

ORIGINAL ARTICLE

Secondary soy allergy in children with birch pollen allergy may cause both chronic and acute symptoms

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Abstract

Background: Secondary soy allergy occurring in tree pollen allergic patients may cause acute symptoms.

Methods: We selected children with birch pollen allergy suspected of also being soy allergic (SA). Soy allergy was proven based on one of the following: (i) a clear-cut clinical history; (ii) a positive provocation test; and (iii) elimination and reintroduction of soy. Skin prick tests (SPT) were performed with a commercial soy extract and with soy flour. Specific IgE to Gly m 4, Gly m 5, and Gly m 6 was determined by means of ImmunoCAP and ISAC. Eight soy-tolerant atopic children being CAP rGly m 4-negative served as a control group for skin testing.

Results: Of 15 subjects with birch pollen allergy and being suspected of soy allergy, eight of them proved to be SA; 7/15 subjects proved to be soy tolerant (ST). Besides acute symptoms in 8/8 SA subjects, 3/8 subjects also had been suffering from severe chronic complaints because of soy allergy. SPT with commercial soy extract was negative in all SA and ST subjects tested. SPT with soy flour was positive in 8/8 SA and in 5/6 ST subjects, but negative in all 8 controls ($p < 0.0001$); the median weal diameter was 7.7 mm in SA subjects, compared to 3 mm in ST subjects ($p < 0.01$). The median IgE level to rGly m 4 using CAP and ISAC was, respectively, 32.4 kU/l and 4.0 ISU in SA subjects, compared to 6.2 kU/l and 0.4 ISU in ST subjects ($p < 0.05$). Analysis of IgE to nGly m 5 and nGly m 6, using CAP or ISAC, showed no significant differences between SA and ST subjects.

Conclusions: Secondary soy allergy may cause severe chronic besides acute symptoms. SPT with soy flour is a sensitive and specific tool in detecting soy sensitization. SPT with soy flour, CAP rGly m 4, and ISAC rGLY m 4 are valuable tools in the diagnosis of birch-pollen-associated secondary soy allergy.

Secondary soy allergy may develop in patients with birch pollen allergy as a consequence of cross-reactivity between soy and birch pollen (1). Gly m 4, a soy protein belonging to the PR-10 protein family, has been shown to be the major soy allergen for birch pollen allergic patients with soy allergy (2). The symptoms experienced by those patients when ingesting a soy-containing product are typically acute and may vary from mild to severe (1–3). Differences in the severity of symptoms can partly be explained by differences in Gly m 4 content of soy products, which may depend on food processing (2). The degree of cross-reactivity with Gly m 4 in highly Bet v 1-sensi-

tized patients has been found to be 70%. About 10% of those Gly m 4-sensitized patients report clinical soy allergy. Skin prick tests (SPT) with a commercial extract and with soy flour were found positive in the majority of patients with soy allergy tested (2, 3). However, a comparison with soy sensitized patients without clinical allergy has not been made.

In a study on soy allergic (SA) patients either with or without Bet v 1-sensitization, it was recently shown that IgE-reactivity to the soy storage proteins Gly m 5 and Gly m 6 was more frequently seen in subjects with severe or moderate soy-related symptoms than in subjects with mild symptoms (4).

In children, soy allergy is mainly known as a primary food allergy occurring at young age, and the condition often is outgrown during childhood (5, 6). Secondary soy allergy in relation to birch pollen allergy has been described mainly in adults (1, 2). However, a few cases have been reported in children (3, 7).

It was the purpose of this study to describe the clinical presentation of soy allergy in children with birch pollen allergy and to evaluate the results of SPT and of sIgE to Gly m 4, Gly m 5, and Gly m 6 in birch pollen allergic children with soy allergy, compared to birch pollen allergic children with soy sensitization only.

Materials and methods

Patients

At the out-patient allergy clinic of our pediatric department, we selected subjects with birch pollen allergy who were suspected of also being SA. Birch pollen allergy had been diagnosed based on typical allergic symptoms during the birch pollen season in combination with a positive IgE response to birch or rBet v 1. The age at first presentation of symptoms related to birch pollen allergy was noted. Soy allergy was suspected based on clinical history. It was considered proven in case of (i) a clear-cut clinical history of an acute reaction to soy; (ii) a positive soy provocation test; (iii) elimination and reintroduction of soy, respectively, resulting in disappearance and (re)appearance of allergic symptoms. Soy provocation was performed in subjects with acute symptoms suspected of being related to soy. Elimination and reintroduction of soy were carried out in subjects with chronic symptoms suspected of being caused by soy. Other documented respiratory or food allergies were registered. We especially recorded signs and symptoms of oral allergy syndrome (OAS).

