

## Evaluation of allergy to soy in patients with atopic dermatitis older than 14 years of age

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Atopic dermatitis is associated with food allergies. The aim of this study is to evaluate soy allergy in patients suffering from atopic dermatitis. Altogether 228 persons were included; specific IgE, skin prick tests, atopy patch tests, challenge tests with soy and history of soy allergy were evaluated. Soy allergy was confirmed in eight patients (3.5%, in four patients with worsening of atopic dermatitis, in four patients with oral allergy syndrome), sensitisation to soy was found in another 47 patients (20%) with no clinical manifestation after soy ingestion. Dependence was confirmed statistically between soy allergy and pollen allergy and soy sensitivity and pollen allergy. About 20% of patients suffering from atopic dermatitis are sensitised to soy. Clinical symptoms of soy allergy occur only in 3.5% of patients suffering from atopic dermatitis.

**Keywords:** soy allergy; specific IgE; skin prick tests; atopic dermatitis; pollen allergy

### Introduction

Allergenicity of soybean proteins has been documented since 1980s and allergy to soy has been described primarily in young children with atopic dermatitis (Niggeman, Sielaff, Beyer, Binder, & Wahn, 1999; Sampson & Scanlon, 1989; Sicherer, Sampson, & Burks, 2000) affecting approximately 0.4% of children (Savage, Kaeding, Matsui, & Wood, 2010).

The main symptoms triggered by soy ingestion are in general gastrointestinal (vomiting, diarrhoea, bloody stool and abdominal pain), skin related (urticaria, angioedema, noneczematous rash and atopic dermatitis), lower respiratory tract (wheezing, coughing and difficulty breathing) and upper respiratory tract (rhinitis and nasal congestion). Soy has not been shown to be a common cause of severe or fatal reactions until a recent report of severe food-allergic reactions in Sweden collected by Foucard and Malmheden Yman (1999). Most patients with soy allergy are likely to develop soy tolerance by late childhood (Savage et al., 2010). Epidemiologic data on soybean allergy in adults are rare (Besler, Helm, & Ogawa, 2000; Sicherer, Sampson et al., 2000) and just a few papers on clinical aspects of soy allergy have been published within the recent years.

Routine diagnostic work-up of suspected allergy to food in subjects with atopic dermatitis includes *in vivo* or *in vitro* detection of specific IgE (sIgE) by means of skin

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prick tests (SPTs) or serologic assays (Rancé, Abbal, & Lauwers-Cancès, 2002; Sampson & Ho, 1997; Sporik, Hill, & Hosking, 2000). However, the results of SPTs as predictors of allergen-mediated skin reactions are frequently disappointing since their correlation to the appearance of delayed eczematous reactions may be poor. A correct diagnosis of food allergy is based on the response to the elimination of the food from the diet, followed by the appearance of clinical symptoms after clinical exposure performed by a controlled food challenge (Bindslev-Jensen, 2001; Sampson, 2001). On the other hand, according to Sicherer (2002), when an individual has experienced an acute allergic reaction with typical symptoms, other potential triggers are excluded and there is evidence of sIgE antibody (skin prick test or specific serum IgE level), then the diagnosis is essentially secured and further testing (such as an oral food challenge) is warranted. Recently, atopy patch tests (APTs) with food allergens have been introduced as a procedure enabling the identification of atopic dermatitis patients reacting with eczematous lesions to the administration of the offending food (Roehr et al., 2001).

Many epidemiological investigations have suggested that food allergy is a risk factor for the appearance of other allergic disease in later childhood (Al-Hammadi et al., 2011; Hill et al., 2008; Novembre et al., 2001; Östblom, Lilja, Pershagen, Hage, & Wickman, 2008; Punekar & Sheikh, 2009; Wuthrich & Schmid-Grendelmeier, 2002). According to their results, atopic dermatitis associated with food allergy accelerates the subsequent progression of allergic march (asthma bronchiale and rhinitis).

