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Possible induction of oral allergy syndrome during specific immunotherapy in patients sensitive to tree pollen

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Background:

Many studies have shown that specific immunotherapy may prevent the development of allergies to new allergens. Recently, however, there have been sporadic reports on the possibility of new allergies developing during immunotherapy. The aim of this study was to evaluate the possibility of the occurrence of food allergy and changes of sIgE concentration in patients sensitive to tree pollen during specific immunotherapy.

Material/Methods:

We examined 12 patients subjected to desensitization treatment of pollinosis caused by allergy to the pollen of Betulaceae trees, in whom only Bet v 1 sIgE was found in serum prior to immunotherapy. The control group included 8 allergic patients who did not consent to this treatment.

Results:

Bet v 2 sIgE was detected after 6 months in 3 patients (25%) and after 18 months in another 2 patients (41.7% total). In 2 cases, oral allergy syndrome (OAS) occurred in the course of therapy. These findings were accompanied by a concomitant decrease in nasal and ocular allergic signs during the birch pollen season in the overwhelming majority of patients (91.7%). In the control group, no serum occurrence of Bet v 2 sIgE was found during the 18-month observation period. Although no OAS signs appeared in any patient, the symptomatic intensity of pollinosis was not reduced.

Conclusions:

Due to the limitations of currently used vaccines, new allergies may be induced during immunotherapy. In sporadic cases these may be accompanied by the occurrence of specific clinical manifestations, usually mild.

key words:

desensitization • new allergy induction • birch pollen

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BACKGROUND

The results obtained in epidemiological studies show that the incidence of allergic diseases has been rapidly growing over the last few decades, reaching over 20% of the population in industrialized countries [1].

Although conventional pharmacological therapy of allergic diseases is very effective and usually well tolerated, it is merely symptomatic treatment. Specific immunotherapy is now believed to be the only treatment providing the chance of a complete cure [2], and capable of changing the natural course of the disease, decreasing the risk of developing bronchial asthma in patients with allergic rhinitis [3,4]. The efficacy of specific immunotherapy has been proven in most published reports of randomized double blind placebo controlled studies, including patients allergic to tree pollen [5,6]. Some investigators have also confirmed the beneficial effect of specific immunotherapy combined with the use of pollen vaccines in the alleviation of clinical manifestations of oral allergy syndrome (OAS) [7–9]. A review of the research published in recent years also seems to indicate unequivocally that specific immunotherapy not only shows beneficial effects on the course of allergic diseases, but also reduces the likelihood of developing allergy to new allergens [10,11].

It should be noted that the groups of persons allergic to a specific agent are highly heterogeneous. Two persons allergic to birch pollen, despite identical clinical manifestations appearing in the pollen season, may in fact be allergic to different proteins (allergens) of birch pollen. A physician trying to diagnose an allergy by means of skin tests generally has only standard preparations at his disposal, which generally do not allow one to determine precisely which are the causative allergen(s) for a given patient. Similarly, the currently used vaccines, in spite of the fact that they are usually well standardized, contain a mixture of birch pollen proteins, and thus varying potential allergens. As a rule, in the information materials provided by pharmaceutical companies and in the sparse publications, only the content of the primary allergen is given [6]. There is practically no evidence as to the presence of other allergens in such vaccines, although their occurrence is known and confirmed by, among other methods, Western blot tests using sera of allergic patients. Therefore, as a part of immunotherapy, we co-administer the proteins to which the patient actually reacts, together with other birch pollen proteins, potentially allergenic. Such an approach entails the threat of unintentional induction of new allergic reactions to other components of the allergen source.

Over the past several years we have conducted desensitization of a large number of patients, with clear clinical improvement in the overwhelming majority. However, in some patients with allergy to birch pollen, OAS has occurred during desensitization, even outside the pollen season, usually with mild intensity of symptoms and mainly after eating an apple. In an attempt to explain this effect, the experiment described below was designed and conducted between 2002 and 2003.

MATERIAL AND METHODS

We enrolled 12 patients in the study: 7 women and 5 men, 19–31 years of age (mean age 24.6 ± 4.1 SD). The following inclusion criteria were used:

1. seasonal allergic rhinitis due to allergy to Betulaceae trees (birch, alder, hazel) with typical signs lasting at least two pollen seasons;
2. positive skin-prick tests for the allergens of birch, alder and hazel pollens;
3. positive provocation test with birch pollen allergen evaluated on the basis of clinical signs and rhinoscopic examination;
4. presence of serum Bet v 1 sIgE prior to desensitization.

