positivity for pollens, dust mite, molds, animal dander, egg, pea, peanut. If we consider in particular the positivity of the skin prick test to birch pollen, this was more prevalent, but not significantly different in soy-allergic children than in soy-tolerant children (7/8 = 87.5% in soy-allergic children and 42/76 = 55% in soy-tolerant children). Furthermore, children in the soy-allergic group have a higher prevalence of cow milk skin prick test positivity than children in the soy-tolerant group (4/8 = 50% in soy-allergic children and 22/113 = 19% in soy-tolerant children).

In soy-allergic children, cow milk intolerance was more prevalent than in soy-tolerant children (4/8 = 50% in soy allergic versus 19/123 = 15% in soy tolerant, $P < .05$); a previous history of soy allergy was also more prev-

Table 1. Sex, Age, Clinical Diagnosis, History of Soy and Milk Allergy in Children with Soy Positive Challenge

Patient	Sex	Age, yr:mo	Clinical Diagnosis*	History of Soy Allergy	History of Cow Milk Allergy
1	F	10.10	A, P, OAS, FA	†	pos
2	M	5.10	A, P, OAS, FA	†	neg
3	M	1.11	AD, FA	pos	pos
4	M	1.8	AD, FA, P, OAS	pos	pos
5	M	5.10	A, AD, FA, P, OAS	pos	pos
6	M	3.11	A, AD, FA, U, OAS	†	pos
7	F	4.6	FA, OAS	†	neg
8	F	6.7	A, AD, FA, P, OAS	pos	neg

* A = asthma, FA = food allergy, OAS = oral allergy syndrome, AD = atopic dermatitis, P = pollinosis, and U = urticaria.

† No previous soy feeding.

Table 2. Positive Oral Soy Challenges^a: Amount of Soy Eliciting Symptoms, Reaction Time from Last Given Dose, Symptoms, After Challenge Fecal Occult Blood, Soy Skin Prick Test, and RAST Results

Patient	Eliciting Dose	Reaction Time	Symptoms	Occult Blood	Soy Skin Prick Test	Soy RAST Class
1	2 cps	5'	labial itching	—	2+	2
2	20 cps	10'	vomiting, tongue itching	—	1+	2
3	4 cps	10'	urticaria	—	2+	4
4	200 cc	4 hr	perioral erythema	—	3+	3
5	1 cps	5'	abdominal pain, vomiting, malaise, collapse	not done	3+	6
6	200 cc/daily	3 d	abdominal pain, gastrointestinal disorders	—	2+	3
7	1 cps	15'	nasal itching, perioral erythema, burning lips, frequent urination	+	2+	1
8	200 cc/daily	7 d	fecal gross blood, abdominal pain	+	2+	0

1 cps = 88 mg soy protein/capsule.

alent (4/4 = 100% versus 9/39 = 23%, $P < .05$). Soy-allergic children were younger than soy-tolerant children (median age 4 years 2 months in the soy-allergic patients and 10 years 5 months in the soy-tolerant group).

DISCUSSION

In this study, the prevalence of soy allergy determined by DBPCFC in a group of soy skin prick test-positive, atopic children is 6.1% (8/131) while none of 131 children with negative skin prick tests to soy reacted to the challenge. The prevalence of soy allergy in this study is similar to that previously reported for differently selected groups of atopic children.⁹⁻¹¹ Giampietro et al⁹ and Bock and Atkins¹⁰ reported soy allergy in approximately 3% of children with food allergies. Sampson¹¹ reported a prevalence of 5% in a younger group of patients with atopic dermatitis. If we consider the prevalence in the literature of allergic adverse reactions to other foods as stated by DBPCFC, we found that soy allergy is much less prevalent than allergy to milk, egg, and peanuts.^{10,11}

The prevalence of soy skin prick test positivity in our study (21%) is similar to the prevalence (22%) of humoral sensitization to soy recently reported by Giampietro et al⁹ in 317 children with history and symptoms suggestive of food allergy. This prevalence is also not different from the prevalence of egg (26%), milk (16%), and pea (16%) sensitization and is greater than sensi-

tization to peanuts (8%). The degree of skin prick test positivity is very low: only 8% had a skin prick test positivity to soy greater than 2+.