### **The aim**

The aim of this study is to evaluate the occurrence and symptoms of soy allergy in patients suffering from atopic dermatitis. Analysis of results according to the age, the gender, the occurrence of other signs of atopy such as rhinitis, asthma bronchiale, pollen allergy, the onset of atopic dermatitis and the occurrence of atopic diseases in their family history.

### **Methods**

Patients suffering from atopic dermatitis were examined at the Department of Dermatology and Venereology, University Hospital and Medical Faculty of Charles University, Hradec Králové, Czech Republic from January 2005 to April 2012.

*Inclusion criteria:* age 14 years or over, atopic dermatitis according to the Hanifin and Rajka (1980) criteria.

*Exclusion criteria:* long-term therapy with systemic corticosteroids and cyclosporin, breastfeeding and pregnancy.

### **Examinations**

Complete dermatological and allergological examination was performed in all the included patients with the evaluation of the occurrence of asthma bronchiale and pollen allergy at allergological outpatient department.

*Personal history:* The onset and the course of atopic dermatitis were recorded in all the patients (the onset under five years of age or later, the occurrence of atopic diseases in

patient's family). Patients were asked about all kinds of allergy and the detailed personal history of possible food allergy was taken in all the included patients.

### **Skin prick tests, specific IgE and atopy patch tests**

After the discontinuation of antihistamines and topical steroids for at least five days and systemic steroid therapy and phototherapy at least two months, the SPT and the APT were performed. The serum level of the sIgE has been examined. The patients were allowed to treat themselves with a low-potency topical corticosteroid. No other anti-inflammatory substances nor UV therapy were applied.

#### ***Skin prick test***

Commercial food extracts with soy allergens Alyostal (Stallergens, France) were used for SPTs.

SPTs were placed on the volar side of the forearm according to the extent of atopic dermatitis. SPTs were carried out by a standardised method using lancets with a 1 mm tip. The results were read after 15 minutes and were assessed by comparison with the wheal induced by histamine (10 mg/ml) and negative control. A wheal with a diameter greater than 3 mm in comparison with a negative control was scored as a positive result.

#### ***Specific IgE***

The level of sIgE to soy allergens has been measured with the method of CAP (system fluorescent enzyme immuno assay [FEIA] – Pharmacia Diagnostics, Uppsala, Sweden). The level of sIgE higher than 0.35 U/ml was assessed as positive.

#### ***Atopy patch tests***

APTs were performed on non-lesional, non-abraded and untreated skin of the back during a remission.

The technique similar to conventional patch tests has been used in performing atopy patch testing – CURATEST F strip (Lohmann & Rauscher International GmbH & Co.KG D-56579, Rengsdorf, Germany) with 12 mm cup size. APTs were performed with soy flour. Soy powder was dissolved in distilled water (1 g/10 ml). The occlusion time of APTs was 48 hours, the first results were evaluated 30 minutes after the removal of the tests and the second results were analysed 72 hours after the application of the tests. Grading of positive APT's reactions was similar to the criteria used in conventional contact allergy patch testing with the modifications of the European task Force on Atopic Dermatitis (EFTAD) Consensus Meetings (Darsow et al., 2004).

### **The evaluation of pollen allergy**

The occurrence of pollen allergy was determined according to the history about the pollen allergy and according to the sIgE level and to the SPT results for pollen (containing Bet v 1 and Bet v 2 allergens and for pollen containing homologous allergens). Commercial extracts Alyostal (Stallergens, France) was used for SPT. The level of sIgE has been measured with the method of CAP (system FEIA – Pharmacia Diagnostics, Uppsala, Sweden). The level of sIgE higher than 0.35 U/ml was assessed as positive. Allergy to

pollen was defined as having a clear history of allergic reaction to pollen with the positive results in SPT or sIgE to pollen containing Bet v 1 and Bet v 2 allergens.