The exclusion criteria were as follows:

1. positive apple skin prick tests;
2. presence of serum Bet v 2 sIgE and apple allergens prior to desensitization;
3. history of OAS prior to desensitization;
4. allergy to inhaled allergens other than tree pollen allergens.

German-made devices and preparations manufactured by Allergopharma were used for the skin prick tests, provocation tests and sIgE level determination (skin prick tests: 108-birch, 115-alder, 129-hazel, 531-apple; nasal provocation test 108-birch; IgE determination – ELISA, Mini RV System, allergen discs: x901 [Bet v 1], x907 [Bet v 2], f49 [apple]).

For each patient enrolled in the study, at the beginning of June, when the birch pollen season was over, a yearlong course of specific immunotherapy was started, using the German NovoHelisen Depot vaccine (composition: birch – 100% or birch/alder/hazel – 35%/30%/35%) or the French Phostal vaccine (composition: 702 – *Betulaceae*). The sIgE level was determined immediately before the immunotherapy and at 6, 12 and 18 months of therapy. Determination was made at the end of May and the end of November. This timing was based on the intention to eliminate the effect of direct exposition to the natural allergen present in the atmosphere (pollen).

The control group included eight patients of equivalent age meeting all of the above-mentioned inclusion and exclusion criteria who did not agree to desensitization treatment. During the pollination season, these patients received an antihistaminic drug (Cetirizine) and a topical nasal steroid (Fluticasone propionate).

Computer software (STATISTICA 5) was used for statistical calculations. Because of the small number of patients in the study group ($n=12$) we used the nonparametrical Wilcoxon test to explore the differences between the sIgE values in the course of desensitization. The results were considered statistically significant if p was equal to or less than 0.05.

The research protocol of this study was approved by the local ethics committee.

RESULTS

The results of the sIgE assay in the desensitized group are shown in Table 1.

After a six-month period of desensitization, Bet v 2 antibodies appeared in three of the desensitized patients (25%), including two cases of class I antibodies (Phostal desensitization), and one case of class III antibodies (desensitization using the preparation NovoHelisen Depot – 100% birch com-

Table 1. Concentrations of sIgE before and during immunotherapy (U/ml).

Nr	Before immunotherapy			After 6 months of immunotherapy			After 12 months of immunotherapy			After 18 months of immunotherapy		
	Bet v 1 (x 901)	Bet v 2 (x 907)	Apple (f 49)	Bet v 1 (x 901)	Bet v 2 (x 907)	Apple (f 49)	Bet v 1 (x 901)	Bet v 2 (x 907)	Apple (f 49)	Bet v 1 (x 901)	Bet v 2 (x 907)	Apple (f 49)
1	13.20	<0.35	<0.35	14.02	<0.35	<0.35	15.72	<0.35	<0.35	7.12	<0.35	<0.35
2	5.12	<0.35	<0.35	5.02	<0.35	<0.35	6.01	<0.35	<0.35	4.28	<0.35	<0.35
3	4.54	<0.35	<0.35	4.22	<0.35	<0.35	3.87	<0.35	<0.35	2.13	<0.35	<0.35
4	11.70	<0.35	<0.35	12.32	<0.35	<0.35	13.45	<0.35	<0.35	13.01	<0.35	<0.35
5	2.59	<0.35	<0.35	2.60	<0.35	<0.35	1.81	<0.35	<0.35	0.45	<0.35	<0.35
6	16.57	<0.35	<0.35	16.63	3.67	2.91	16.11	4.08	3.01	15.98	1.11	1.12
7	5.80	<0.35	<0.35	6.02	<0.35	<0.35	5.48	<0.35	<0.35	3.12	0.65	<0.35
8	12.03	<0.35	<0.35	12.05	<0.35	<0.35	11.48	<0.35	<0.35	9.71	<0.35	<0.35
9	1.37	<0.35	<0.35	1.78	<0.35	<0.35	0.97	<0.35	<0.35	1.11	0.58	<0.35
10	13.53	<0.35	<0.35	14.25	<0.35	<0.35	14.20	<0.35	<0.35	5.43	<0.35	<0.35
11	1.32	<0.35	<0.35	1.55	0.62	<0.35	1.38	0.69	<0.35	0.42	0.55	<0.35
12	12.01	<0.35	<0.35	12.80	0.69	0.40	14.32	0.70	0.36	8.32	0.52	0.38
a. v.	8.32			8.61			8.73			5.92		
13	2.15	<0.35	<0.35	2.05	<0.35	<0.35	2.44	<0.35	<0.35	4.01	<0.35	<0.35
14	8.03	<0.35	<0.35	9.11	<0.35	<0.35	9.33	<0.35	<0.35	8.12	<0.35	<0.35
15	15.22	<0.35	<0.35	7.22	<0.35	<0.35	12.81	<0.35	<0.35	5.42	<0.35	<0.35
16	1.43	<0.35	<0.35	1.04	<0.35	<0.35	1.14	<0.35	<0.35	1.11	<0.35	<0.35
17	6.22	<0.35	<0.35	2.12	<0.35	<0.35	5.30	<0.35	<0.35	3.26	<0.35	<0.35
18	2.60	<0.35	<0.35	1.78	<0.35	<0.35	3.21	<0.35	<0.35	1.98	<0.35	<0.35
19	4.76	<0.35	<0.35	0.79	<0.35	<0.35	4.02	<0.35	<0.35	1.17	<0.35	<0.35
20	9.33	<0.35	<0.35	6.21	<0.35	<0.35	9.04	<0.35	<0.35	7.14	<0.35	<0.35
a. v.	6.22			3.79			5.91			4.03		

