

The effect of allergen-specific immunotherapy on offspring

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ABSTRACT

Background: The incidence of allergic diseases has increased worldwide. Thus, there is a need for effective primary prevention of allergies.

Objective: The aim of the present study was to examine how allergen-specific immunotherapy (ASIT) affects the development of allergies in the generation of children whose parents were subjected to this method of treatment.

Methods: A total of 194 children with at least one parent with allergy subjected to ASIT were enrolled. These patients were compared with control individuals without ASIT. Their risk of allergy, based on medical history, examination, allergy skin-prick tests, serum total immunoglobulin E and specific immunoglobulin E concentrations was assessed.

Results: The children of parents subjected to immunotherapy showed significantly reduced clinical symptoms of allergic disease. The odds ratios (OR) of any allergic disease and asthma were significantly lower in children with one or both parents with allergy after ASIT compared with the children with parents with allergy and without ASIT: OR 0.73 (95% confidence interval [CI], 0.59–0.86) versus OR 1.85 (95% CI, 1.73–2.2) for any allergic disease and OR 0.63 (95% CI, 0.53–0.79) versus OR 1.36 (95% CI, 1.22–1.67) for asthma.

Conclusion: The phenomenon of reducing the risk of allergies in children whose parents were desensitized might be important in the primary prevention of allergies.

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Allergic diseases are becoming more prevalent worldwide. The high prevalence among children is particularly alarming. The incidence of allergic disease varies from 0.5 to 56%, depending on the study.^{1,2} The highest rates are observed in developed countries, which indicates the impact of civilization on the development of allergies.^{1,2} The current strategy primarily focuses on secondary and tertiary prevention: preventing the further development of allergic disease and alleviating allergy symptoms. Preventing the development of allergic disease as a primary prevention is a much more difficult challenge. Eliminating an allergen and reducing allergen exposure represents the most common method of primary prevention.^{3–5} However, this strategy is not as effective as expected because the same genotype (the potential patient) creates different phenotypes under different environmental conditions.

Similar doubts have been raised concerning the importance of breast-feeding as a protection against allergies. The results of previous studies have been inconclusive.^{6,7} Nevertheless, the European Acad-

emy of Allergy and Clinical Immunology recommends breast-feeding until 6 months of age.⁷ Dietary interventions used in nursing mothers and children in infancy have also raised doubts. Avoiding various foods can be risky and can negatively affect the development of a child.^{6,8} Unfortunately, there is no evidence for the protective role of probiotics, despite the increasing amount of research in this area.^{9,10} However, a negative role has been established for tobacco smoking and passive smoking in pregnant women or children⁶ because these factors lead to the development of inhalation allergies and respiratory diseases. This finding is consistent with the “hygiene theory,” which, however, does not explain the development of allergic diseases.

Of the various methods for treating allergic diseases (secondary and tertiary prevention), allergen-specific immunotherapy (ASIT) is particularly important. For example, immunotherapy has been demonstrated to reduce the risk of asthma development in children with allergic rhinitis.^{11,12} Although increasingly well documented, the importance of immunotherapy still requires more research, particularly in a multigenerational observation. The aim of the present study was to examine how ASIT affects the development of allergies in the generation of children whose parents were subjected to this method of treatment.

METHODS

A total of 11,450 patients were screened after injection ASIT by using the following criteria:

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A. Main group (group A): (1) age between 18 and 45 years; (2) received ASIT treatment against common inhalant allergens within a minimum of 24 months (seasonal or preseasonal) and possessed one or more forms of the following allergic diseases: bronchial asthma, period or chronic allergic rhinitis, or atopic dermatitis; (3) had a child or children who were born at least 9 months after the end of ASIT and was >12 months old; and (4) written consent of the patient to conduct allergy testing on his or her children (as described in item 3) who have completed the first year of life.

B. Control group (group B): (1) age between 18 and 45 years; (2) possessed one or more forms of the following allergic diseases: bronchial asthma, period or chronic allergic rhinitis, or atopic dermatitis treated for a minimum of 24 months with the use of symptomatic allergic treatment and without the inclusion of immunotherapy; (3) had a child or children who were born at least 9 months after symptomatic allergic treatment and were >12 months old; and (4) written consent of the patient to conduct allergy testing on his or her children (as described in item 3) who had completed the first year of life.

A total of 176 patients in group A and 181 patients in group B were included. The study was approved by the local ethics committees of the Medical University of Silesia in Poland. All the patients provided written informed consent. Both parents also signed an assent form to allow their child to participate in the study. In addition, children >7 years old expressed a written consent of acquiescence.

Retrospective Analysis

All data for the screened subjects were collected based on a medical history, results of skin-prick tests, total immunoglobulin E (IgE) and specific IgE (sIgE) values, spirometry, history of treatment, and analysis of desensitization monitoring cards (in group A with ASIT). The methods for the skin-prick test and the total and sIgE measurements are described in the prospective analysis section. Asthma was diagnosed according to the Global Initiative for Asthma (GINA) criteria and spirometry with a positive reversibility test result (Lungtest 1000, MES, Krakow, Poland). For a positive test result, an increase in the forced expiratory volume in 1 second of $\geq 12\%$ or an increase of 200 mL was necessary, in accordance with the criteria of the American Thoracic Society and European Respiratory Society.¹³ Before testing, the patients did not use a short-acting β -2 agonist for 8 hours, ipratropium and theophylline derivatives for 24 hours, a long-acting β -2 agonist for 48 hours, or tiotropium for 72 hours. Current smokers refrained from smoking for 1 hour before testing. Testing was delayed for 4 weeks in the case of respiratory tract infections.