### **Open exposure test**

The open exposure test (OET) with soy flakes was recommended to perform in some patients suffering from severe form of atopic dermatitis with the positive results in sIgE or SPT or APT to soy under medical supervision. In patients with mild and moderate form of atopic dermatitis it was recommended to perform the OET with the common ingestion of soy in a form of some concentrated soy products in a home setting. The patients with severe allergic reaction to some food in their history were excluded from this testing.

The elimination diet was introduced following the patient's informed consent before the OET. We recommended to eliminate soy and soy products; vegetable and fruits were allowed only after thermal modification, but parsley, celery and seasoning were not allowed. The OET was performed in the period with milder symptoms of atopic dermatitis out of pollen season.

In OET the dose of 100 g of soy flakes was given. This dose was divided into incremental doses given during 60 minutes. The first day the patient consumed the dose at 8:00 am, the reaction was observed and, in the case of no response, the second dose of food was consumed at 6:00 pm. If no response resulted, the last dose challenge was administered the next day at 8:00 am. The reaction after the last dose was observed and the severity of atopic dermatitis was evaluated during next 48 hours. The skin was scored by the Scoring Index of Atopic Dermatitis system; affected skin area, intensity criteria and subjective parameters are evaluated by this system) before OET and then 24 and 48 hours after OET.

### **Statistical analysis**

To evaluate, if there is some dependence between atopic dermatitis patients suffering from soy allergy (or sensitisation) and the occurrence of asthma bronchiale, rhinitis, pollen allergy, family history, onset of atopic dermatitis and to the gender. Pairs of these categories were entered in contingency tables and the chi-square test for independence of these variables was performed with the level of significance set to 5%.

To evaluate if there is some association in atopic dermatitis patients suffering from soy allergy (or soy sensitisation) to age we used the unpaired *t*-test to check the dependence or independence of the age of patients on soy allergy and sensitivity. The results were processed at the Department of Medical Biophysics of Medical Faculty of Charles University in Hradec Králové.

### **Results**

Altogether 228 persons suffering from atopic dermatitis were included in the study: 70 men, 158 women entered the study with the average age of 26.4 (s.d. 9.1 years, min.14 max. 63 years) at the beginning of the study. The patients' characteristics are demonstrated in [Table 1](#).

#### ***Reactions in 228 patients***

In personal history about soy allergy, positive results were recorded (oral allergy syndrome, OAS) in four patients. Positive reactions to soy were recorded in 46 patients in

SPT, sIgE to soy was positive in 13 patients and APT with soy were evaluated with positive reaction in 14 patients – altogether the positive results were recorded in 55 patients out of 228 in SPT and/or sIgE and/or APT. The OET was recommended according to these results to perform in 51 patients without personal history of soy allergy; the positive results in OET were recorded in four patients (three patients – worsening of atopic dermatitis, one patient – early allergic reaction as maculopapulous rash and worsening of atopic dermatitis).

Soy allergy was confirmed in eight patients (four patients with positive results in personal history and in SPT and/or sIgE and/or APT, another four patients with positive results in the OET and in SPT and/or sIgE and/or APT).

Sensitisation to soy without clinical symptoms of food allergy was recorded according to the positive results in SPT and/or sIgE and/or APT in 47 patients (20%).

The characteristics of these eight patients with soy allergy are recorded in Table 2.

The level of sIgE to soy from 0.52 to 1.54 U/ml was recorded in patients with confirmed soy allergy; the level from 0.39 to 1.4 U/ml was recorded in patients with sensitisation to soy.

No positive results to soy (personal history, sIgE, SPT and APT) were recorded in 173 patients (76%).

We used the unpaired *t*-test to check the dependence or independence of the age of patients on soy allergy and sensitivity. It turned out that the dependence was found only in the case of age and sensitivity. The mean age of soy sensitive patients was 23.5 years while the age of non-sensitive patients was 27.4 years.