1–12 – desensitized patients; 13–20 – control group; a.v. – average values for Bet v 1

position). In the latter case, antibodies against apple allergens were also present, and the patient noticed mild OAS symptoms (burning lips and tongue after having eaten apple and kiwi). These symptoms were aggravated in the 2003 pollen season. The remaining patients did not report similar symptoms, including the other patient in whom IgE antibodies against apple allergens turned positive after half a year's time (desensitization with Phostal). This situation did not change considerably over the following 6 months.

After another six months of immunotherapy, Bet v 2 antibodies appeared in two additional patients, one desensitized with Phostal, the other with NovoHelisen Depot 108; there were statistically significant differences ($p=0.043$) between the first examination (before immunotherapy) and the fourth (after 18 months of immunotherapy). The antibody titres were within class I. In one Phostal-desensitized patient mild OAS occurred after eating apples, peaches and cherries in the 2003 pollen season. Clinical manifestations subsided after a few weeks without any further treatment.

In the first patient with OAS (item 6 in table 1), the titre of Bet v 2 sIgE (determination after 18 months) dropped to class II level. At the same time, the clinical manifestations of OAS were clearly reduced in the second half of 2003 compared with the results from the first half of the year.

It follows from the compilation of data presented here that in 10 out of 12 desensitized patients an elevation of Bet v 1 sIgE was found at 6 and 12 months of immunotherapy, whereas a clear decreasing tendency could be seen at 18 months.

At the same time, in the pollen season of 2003, in as many as 11 desensitized patients (91.7%), a definite reduction of clinical nasal and ocular manifestations was observed in comparison with the manifestations they had experienced in the previous years. No similar effect was observed in the control group. There was no improvement in any of the control group patients; in one of them, manifestations of bronchial asthma additionally occurred (cough and dyspnea in

the pollen season, auscultatory abnormalities and signs of obturation on spirometric examination).

After the first six months of observation, a decrease in Bet v 1 sIgE was found in the control group, as opposed to the desensitized group. The levels were found to be elevated again after six months (determined outside the pollen season; the difference was statistically significant at the level of $p=0.028$), whereas six months later another decreasing tendency could be observed, with a statistically significant difference ($p=0.0076$) between the first examination (before immunotherapy) and the fourth (after 18 months of immunotherapy). In none of the patients in that group did Bet v 2 or apple sIgE appear during the observation period.

DISCUSSION

In 1987 Amlot et al. described and defined a complex of clinical manifestations called oral allergy syndrome [12]. The syndrome occurs in persons with pollinosis immediately following the intake of specific fruits or vegetables; most often it is manifested with pruritus and edema of the oral and pharyngeal mucosa, sometimes lips, rarely the larynx. The most frequently observed patients are persons allergic to birch pollen in whom the OAS is triggered immediately following the intake of fresh fruit. Cross allergy to apple is the predominant feature.

Several mechanisms are assumed to account for the syndrome [13]. The presence of common allergen epitopes for plant pollen and fruit and vegetables is considered one of the most significant factors [14,15].