Soy provocation

The subjects were on a soy-free diet for at least 8 wk at the time of challenge. We performed an open challenge with Alpro soya natural drink® (Alpro, Wevelgem, Belgium). It was started with the application of one drop of soy drink at the inner side of the lower lip. If no reaction occurred within 15 min, increasing doses of 1, 2, 5, 10, 20, 40, 80 ml soy drink were given at 20-min intervals, until appearance of objective allergic symptoms or until reaching the total dose of 158 ml. The children were kept under control for 2 h after the challenge. If no symptoms occurred within that time interval, the parents were asked to give the child a daily volume of 120 ml soy drink in the next 2 wk, while continuing their diet otherwise unchanged. Re-evaluation was provided after 2 wk or earlier in case of complaints (8–10).

Elimination and reintroduction of soy

Elimination of soy from the diet for at least 8 wk, followed by its reintroduction, was performed out of the pollen season, without any other change in the diet or in the thera-

peutic approach. For the reintroduction of soy, we proposed Alpro soya natural drink® (Alpro) or a soy-containing pasta (Lotus Speculoospasta®; Lotus Bakeries, Lembeke, Belgium), depending on the former consumption habits of the subject. The content of soy flour in the soy drink and in the pasta is 6.4 g/100 ml and 4.5 g/100 g, respectively. The other ingredients of the soy drink and of the pasta were known to be well tolerated by the subjects. Reintroduction of soy was carried out at home by means of daily increasing doses of soy drink or pasta until appearance of symptoms or until the formerly ingested amount was reached. This amount was then to be maintained for at least 2 wk. The amounts taken were recorded. The subjects were scheduled for a control visit at the end of this period or earlier in case of complaints.

Skin prick tests

SPT were performed by means of a microlance (HAL prick-lancet, The Netherlands) with a commercial extract of soy (HAL, The Netherlands) and with a 1/10 w/v dilution of soy flour (Sojameel, Biofresh, Genk, Belgium). Histamine diphosphate (1 mg/ml) and Coca solution in 50% glycerol were used as positive and negative control, respectively. Results were evaluated according to the recommendations of the European Academy of Allergy and Clinical Immunology (11). In summary, weal reactions were recorded after 15 min; orthogonal diameters were measured and mean diameters were calculated. An SPT response was considered positive when the mean weal diameter was 3 mm or more, after subtraction of the weal produced by the negative control. To exclude non-specific positive SPT results, a control group of 8 atopic but soy-tolerant children being CAP rGly m 4-negative was included.

Determination of total and specific IGE

Total IgE and specific IgE to soy, rGly m 4, and rBet v 1 using the ImmunoCAP® FEIA system (Phadia AB, Uppsala, Sweden) were determined according to the manufacturer's instructions. Prototype ImmunoCAP tests with purified native Gly m 5 and Gly m 6 were developed by conjugation of the allergens to CNBr-activated ImmunoCAP matrix according to the standard method of Phadia AB, as described elsewhere (12). Both commercial and experimental ImmunoCAP responses were considered positive if IgE values were 0.10 kU/l or greater.

IgE levels to rGly m 4, nGly m 5, nGly m 6, and rBet v 1 were also determined by using the ImmunoCAP® ISAC microarray (Phadia AB). Samples were analyzed according to the manufacturer's recommendations. Therefore, we used the reagents of the 'Assay Kit IgE' using a fluorescence-conjugated anti-human IgE (mouse monoclonal antibody) (13). Results were expressed as ISAC standard units and considered positive if ≥ 0.3 ISU. Measurement of sIgE using the ImmunoCAP system will from here on be referred to as 'CAP' and analysis of sIgE using ImmunoCAP ISAC will be referred to as 'ISAC'.

Statistics

Results were analyzed by means of Fisher exact, Mann-Whitney U or Spearman rank test. For calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and efficiency of SPT, CAP rGly m 4, and ISAC rGly m 4, we took percentile 25 of the respective values in the SA group as cutoff.