We used the contingency table to verify that there was a dependence between soy allergy and pollen allergy (*p* value = 0.00047) and that there was dependence between soy sensitivity and pollen allergy (*p* value = 0.00001).

Table 1. Examined patients – characteristics.

| Patient older 14 years of age suffering from atopic dermatitis – characteristics           |                                                   |
|--------------------------------------------------------------------------------------------|---------------------------------------------------|
| Total no. of patients                                                                      | 228                                               |
| Average age                                                                                | 26.4 s.d. 9.1 years, min age 14, max age 63 years |
| Sex, no.                                                                                   |                                                   |
| Male                                                                                       | 70                                                |
| Female                                                                                     | 158                                               |
| <i>Positive results to soy in sIgE and/or SPT and/or APT (number of patients) 55 (24%)</i> |                                                   |
| Specific IgE                                                                               | 13 (5.7%)                                         |
| Skin prick tests                                                                           | 46 (20%)                                          |
| Atopy patch tests                                                                          | 14 (6%)                                           |
| <i>Number of patients with confirmed soy allergy: 8 (3.5%)</i>                             |                                                   |
| Clear history of allergic reaction (OAS)                                                   | 4 (1.75%)                                         |
| Confirmed allergy to soy in OET (number of patients) (worsening of atopic dermatitis)      | 4 (1.75%)                                         |
| <i>Other atopic conditions (number of patients)</i>                                        |                                                   |
| Asthma bronchiale                                                                          | 84 (37%)                                          |
| Rhinitis                                                                                   | 166 (73%)                                         |
| Pollen allergy                                                                             | 72 (31%)                                          |
| Positive result in family history about atopy                                              | 128 (56%)                                         |
| Onset of atopic dermatitis under 5 years of age                                            | 176 (77%)                                         |

Table 2. Characteristics of eight patients with soy allergy.

| Patient, sex, age | IgE total IU/ml | Personal history to soy | sIgE U/ml to soy | SPT soy | APT soy | Pollen allergy | Allergy to soy – skin symptoms                               | Allergy to other foods or food intolerance | Sensitisation to other foods |
|-------------------|-----------------|-------------------------|------------------|---------|---------|----------------|--------------------------------------------------------------|--------------------------------------------|------------------------------|
| W, 17             | 7733            | –                       | –                | +       | +       | +              | Maculopapulous rash, pruritus worsening of atopic dermatitis | Wheat                                      | Celery                       |
| W, 22             | 552             | OAS                     | –                | +       | –       | +              | –                                                            | Apple, plums                               | Carp, celery, egg            |
| M, 25             | 475             | OAS                     | 1.54             | +       | +       | +              | –                                                            | Peanuts, apple, almonds                    | Celery, rice                 |
| W, 42             | 751             | OAS                     | 0.52             | +       | –       | +              | –                                                            | Egg, wheat                                 | Celery, nuts                 |
| W, 19             | 259             | OAS                     | –                | +       | +       | +              | –                                                            | Egg                                        | Celery, wheat, sea fish      |
| M, 21             | 181             | –                       | –                | –       | ++      | +              | Worsening of atopic dermatitis                               | –                                          |                              |
| W, 56             | 100             | –                       | –                | –       | ++      | +              | Worsening of atopic dermatitis                               | Nuts, apple, wheat                         |                              |
| W, 35             | 11,924          | –                       | 1.3              | +       | –       | +              | Worsening of atopic dermatitis                               | Peanuts, poppy seed, wheat, fish, chicken  |                              |

Mm, man; W, woman; OAS, oral allergy syndrome; OET, open exposure test; SPT, skin prick tests; APT, atopy patch tests; +, positive results; – negative results.

We used the contingency table to verify that there was no dependence between soy allergy, gender, asthma bronchiale, rhinitis, family history and the onset of atopic dermatitis. Also, there was no dependence between soy sensitivity versus gender, asthma bronchiale, rhinitis, duration of eczematic lesions and family history. But we found significant dependence ( $p$  value = 0.011) between sensitivity and the onset of atopic dermatitis under five years of age. Sensitivity to soy is higher (89.4%) in patients with the onset of atopic dermatitis under five years of age but it was lower (71.5%) for those with later onset of atopic dermatitis.