At present at least seven birch pollen antigens have been well identified that may have an allergic effect [16]. Bet v 1 is the allergen that was identified the earliest, and is believed to be the most significant allergen in birch pollen [17–19]. A considerable homology in the structure of Mal d 1 (the main apple allergen) and Bet v 1 has been revealed in numerous studies using various techniques [20]. The homology is related to the amino acid structure (ca. 64%) and to the allergen-coding DNA (ca. 55%) [21].

Bet v 2 (profilin) is another important birch pollen allergen [22]. The function of profilins is to stabilize the actin, the mechanism of action being associated with the phosphatidylinositol metabolic pathway. Profilin molecules have a molecular weight of 12–15 kDa and are composed of over a hundred amino acids; in plants, they show over 70% structural homology. This particularly applies to the spatial structure and sequence of the last 9 amino acids [23]. Numerous studies have shown that in the case of allergy to birch pollen, it is usually hypersensitivity to Bet v 1 alone that develops, with less frequent Bet v 1 and Bet v 2 combined sensitivity, or Bet v 2 sensitivity [24]. Bet v 2 has lower allergenicity than Bet v 1 [25], but it seems that in persons who are also allergic to Bet v 2 there is a stronger tendency for food allergy to develop, the manifestation of which may be OAS [26]. This is due to the fact that, owing to the similar structure of the allergens, a person allergic to one species of profilin (e.g. Bet v 2 of birch pollen) may exhibit allergic reactions to profilin of other species (e.g. apple) [27].

Many recent studies have shown that correctly applied specific immunotherapy may prevent the development of aller-

gies to new allergens [28]. In recent years, however, there have been sporadic reports on the possibility of developing new allergies during immunotherapy. Hypersensitivity to new allergens was observed in five patients by Obtulowicz et al., who desensitized a group of 50 patients over a period of 3 years [29]. Van Ree et al. have described cases of hypersensitivity to shrimp in patients desensitized with mite vaccines [30]. Moverare et al., as in our study, determined the levels of sIgE Bet v 1, Bet v 2 and Bet v 4 antibodies during immunotherapy. They also observed the appearance of Bet v 2 sIgE in as many as 65% of patients in whom no presence was previously found, although this effect was not considerable (class I antibody titres) and occurred only after the first year [31]. Similar observations were made in patients undergoing immunotherapy for allergy to grass pollen by Ball et al., who did not observe any tangible clinical consequences of the effect recorded [32].

In our material, OAS signs occurred in two patients. In some cases, Bet v 2 antibodies appeared as early as 6 months into immunotherapy, including one case of class III antibodies. It is worth noting that there was an increase in the Bet v 1 sIgE in the initial phase of immunotherapy, and that at the same time a decrease in the Bet v 1 sIgE concentration was observed in the control group. The increased incidence of OAS observed in the pollen season was quite typical. The increased pollen-induced production of sIgE also brings about increased reaction to fruit [33].

In summation, however, one should note that, despite the above-mentioned adverse effects, the overwhelming majority of our patients assessed the results of their immunotherapy in a positive way. The aim of this study is not, therefore, to discourage physicians from applying specific immunotherapy, but merely to draw their attention to some relatively rare, and fortunately not dangerous adverse effects.

The number of patients enrolled in this study was rather small, and the results should be considered preliminary. The possibility that the development of OAS in desensitized patients is related to the natural course of the disease cannot be ruled out. Nevertheless, both the findings obtained in this study, and the results published by other investigators [34], seem to imply that immunotherapy itself and immunotherapy-related factors induce food hypersensitivity, at least in some patients.

Currently, there are very intensive studies in progress of new methods of immunotherapy, with particular focus placed on recombinant allergens [35]. The improvement of these new methods will probably contribute to elimination of the negative consequences related to the use of currently applied methods and the development of increasingly better, although still imperfect, vaccines [36].

CONCLUSIONS

1. Allergies to additional allergenic pollen components may be detected during specific immunotherapy, which may be demonstrated by means of several different methods, including determination of the level of relevant sIgE. This phenomenon results from the imperfect character of the currently used desensitizing vaccines. In some cases specific clinical manifestations (e.g. OAS) may coexist.

2. Since the positive results of immunotherapy definitely outweigh its negative results, this therapeutic modality should be applied without hesitation whenever commonly recognized indications exist.

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