

Soy allergy is not common in atopic children: a multicenter study

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The aim of the present study was to evaluate the prevalence of soy allergy (positive skin test and positive challenge test) in a large cohort of atopic children, many of them soy fed early in life for several months.

In order to investigate the prevalence of soy allergy, two groups of children were enrolled into the study. The first group comprised a cohort of 505 children with personal history suggestive of food allergy. The second group included 243 children born of atopic parents, who had been soy protein formula fed for the first six months of life for the prevention of cow's milk allergy and who had been prospectively followed up, from birth to 5 years.

As regards the prevalence of soy allergy in the cohort of children suffering from allergic disease: 31/505 children (6%) had positive skin prick test to soy, however only six of the 31 children with positive skin prick test to soy had positive challenge test to soy.

With regard to the prevalence of soy allergy in the children who had been soy protein formula fed in the first six months of life (second group): 14/243 children (6%) had positive skin prick test to soy, but the double blind placebo control oral food challenge to soy was positive in only one of these 14 children. In conclusion documented soy allergy is not common in atopic children.

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Soybeans are a primary foodstuff in Asia where they have been used for infant nutrition by the Chinese and the Japanese for many centuries. On the contrary soy protein was not common in the Western diet and the first usage of a soy product such as a cow's milk (CM) substitute was reported in 1909 (1). A soy protein formula (SPF) was used for feeding babies with adverse reaction to CM proteins for the first time in 1929 (2). Subsequently, SPFe have been widely used for feeding babies with this disorder. These formulae were the only available CM substitute, and they ensured not only survival but also a normal life to many children affected by the wide spectrum of clinical manifestations of cow's milk allergy (CMA) (2–8).

In the last decade, the allergenicity of SPFe has been emphasized mainly in children with CMA and, as a consequence, at present, SPFe are not recommended for feeding babies with CMA (9–13). However, surprisingly, very few studies employed

the challenge test for the diagnosis of soy allergy, even in patients with suspected soy-allergy (14–20). In most studies the diagnosis of soy allergy was based on clinical evaluation or anedoctal case history reported by parents and was not substantiated by scientific diagnostic criteria: no challenge test to soy was made, nor was data on specific IgE to soy available (skin test and/or RAST), as we have pointed out (21,22). Recently it has been shown that SP intolerance frequently occurs in babies with multiple food proteins intolerance. However, intolerance to different proteins, such as CM, soy, rice and even to hydrolysates, indicates that this group of babies represents a rather peculiar entity (23).

The aim of the present study was to evaluate the prevalence of soy allergy (positive skin test and positive challenge test) in a large cohort of atopic children, many of them SPF fed early in life for several months.

Subjects and methods

In order to investigate the prevalence of soy allergy, two groups of children were enrolled into the study. The first group comprises a cohort of 505 children with personal history suggestive of food allergy who consecutively attended the Pediatric Allergy Clinic from September to December 1994 at the following institutions: Department of Pediatrics of the Rome "La Sapienza" University; Lugo Hospital of Lugo (Ravenna); San Giuseppe Hospital, Milan; Pinerolo Hospital of Pinerolo (Torino). The median age of the children was 69 months (range: 6–168 months) and 277 were males (55%) and 228 females (45%); 312/505 (62%) were suffering from atopic dermatitis (AD), and in 58% of the children with AD (181), it was confirmed that food allergy (cow's milk, egg, wheat) was the main triggering factor; 28/505 (5%) from urticaria and 14/505 (3%) from food-induced anaphylaxis (cow's milk); 151/505 (30%) children also had asthma and/or rhinitis.

The second group included 243 children born of atopic parents, who participated in a large study for the prevention of CMA. As dietary intervention these children had been SPF fed for the first six months of life and prospectively followed up, at 3, 6, 9, 12 and every 6 months to 5 years. As regards the parental history of atopy, 73% of the children had uniparental and 27% biparental. Atopic parents was defined as a parent affected by: asthma, or allergic rhinitis, or atopic dermatitis, with positive SPT and/or RAST to various allergens. All the babies received the same soy-formula (Isomil, Ross, Lab). The median age was 59 months (range 43–71 months) for 131 males (54%) and 112 females (46%). During the 5 years follow-up 12/243 (5%) of the children developed symptoms due to food allergy (FA): 8/12 had food-induced AD, 3/12 food-induced urticaria, and 1/12 CM-induced anaphylaxis; 37/243 children were affected by asthma and/or rhinitis.

The diagnosis of AD was made according to the Sampson criteria (24). For the diagnosis of FA, the presence of either skin, gastrointestinal, and/or respiratory symptoms, which occurred after a double blind placebo controlled oral food challenge (DBPCOFC) with the offending food was required. Cow's milk and egg were the most common offending foods. For the diagnosis of asthma, three episodes of wheezing without fever were required. For the diagnosis of rhinitis, a nasal discharge and/or blockage occurring continuously for at least 4 weeks along with the typical pale aspect of an allergic mucosa on rhinoscopy, without any sign of infective rhinitis in other relatives, was required.

The prevalence of soy sensitization in the two groups of children was evaluated by a skin prick test

(SPT) and DBPCOFC. SPT was done by the prick method on the volar surface of the forearm. Standardized soy glycerinized extract (1:20 wt/vol) was used (Lofarma Laboratories, Milan, Italy). Histamine 1mg/ml and glycerinated saline solution were performed as positive and negative control. SPT was considered positive when the wheal was at least 3 mm greater than the negative control. In the children with positive SPT to soy, DBPCOFC was performed as follows: a drop of the SPF ready to feed (Isomil, Abbott) or placebo was put upon the inner border of the lower lip, and a further 5 ml were given after 5 minutes. If no symptoms, 100 ml were given after 30 minutes. After the last administration, the children were kept under observation for at least 4 h and then discharged. Orange juice was used as placebo. The children were seen 7 days following the DBPCOFC to evaluate possible late reactions.