Infants and children with positive skin prick tests to soy appear to be a more highly sensitized group than those with negative skin prick tests as they have a significantly greater prevalence of skin prick tests positive for pollens, molds, animal dander, egg, pea, and peanut. On the contrary, the prevalence of cow milk sensitization is similar in the soy skin prick test positive and negative patients (20% and 14% respectively).

Soy formula feeding in the first year of life does not seem to affect the prevalence of soy sensitization and the prevalence of soy clinical allergy in soy sensitized children. On the contrary, infants with documented soy clinical allergy are more likely to have cow milk clinical allergy than infants without soy allergy: four of eight (50%) soy-allergic patients are currently allergic to cow milk while only 19 out of 123 (15%) soy-tolerant patients are allergic to cow milk.

In our study no child with a negative skin prick test to soy had a positive soy challenge. These data agree with Sampson's observations of patients with atopic dermatitis: he reported positive soy challenges only in patients with positive soy skin prick tests.¹² In the literature, non-IgE mediated soy adverse reactions with diarrhea have been reported especially in infants with protein intolerance. Probably the neg-

ativity of the soy challenges in our patients with negative soy skin prick tests is related to the fact that our study group includes atopic children with IgE-mediated reactions and not infants with protein intolerance. The prevalence of soy allergy in the entire atopic group of 704 children cannot be determined from our study; however our hypothesis is that clinically relevant soy allergy in atopic children is present mostly in patients with skin prick test positivity to soy while it is rare in children with negative skin prick tests to soy. If this hypothesis is true, a further study that includes challenges in all the negative soy skin prick test children would yield a total prevalence of about 1.1% (8/704).

From our data we can also assume that there may be a correlation between soy allergy and the oral allergy syndrome, based on the history of oral allergy syndrome with other foods in 7/8 patients, on the clinical manifestations of oral allergy symptoms at soy challenge in 3/8 patients, and on the skin prick test positivity to birch pollen in 7/8 patients. Whether soy allergy is in some way an expression of a cross reactivity with pollen allergens, particularly birch pollen, requires further study.

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REFERENCES

1. Hill L, Stuart H. Soybean food preparation for feeding infants with milk idiosyncrasy. *JAMA* 1929;93:985-7.
2. Messina M, Messina V. Increasing use of soyfoods and their potential role in cancer prevention. *J Am Diet Assoc* 1991;91:836-40.
3. Panizon F, Ventura A. L'enteropatia da ipersensibilit  alle proteine del latte vaccino. *Prospettive in Pediatria* 1980;40:347-58.
4. Bock SA, Lee WY, Remigio LK, May CD. Studies on hypersensitivity reactions to foods in infants and children. *J Allergy Clin Immunol* 1978;62:327-34.
5. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr* 1985;107:669-75.
6. Diagnostica delle Allergopatie: Memorandum della Societ  Italiana di Allergologia. *Boll SIAIC* 1992;5(4):9-24.
7. Kjellman NIM, Johansson SGO, Roth A. Serum IgE levels in healthy children quantified by a sandwich technique (PRIST*). *Clin Allergy* 1976;6:51-9.
8. Leinhas JL, McCaskill CC, Sampson HA. Food allergy challenges: guidelines and implications. *J Am Diet Assoc* 1987;87:604-8.
9. Giampietro PG, Ragno V, Daniele S, et al. Soy hypersensitivity in children with food allergy. *Ann Allergy* 1992;69:143-6.
10. Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 1990;117:561-7.
11. Sampson HA. The role of food allergy and mediators release in atopic dermatitis. *J Allergy Clin Immunol* 1988;81:635-45.
12. Ortolani C, Pastorello EA, Farioli L, et al. IgE-mediated allergy from vegetable allergens. *Ann Allergy* 1993;71:470-6.

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