Results

Subjects and symptoms

Fifteen subjects (nine boys and six girls) entered the study. The mean age of the study population was 10.2 yr (range 4.7–16 yr). Age, duration of tree pollen allergy, and presenting symptoms at enrollment are depicted in Table 1. Eight of fifteen subjects were shown to be SA. Those eight subjects will be further referred to as SA, whereas the soy tolerant (ST) subjects will be referred to as ST. Table 1 summarizes the way of diagnosis of soy allergy, the symptoms subsiding on elimination or elicited by provocation/reintroduction of soy, as well as the eliciting soy dose. All eight SA subjects showed acute objective symptoms at the acute event or on provocation/reintroduction of soy. Four of them experienced anaphylaxis. Two of eight SA subjects also experienced subjective symptoms of OAS. Three of eight SA subjects (subject C, F, and G) had been suffering from chronic severe generalized itching lasting for 12–20 months. Of those three subjects, two also had experienced some episodes of urticaria; the third subject also had been suffering from chronic diarrhea and generalized atopic dermatitis. The generalized itching in those three subjects only could be controlled by the daily intake of high-dose antihistamines all year round. Those chronic complaints subsided completely in subject C and G on the sole withdrawal of soy from the diet, while in subject F only minor eczematous lesions in the knee folds persisted. Furthermore, after elimination of soy from the diet, antihistamines could be stopped out of the pollen season in all three subjects. Noteworthy, before the start of the soy-elimination diet, all three subjects had been consuming soy products daily: it concerned daily ingestion of soy drink in subject F and of a soy-containing pasta in subject C and G. In all eight SA subjects, the soy-related symptoms occurred and/or persisted out of the birch pollen season. The age at investigation, the duration of tree pollen allergy at the time of investigation, and the frequency of OAS were not significantly different in the SA group compared to the ST group (Table 2).

Skin prick tests

SPT results in SA and ST subjects are shown in Table 3. SPT with soy flour was positive in 8/8 SA and in 5/6 ST subjects, while it was negative in all controls (SA + ST compared to controls: Fisher's exact test $p < 0.0001$). The median weal diameter of SPT with soy flour was significantly larger in SA subjects compared with ST subjects (Table 2). The diagnostic

capacity of SPT with soy flour at cutoff 7 mm is shown in Table 4.

Total and specific IgE

Table 3 shows the total IgE levels, the IgE responses determined by means of CAP to soy, rGly m 4, nGly m 5, nGly m 6, and rBet v 1 and the IgE responses determined by means of ISAC to rGly m 4, nGly m 5, and nGly m 6. The median value and the interquartile ranges of IgE responses to soy and rGly m 4 in the SA group compared with the ST group are given in Table 2. The ratio CAP rGly m 4 to total IgE could be calculated in 8/8 SA and in 5/7 ST subjects; range, median value, and interquartile range of this ratio in both groups are shown in Table 2. A significant correlation between IgE responses to rGly m 4 using CAP and ISAC was found (Spearman rank: $p < 0.05$). There was no correlation between CAP soy and CAP rGly m 4. The diagnostic capacity of CAP rGly m 4 at cutoff 17.6 kU/l and of ISAC rGly m 4 at cutoff 1 ISU is shown in Table 4.

CAP nGly m 5 and nGly m 6 was positive in 2/8 SA subjects and in 2/6 ST subjects (ns). IgE responses to nGly m 5 or nGly m 6 using ISAC were found in 4/7 and 2/7 SA subjects, respectively, compared to 1/5 ST subjects (ns).

CAP rBet v 1 was positive in 7/7 SA and in 5/5 ST subjects (Table 3). The two subjects in whom CAP rBet v 1 was not determined were birch-CAP positive, with values of > 100 kU/l (subject C) and 5.47 kU/l (subject I).

Discussion

Secondary soy allergy due to cross-reactivity between Bet v 1 and Gly m 4 has been described mainly in adults and it has been reported to cause acute allergic symptoms on soy ingestion (1–4). Here, we report on secondary soy allergy in eight children. Besides acute symptoms to soy occurring in all eight subjects, three of them also had been suffering from moderate to severe chronic symptoms because of secondary soy allergy. Indeed, those three subjects had been bothered with severe generalized itching and with recurrent urticaria or generalized atopic dermatitis and chronic diarrhea, which all subsided on the sole withdrawal of soy from the diet. To our knowledge, this is the first document describing chronic symptoms caused by secondary soy allergy. Noteworthy and somewhat surprising, on reintroduction of soy, all three subjects showed immediate allergic symptoms, with signs of mild to moderate anaphylaxis in two of them. This dual reaction pattern, with chronic and acute manifestations of allergy, might be the expression of different activation pathways: the chronic symptoms may be explained by the activation of low-affinity IgE receptors on eosinophils or by the involvement of activated T cells, whereas the acute symptoms are due to IgE-mediated mast cell activation. A depletion of mast cell mediators, caused by ongoing ingestion of soy, may explain the absence of acute symptoms during the period of daily soy-intake (14, 15).