## Discussion

### *Soy allergy and atopic dermatitis*

Atopic dermatitis is a chronic intermittent inflammatory skin disease that may be in some cases associated with food allergies. Soy allergy is one of the most common food allergies in childhood, yet few data are available regarding its natural history (Savage et al., 2010). It is generally suggested that soy allergy is outgrown in the preschool years, although no large studies have focused on this question (Savage et al., 2010). Epidemiologic data on soybean allergy in adults are rare and just a few papers on clinical aspects of soy allergy have been published within the recent years (Besler et al., 2000; Sicherer, Sampson et al., 2000).

Soy consumption has increased in Europe during the past years and, in the food industry, large quantities of soya bean protein products are used for the formulation of end-products destined for human consumption (Hessing, Bleeke, Tsuji, Ogawa, & Vlooswijk, 1996). In Central Europe, soy is a clinically relevant birch pollen-related allergenic food as well. Cross-reaction is mediated by a Bet v 1 homologous protein, Gly m 4. Additionally, birch pollen allergic patients might acquire through Bet v 1 sensitisation allergies to mungbean or peanut, in which Vig r 1 and Ara h 8 are the main cross-reactive allergens (Balmer-Weber & Vieths, 2008). Despite the considerable amount of IgE reactive soy proteins described so far, just a few allergens have been thoroughly characterised and there is still a considerable lack of knowledge (Gonzalez, Polo, Zapatero, Caravaca, & Carreira, 1992; Mittag et al., 2004).

### *Soy allergy, soy sensitivity, dependence on gender, the occurrence of asthma bronchiale, rhinitis, family history and the onset of atopic dermatitis*

The diagnosis of soy allergy was made in eight patients from 228 (3.5%), in another 47 patients (20%) positive results in SPT and/or APT and/or in sIgE were recorded; these patients are sensitised to soy without clinical symptoms after soy ingestion. We found significant dependence between sensitivity to soy and the onset of atopic dermatitis under five years of age. It means that patients with the onset of atopic dermatitis under five years of age suffer more often from sensitisation to soy in comparison with patients with later onset of this disease. We confirmed that there is no dependence between the occurrence of soy allergy with respect to the gender, the occurrence of asthma bronchiale, rhinitis, family history and the onset of atopic dermatitis under five years of age. Also, there was no dependence between sensitivity to soy versus gender, asthma bronchiale, rhinitis, duration of eczematic lesions and family history. According to some studies, early onset of atopic dermatitis was found to be associated with high-risk IgE levels in food sensitisation (Al-Hammadi, Zoubeidi, & Al-Maskari, 2011; Hill et al., 2008; Novembre et al., 2001; Östblom et al., 2008; Puneekar & Sheikh, 2009; Wuthrich &

Schmid-Grendelmeier, 2002). According to their results, atopic dermatitis associated with food allergy accelerates the subsequent progression of allergic march (asthma bronchiale, rhinitis). In comparison with other studies, early onset of atopic dermatitis or female gender increased the likelihood that allergic disease would improve (Kijima et al., 2013). Kijima's results also suggest that a certain genetic background influences the onset and comorbidity of allergic diseases. In our study, we did not confirm any dependence between patients suffering from soy allergy or soy sensitisation to the occurrence of atopic disease in family. The explanation for our different results may be the fact that in our study we evaluated only allergy to soy and not to other kind of food allergies.