Prospective Procedures

All the children of the screened patients were subjected to the following procedures:

1. Medical examination with ENT and dermatologic assessment.

2. Determination of IgE concentration. The concentrations of total IgE and allergen-sIgE were measured by using the Pharmacia CAP system FEIA (Pharmacia AB, Uppsala, Sweden); the values are shown in kU/L.¹⁴ This analysis was performed for the following sIgE allergens: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternata*, *Cladosporium herbarium*, dog, cat, grass mix, birch, alder, hazel, mugwort, egg, cow's milk, cod, wheat flour, soy, hazelnut, apple, potato, tomato, carrot, pork, and beef. IgE values of >0.35 kU/L were considered a positive result.

3. Skin-prick tests. In this study, skin-prick tests that corresponded to allergen-sIgE were performed (Allergopharma, Reinbeck, Germany). The tests were performed according to previously described guidelines.¹⁵

4. A retrospective analysis of medical interventions before this study (hospitalization, use of antiallergic drugs, infections of the upper and/or lower respiratory tract, the need for antibiotic therapy, nebulized, and systemic steroid therapy).

5. The assessment of asthma criteria according to GINA.

Statistical Analysis

Statistica software 8.1 version (SoftPOL, Cracow, Poland) was used. Continuous data were described as a mean and standard deviation. Categorical data were described as percentages. The clinical and demographic data were compared between the groups by using a χ^2 analysis. A one-way variable analysis was used to compare the nonparametric variables of the analyzed groups. The Spearman rank correlation test was used to compare nonparametric values. Odds ratios with 95% confidence intervals were calculated to assess the risk of asthma or any allergic disease. *P* values of <0.05 were considered significant.

RESULTS

The characteristics and comparisons of parent groups are presented in Table 1. A total of 194 children of the patients in group A (A1) and 195 children of the patients in group B (B1) completed the examination procedures. Dropout was dependent on the following factors: withdrawal of the consent of the parents or child, a lack of cooperation, the absence of allergy procedures, or the presence of other diseases during the study. The basic characteristics of the children are shown in Table 2.

The children of the parents who underwent a course of immunotherapy showed statistically fewer clinical symptoms of allergic disease: (1) symptoms of dry skin

Table 1 The characteristics of the parent groups (A and B) are shown

	Group A	Group B	<i>p</i>
Total no.	179	181	0.43
Women, no. %	87 (48.6)	90 (49.7)	0.47
Age, mean $\pm$ SD, y	26.8 $\pm$ 7.1	24.9 $\pm$ 8.5	0.62
Urban/rural, no. parents	102/77	112/69	0.33
Allergy duration, $\pm$ SD, y	14 $\pm$ 9.1	16.8 $\pm$ 3.1	0.27
Pollen allergy, no. parents	57	49	0.17
House-dust mite allergy, no. parents	44	51	0.21
Mold allergy, no. parents	12	9	0.38
Cat allergy, no. parents	8	10	0.43
Polysensitization, no. parents	58	62	0.62
Bronchial asthma, no. parents	46	51	0.32
Allergic rhinitis, no. parents	152	163	0.77
Atopic dermatitis, no. parents	27	24	0.43
Total serum IgE level, $\pm$ SD, kU/L	189.5 $\pm$ 89.6	212.8 $\pm$ 90.66	0.41

A = study group; B = control group; SD = standard deviation; IgE = immunoglobulin E.

Table 2 The characteristics of the children (groups A1 and B1) of the parents in groups A and B, respectively

	Group A1	Group B1	<i>p</i>
Total no.	194	195	0.29
Girls, %	102	98	0.43
mean age $\pm$ SD, y	5.1 $\pm$ 0.9	4.6 $\pm$ 1.5	0.51
Positive skin-prick test result, no. children	59	98*	0.02
Positive sIgE value, no. children#	71	103*	0.04
Polysensitization, no. children	23	54*	0.006
Food allergy, no. children	37	32	0.42
Early childhood bronchial asthma, no. children	11	23*	0.004
Wheezing, no. children	78	96*	0.05
Allergic rhinitis, no. children	20	48*	0.005
Atopic dermatitis, no. children	49	72*	0.01
Multiorgan disease, no. children	9	20*	0.03
Total serum IgE value, mean $\pm$ SD, kU/L	139.5 $\pm$ 47.1	180 $\pm$ 56.8*	0.03

A1 = children of the parents from study group; B1 = children of the parents from control group; A = study group; B = control group; SD = standard deviation; sIgE = specific-immunoglobulin E.

*A statistically significant difference for the group by using one-way analysis of variance.