Unlike another pediatric study, which reported soy-related symptoms occurring during the birch pollen season, the

Table 1 Age, duration of tree pollen allergy, presenting symptoms, way of diagnosis of soy allergy/tolerance, symptoms of soy allergy, and other allergies documented in fifteen subjects with tree pollen allergy

Soy allergy									
Subject	Age of subject/ tree pollen allergy (yr)	Presenting symptoms	Way diagnosis soy allergy/tolerance	Symptoms*					
				Elicited by soy					
				Subsided on soy elimination	On reintroduction	At acute event/provocation	Eliciting soy dose (mg)	Time lapse* (min)	Other documented allergies
A	12.5/6.5	An;As;OAS; RhC	Clear cut history	na	na	An (A; Ab; Dy;RhC;Wh)	nd	2	GP;Fs
B	5/2.5	RhC;OAS	Provocation	na	na	RhC; T _T	3200	100	GP;HDM;Fs
C	13/9	As;Ig;OAS; RhC;U	E/R	Ig; U	An (Ig; RhC; T _T)	na	225	5	GP;fish;Fs
D	7.2/1	An;RhC	Clear cut history	na	na	An (A; Sw)	nd	5	GP
E	8.2/1	OAS;RhC	Clear cut history	na	na	OAS;Ho;Sw	1600	2	Fs
F	4.8/2.5	As;D _{ch} ;E;Ig; OAS;RhC	E/R	Ig; D _{ch} ;E	An (Ig;R; D)	na	1600	20	HDM;GP;K;B;Fs
G	12.9/5	As;Ig;OAS; RhC;U	E/R	Ig; U	I; U	na	225	120	GP;Fs
H	15.6/7	OAS;RhC	Clear cut history	na	na	OAS;Ls	nd	2	HDM;GP;Fs
I	14.5/10	As;E;OAS;RhC	E/R	None	None	na	na	na	CM;HDM;GP;Fs
J	16/7	As;OAS;RhC	E/R	None	None	na	na	na	GP;P;Fs
K	8.4/5	As;RhC;H _{ch}	E/R	None	None	na	na	na	GP;WP
L	4.7/2	As;E;RhC	Provocation	na	na	None	na	na	CM;egg;HDM;GP
M	11.5/1	RhC;U	Provocation	na	na	None	na	na	HDM;GP
N	8.8/6	As;E;OAS;RhC	E/R	None	None	na	na	na	Clad;GP;P;Fs
O	10.1/3.5	As;E;OAS; RhC;U	E/R	None	None	na	na	na	HDM;GP;Fs

*A, angioedema; Ab, abdominal pain; An, anaphylaxis; As, asthma; D, diarrhea; D_{ch}, chronic diarrhea; Dy, dyspnea; E, eczema; H_{ch}, chronic headache; Ho, hoarseness; I, itch; Ig, generalized itch; Ls, lip swelling; OAS, oral allergy syndrome; R, rash; RhC, rhinoconjunctivitis; Sw, swallowing difficulty; T₁, throat tightness; U, urticaria; Wh, wheezing. E/R, elimination/reintroduction.

Allergies documented other than tree pollen and soy allergy: GP, grass pollen; HDM, house dust mite; Fs, fruit, secondary to pollen allergy; K, kiwi (primary); B, banana (primary); CM, cow's milk; P, pets; WP, weed pollen; Clad, cladosporium.

na, not applicable; nd, not done.

*Time lapse between start of ingestion of soy and appearance of symptoms.

Table 2 Age, duration of tree pollen allergy, oral allergy syndrome (OAS), skin prick tests (SPT) with soy flour, CAP soy, CAP rGly m 4 and ISAC rGly m 4 in soy allergic and soy-sensitized but tolerant subjects.