Before the enrolment of the children, four meetings were held in Rome to train the investigators in the diagnostic procedures. In addition, two supervisors (G. Bruno and P. Giampietro) twice visited the Clinics, participating in the study to check the diagnostic procedure.

The following formulae were employed: sensitivity = a/b , specificity = c/d , positive predictive accuracy = a/e , negative predictive accuracy = a/f ; (a = children with positive soy SPT and positive soy DBPCOCT, b = all children with positive soy DBPCOCT, c = healthy children with negative soy SPT, d = all healthy children, e = all children with positive soy SPT, f = all children with negative soy SPT).

Results

With regard to the prevalence of soy allergy in the cohort of children suffering from allergic disease and with history suggestive of FA: 31/505 children (6%) had positive SPT to soy, however only six of these 31 children had positive challenge test to soy. Overall 6/505 (1%) children had documented soy allergy and all of them had AD. These six children with positive challenge test to soy experienced the following symptoms at the DBPCOFC: urticaria 4/6 children; vomiting 2/6 children. The clinical relevance of the prick test to soy according to the challenge test is shown in Table 1: the positive predictive value was rather poor in both groups of children, 0.2 and 0.07 respectively.

With regard to the prevalence of soy allergy in the children who had been SPF fed in the first six months of life (second group): 14/243 children (6%) had positive SPT to soy, but the DBPCOFC to soy was positive only in one of these 14 children. Overall of these 243 children, only one year-old boy (0.5%) had documented soy allergy and this patient

Table 1. Clinical relevance of the skin test to soy in relation to the challenge test

	Group A (N° 505)	Group B (N° 243)
Sensitivity	1	1
Specificity	0.95	0.94
Positive predictive value	0.2	0.07
Negative predictive value	1	1

Group A: children with atopic diseases.

Group B: atopic prone children, SPF fed early in life.

experienced urticaria following the DBPCOFC with soy.

Discussion

The results of this study indicate that soy allergy is not common in atopic children suffering from allergic disease suggestive of food allergy, but it is quite rare even in atopic prone children who have been SPF fed in the first six months of life when babies are more susceptible to sensitization by foods. Only 1% of a large cohort of selected children attending a Pediatric Allergic Clinic because they were affected by allergic disorders suggestive of FA had soy allergy. In addition, although the second group of 243 children were genetically predisposed to atopy and have been SPF fed for many months early in life, the prevalence of soy allergy was very low (0.5%). This data is relevant because it is commonly reported that soy is a potent allergen in young babies and therefore SPF should not be given early in life, mainly to atopic prone babies (10–13).

The results here reported are in agreement with our previous data on the safety of SPFe, even when given early in life for feeding babies at high risk of atopic sensitization and with experimental studies which clearly show that soy proteins have poor immunogenicity and allergenicity in comparison to CM proteins and to CM proteins hydrolysates (26–28). Recently, it has been reported that no fatal anaphylactic reaction could be triggered by soy protein in animals sensitized to SPF, whereas anaphylaxis could be triggered with CMP in all animals sensitized to cow's milk (28).

Several studies have been reported in the last decades on the use of SPF for the prevention of atopic disease (29–36), and no case of soy allergy was found in large cohorts of babies soy fed for many months (30–34, 36).

Recently Magnolfi et al. (16), in a large study performed on more than 700 children with atopic disease, found 1% prevalence of soy allergy using DBPCOFC. This data is quite similar to the results of the present study. As other food allergens, soy may cause urticaria, angioedema and anaphylaxis, but the prevalence of these manifestations is un-

known. Anaphylaxis following the ingestion of soy proteins appears to be a rare phenomenon. Johnstone and Roghman (37), in their large experience with SPF in children, confirmed the safety of SPF and the rarity of anaphylactic reactions. To our knowledge, only a few cases of soy anaphylaxis have been reported (38, 39).

Recently, 92 children with CMA not reacting to soy were placed on SF and followed at regular intervals for 1 year to investigate the prevalence of soy allergy. No infant developed soy allergy during the 1 year follow-up on soy formula (40). This study provides further data on the tolerability of SPF in children with CMA and confirms the results of our own study performed on a highly selected population of children with CMA (25).

The results of the present study outline that the diagnosis of soy allergy should always be confirmed with the DBPCOFC. In fact the clinical relevance of positive skin test to soy is rather poor, if not completely unreliable. SPT to soy was positive in 6% both in the 505 children affected by allergic diseases and in the 243 atopic prone children who had been SPF fed, however DBPCOFC was positive only in 1% and 0.5% respectively. We did not perform the challenge test in the children with negative SPT to soy, because it is well established that SPT to foods have a pretty good negative predictive value (16, 41, 42). However, we can't rule out the possibility that a child with negative SPT would have reactions to soy. Nonetheless, these children were daily eating soy protein containing foods, without reactions.

Furthermore, caution should be taken in the evaluation of IgE antibodies to soy. High level of IgE antibodies to soy has been shown in atopic patients with both positive skin prick test and DBPCOFC (43). However, the clinical relevance of such antibodies is not always clear. In a series of 317 children with FA, Giampietro et al. found 69 cases with high levels of IgE antibodies to soy, but only five of them had positive challenge test to soy (15).

In conclusion, this study shows that soy allergy is not common in children with atopic disorders and soy allergy occurs rarely even in children who have been SPF fed early in life. Due to safety, low cost, adequate nutritional value and pleasant taste, SPFe should be considered the first alternative to a CM based formula, in children with CMA.

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