#### ***Soy allergy and soy sensitivity and the dependence to the age***

It turned out that the dependence was found in the case of sensitivity to soy and age. The mean age of sensitive patients was 23.5 years while the age of non-sensitive patients was 27.4 years. It may be connected with the rising occurrence of pollen allergy and rising occurrence of cross-reactivity in recent years. In Central Europe, soy is a clinically relevant birch pollen-related allergenic food. Studies from diverse industrialised regions of the world reveal an increasing prevalence of all clinical manifestations of allergic diseases, prevalence of these diseases has increased two to three times during the past three decades in industrialised countries (Larsen & Hanifin, 2002).

#### ***Soy allergy and dependence to the pollen allergy***

The dependence between soy allergy and pollen allergy was confirmed in our study. Four patients from 228 (1.75%), in addition to positive results in sIgE, SPT or APT, had a clear history after soy ingestion (OAS) since childhood. The OAS is defined as the symptoms of IgE-mediated immediate allergy localised in the oral mucosa. Another term used for this syndrome is pollen-food allergy; the patient is sensitised with pollen via the airways and exhibits an allergic reaction to food antigen with a structural similarity to pollen (class 2 food allergy) (Breiteneder & Ebner, 2000).

#### ***Soy allergy with the symptoms of late skin reaction***

The positive results in OETs after soy ingestion with the symptoms of late reaction as worsening of atopic dermatitis were recorded in another four patients (1.75%), in one of them the maculopapulous rash was also recorded as an early reaction. These patients did not know about their possible reaction to soy. We recommended the elimination of soy and soy products and we evaluated the severity of atopic dermatitis every three months during 1–3 years. These patients eliminated soy from their meal and during the breaking of the diet regimen they could observe the reactions on the skin, such as the pruritus and new eczematic lesions. But atopic dermatitis improved for a longer period of time only in two patients (patient no. 1 with early and late skin reaction and patient no. 6). Other two patients suffered from moderate form of atopic dermatitis with exacerbations of atopic dermatitis as the consequence of other triggering factors, such as stress, inhalant allergens.

#### ***Sensitisation to soy***

The positive results to soy in diagnostic methods (SPT, sIgE and APT) were recorded in 47 patients (20%) without clinical symptoms after soy ingestion, but the dependence

between soy sensitive patients and pollen allergy was confirmed. These patients also described the early reactions after ingestion of different kinds of fruits, vegetables, spices and nuts. The basis of these associations lies in the existence of IgE antibodies against ‘panallergens’ which determines cross-reactivity. The three best-known groups are allergens homologous to Bet v 1, profilins, and lipid transfer proteins. Measurement of allergen concentration in foods is helpful to estimate their allergenicity. The sandwich enzyme-linked immunosorbent assay for the evaluation of profilin concentration in fruits was designed (Abedini et al., 2011). Mal d 1, the major apple allergen shows strong cross-reactivity with IgE specific for the major birch pollen allergen, Bet v 1, and is responsible for birch pollen-related food allergy to apple (Dae et al., 2001).

### **Meaning of the study**

The main strength of this study lies in the evaluation of soy allergy in large group of patients suffering from atopic dermatitis. The diagnostic procedures indicated to confirm the diagnosis of food allergy, in particular late-type reactions, remain time-consuming because food challenges need to be performed. Studies frequently focus on the assessment of sensitisation via IgE to food allergens rather than on the results of oral food challenges, which are still recommended as the diagnostic golden standard. In our study, we confirmed that one-fifth (20%) of patients suffering from atopic dermatitis with positive results in diagnostic method (SPT, APT and sIgE) are sensitised to soy without clinical symptoms of food allergy; we also confirmed that there is a dependence between soy allergy and pollen allergy and soy sensitivity and pollen allergy; it also turned out that there is a dependence between soy sensitivity and age and soy sensitivity and onset of atopic dermatitis.

### **Conclusion**

About 20% of patients suffering from atopic dermatitis are sensitised to soy without clinical reactions after soy ingestion. Soy allergy may play an important role in the worsening of atopic dermatitis acting as a triggering – exacerbating factor only in a minority of these patients. The diagnostic work-up may comprise the challenge tests to confirm the food allergy to soy.

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