	Soy allergic (SA)	Soy tolerant (ST)	p
Age (yr)			
Range	4.8–15.6	4.7–16	ns*
Median	10.3	10.1	
Duration of tree pollen allergy (yr)			
Range	1–9	1–10	ns*
Median	3.7	3.5	
Number of subjects with OAS	7/8	4/7	ns**
SPT soy flour: mean weal diameter (mm)			
Range	5–11.5	2–5.5	<0.01*
Median [IQR]	7.75 [7–8.75]	3 [3–4.5]	
CAP soy (kU/l)			
Range	<0.10–10.50	<0.10–2.83	ns*
Median [IQR]	0.27 [0.10–3.13]	0.40 [<0.10–2.43]	
CAP rGly m 4 (kU/l)			
Range	2.67–>100	0.30–17.20	<0.01*
Median [IQR]	32.36 [17.6–49.05]	2.26 [1.00–16.70]	
ISAC rGly m 4 (ISU)			
Range	0.9–62.00	<0.3–2.1	<0.05*
Median [IQR]	4.0 [1.0–21.0]	0.4 [<0.3–0.7]	
CAP rGly m 4/total IgE			
Range	0.019–0.187	0.004–0.059	<0.01*
Median [IQR]	0.069 [0.053–0.125]	0.007 [0.007–0.018]	

IQR, interquartile ranges are indicated between square brackets.

*Mann–Whitney *U*.

**Fisher exact.

subjects in our study experienced acute soy-related symptoms out of the birch pollen season, which probably is an indication of a more severe allergic sensitization (7, 16).

This is the first study comparing SPT results in soy allergic and soy-sensitized birch pollen allergic subjects. In contrast with the study of Mittag *et al.* (2), SPT with a soy extract only produced weal reactions in some of our subjects, the weal size being smaller than 3 mm. This difference in SPT positivity might be explained by a different Gly m 4 content in the extracts used for skin testing and possibly relates to different extraction procedures. In comparison, the content of Gly m 4 in soy food products has been shown to depend strongly on the degree of food processing (2). In our study, SPT with soy flour was positive in 8/8 SA subjects and in 6/7 soy-sensitized subjects, while it was negative in 8/8 control children. Therefore, SPT with soy flour at a weal diameter cutoff of 3 mm provides a highly specific and sensitive tool in detecting soy-sensitization in patients with birch

pollen allergy. Moreover, as the median weal diameter of SPT with soy flour was significantly larger in SA subjects than in ST subjects, SPT with soy flour provides a valuable tool in the diagnosis of secondary soy allergy in patients with birch pollen allergy. SPT by means of prick-to-prick was also performed with Alpro soya natural drink® (Alpro) or with soy-containing pasta (Lotus Speculoospasta®; Lotus Bakeries), respectively, in two SA subjects having reacted to the drink and in one SA subject having reacted to the pasta, as well as in two atopic controls. In all three SA subjects, the SPT elicited a reaction with weal size comparable to the weal size elicited by soy flour, whereas it was negative in both atopic controls (data not shown). This suggests that in selected cases, skin testing with a specific soy-containing food may be used to detect its possible implication in allergic symptoms.

IgE-mediated responses to rGly m 4, determined by means of CAP or ISAC, were significantly higher in the SA group compared with the ST group. The ratio CAP rGly m 4 to total IgE being significantly higher in the SA group compared with the ST group further illustrates that both groups differ significantly in specific IgE activity to rGly m 4 and not only in concentration of specific IgE (17, 18).

In our study population, sensitivity and specificity of SPT with soy flour at cutoff 7 mm were, respectively, 75% and 100%, whereas CAP rGly m 4 ≥ 17.6 kU/l and ISAC rGly m 4 ≥ 1 ISU showed a sensitivity of, respectively, 75% and 86% and a specificity of, respectively, 100% and 80% for the diagnosis of birch-pollen-associated secondary soy allergy. However, taking into account the small size of our study cohort, we have to stress that our data on specificity and sensitivity at the given cutoff might not be generally applicable.

In previous studies, it has been shown that among highly Bet v 1-sensitized patients, the majority of them displays sensitization to rGly m 4, with 10% of those patients having clinical soy allergy (2). It therefore is important to discern soy sensitized from patients with soy allergy. This becomes even more important in case of chronic symptoms, in order not to miss the involvement of clinical allergy to soy in those subjects. Therefore, in patients with birch pollen allergy with chronic symptoms, performance of SPT with soy flour and determination of sIgE to rGly m 4 using specific cutoff values might be helpful, to detect those subjects who may benefit from a trial with a soy-free diet.