#Any allergen sIgE value of >0.35 IU/L.

and/or atopic dermatitis; (2) cow's milk intolerance symptoms: abdominal pain, spit-up, colic, diarrhea, and allergic skin reactions after ingestion of milk; or (3) present allergic rhinitis.

There were no significant differences in the incidence of wheezing up to 1 year of age, but, in the children whose parents received immunotherapy, fewer diagnoses of early childhood asthma, according to GINA criteria, were observed. All data are shown in Table 2. As illustrated in Table 2, the children from group A1 had a statistically lower mean total serum IgE and less positive results of sIgE.

Phenotype Differences between the Analyzed Children

An additional analysis was performed by using the following key parents of the children analyzed in the present study. There was three subgroups: 1) one parent (mother or father) with allergy subjected to allergen specific immunotherapy (ASIT) and the second parent with allergic disease but without ASIT (A); 2) both parents subjected to ASIT; and 3) both parents without ASIT (A). The odds ratio of any allergic diseases and asthma was significantly lower in the children who had one or both parents with allergy after ASIT (ASIT

Table 3 The influence of different phenotypes of the parents on the presence of allergic disease or asthma in their child

Parent Phenotype (Parent and Parent)	Any Allergic Disease in Their Child, OR (95% CI)	Early Childhood Asthma in Their Child, OR (95% CI)
ASIT and ASIT	0.69 (0.58–0.89)	0.58 (0.53–0.65)
A and ASIT, mother or father	0.82 (0.77–0.91)	0.7 (0.61–0.78)
A and ASIT, mother	0.74 (0.68–0.93)	0.68 (0.59–0.74)
A and ASIT, father	0.91 (0.84–1.03)	0.72 (0.55–0.87)
A and A	1.85 (1.73–2.2)	1.36 (1.22–1.67)

OR = Odds ratio; CI = confidence interval; ASIT = parent with allergy and after allergen-specific immunotherapy, A = parent with any allergic disease.

and ASIT or A and ASIT) than in the children with parents with allergy and without ASIT (A and A). Children who had a mother with allergy after ASIT and father with allergy and without ASIT had lower odds ratio for any allergic diseases (but not for asthma) than in the opposite situation (father with allergy and after ASIT and mother with allergy and without ASIT). The details are shown in Table 3.

DISCUSSION

ASIT has been widely recognized as an effective method of treatment.^{1,2,12} However, based on the data from clinical studies, this treatment is primarily used as a secondary or tertiary prevention.¹⁶ ASIT prevents the appearance of new, and the progression of, existing allergies, *e.g.*, prevention of bronchial asthma in children with allergic rhinitis. Clinicians have attempted to combine ASIT with anti-IgE and/or antihistamines to improve the efficiency of treatment.^{11,17} However, there are no studies that concern the primary prevention in these trials. Decades of ASIT use facilitate a more long-term observation of the effects of this treatment. The impact of ASIT on the next generation is particularly interesting. Regardless of the distribution of the phenotypes of the parents, analysis of the results indicate that the children with at least one parent subjected to an ASIT administration (regardless of the phenotype of the other parent) show less risk for allergies and asthma compared with the children with a parent with allergy but without desensitization.

There was no homogeneity in the phenotypes of the parents in the study groups A and B. However, there was a similar distribution of phenotypes of parents in both groups (two parents with atopy, a single parent with atopy). Thus, the risk of allergy in the phenotype of a particular child was similar in both groups. However, the aforementioned observation emphasizes the fact that convergent results were obtained after a more detailed phenotypic examination of the parents was performed. Significantly, a more frequent lack of aller-

gies in the children whose parent or parents were desensitized was observed, which indicated that ASIT, especially in women with allergy and before procreation, could be used as a primary prevention for the benefit of the next generation. This observation was independent of the type of allergen sensitized. In addition, the observed reduction in the risk of asthma in the children whose parents were desensitized is particularly important information. Asthma is a serious and growing problem in children. Until recently, there were no significant strategies to avoid this disease in this age group.

A limitation of the present study is the small subgroup of patients, which did not facilitate a deeper analysis, *e.g.*, of a specific allergen desensitization effect on reducing the risk of allergic disease in children. Perhaps the medical history (hospital interventions, vaccinations, medications) of the examined children might have a more or less significant effect on the appearance of allergic disease. However, although this hypothesis will require further analysis, this idea does not invalidate the results. Tracing all the possible factors that influence child development and that examine strategies for treating their parents (including immunotherapy) might facilitate the development of a hypothetical model for the primary prevention of allergies. However, the risk of allergy is dependent on many factors. Thus, ASIT cannot necessarily be considered simply as a primary and sole method for the treatment of allergic disease.

Additional follow-up studies of the children will be extremely important in determining their phenotype 10–20 years from now. However, this analysis will require long-term and difficult research. Thus, the observations with regard to the next generation will only be able to address the problem of the primary prevention of allergies.

CONCLUSION

The observed reduction of allergies in the children whose parents had ASIT compared with those whose

parents with allergy did not undergo this treatment might represent a promising factor for the primary prevention of allergy. However, these findings require further research.

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