IgE levels using CAP and using ISAC correlated well for Gly m 4 ($p < 0.05$). Except for the tolerant patient 'N', concordance between the two techniques was good. The discrepancies could perhaps be explained by the difference in the presentation of the allergens. Indeed, allergens, fixed to the matrix of the CAP® or coated to the glass slides of ISAC, possibly do not always show the epitope in the same manner and microchip-based methods as ISAC have limited surface and far less antigen-antibody capacity, hampering a good recognition by IgE antibodies. Lack of correlation between IgE responses to CAP soy and CAP rGly m 4 can be explained by a low Gly m 4 content on the soy ImmunoCAP (3).

It has been suggested that sensitization to Gly m 5 or Gly m 6 is indicative of severe allergic reactions to soy (4).

Table 3 Results of skin prick tests with soy extract and soy flour, total IgE, IgE responses by ImmunoCAP to soy, rGly m 4, nGly m 5, nGly m 6 and Bet v 1, and of IgE responses by ISAC to rGly m 4, nGly m 5, nGly m 6 in soy allergic (SA) and soy tolerant (ST) subjects

Subjects	Skin prick tests (mm)		Total IgE	CAP					ISAC (ISU)		
	Soy			kU/l							
	Extract	Flour	Soy		rGly m 4	nGly m 5	nGly m 6	rBet v 1	rGly m 4	nGly m 5	nGly m 6
Soy allergic											
A	0.0	6.5	41	0.10	2.67	<0.10	<0.10	5.83	0.9	0.7	<0.3
B	2.0	7.5	847	1.15	57.10	<0.10	<0.10	>100.00	3.8	<0.3	<0.3
C	0.0	8.5	2011	10.50	37.60	0.25	0.29	nd	17.0	0.8	0.4
D	0.0	7.5	145	0.44	27.11	<0.10	<0.10	68.70	21.0	0.4	<0.3
E	1.5	5.0	89	<0.10	15.40	<0.10	<0.10	67.10	4.0	<0.3	<0.3
F	1.5	9.0	2504	5.11	>100.00	0.57	1.50	>100.00	62.0	0.9	1.0
G	2.0	11.5	254	0.11	19.80	<0.10	<0.10	>100.00	1.0	<0.3	<0.3
H	1.0	8.0	574	0.10	41.00	<0.10	<0.10	87.70	nd	nd	nd
Soy tolerant											
I	2.0	4.5	nd	2.83	0.30	0.22	0.24	nd	0.4	0.6	0.4
J	0.0	5.5	55	<0.10	1.00	<0.10	<0.10	5.42	nd	nd	nd
K	nd	nd	nd	0.39	16.70	<0.10	<0.10	98.90	0.7	<0.3	<0.3
L	0.0	3.0	317	2.43	2.26	0.21	0.43	18.50	<0.3	<0.3	<0.3
M	0.0	2.0	173	0.94	10.20	<0.10	1.40	8.24	2.1	<0.3	<0.3
N	0.0	3.0	2518	0.40	17.20	<0.10	<0.10	99.20	<0.3	<0.3	<0.3
O	0.0	3.0	431	<0.10	1.89	nd	nd	10.80	nd	nd	nd

Table 4 Diagnostic capacity of skin prick tests (SPT), CAP rGly m 4 and ISAC rGly m 4 at specific cutoff.

Cutoff	SPT 7 mm	CAP rGly m 4 17.6 kU/l	ISAC rGly m 4 1 ISU
Sensitivity (%)	75	75	86
Specificity (%)	100	100	80
Positive predictive value (%)	100	100	86
Negative predictive value (%)	75	78	80
Efficiency (%)	86	87	83

However, this study included Bet v 1-positive as well as Bet v 1-negative subjects. In our study on children with birch pollen allergy, IgE response levels to Gly m 5 and Gly m 6 using CAP or ISAC gave negative or only mildly positive results,

without significant differences between SA and ST subjects. This suggests that those allergens are not involved in birch-pollen-associated secondary soy allergy.

In conclusion, we have shown that secondary soy allergy in birch pollen allergic children may be responsible for chronic allergic symptoms, besides typical immediate manifestations. SPT with soy flour is a specific and sensitive tool for the detection of soy sensitization in children with birch pollen allergy. SPT with soy flour, CAP rGly m 4, and ISAC rGly m 4, each at specific cutoff, are valuable tools in the diagnosis of secondary soy allergy in patients with birch pollen allergy. Whether the cutoff values applied here are generally useful, remains to be investigated on a larger study population.

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