Immunoglobulin E-Mediated Allergies in Lung-Transplanted Adults

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Background. Immunoglobulin E (IgE)-mediated allergy has repeatedly been reported after solid organ transplantation, apparently affecting approximately 10% of pediatric organ transplant recipients. Interestingly, type 1 allergy has not been described in transplanted adults, suggesting a particular propensity in childhood.
Methods. The present cross-sectional study assessed the prevalence of type 1 allergy in 42 adult lung transplant recipients aged 25 to 50 years. Instruments included standardized interviews, skin prick tests, and serum IgE measurements.
Results. Ten of 42 patients (23.8%) displayed elevated specific IgE levels or positive skin prick test results against one or more allergens. Five individuals (11.9%) additionally reported corresponding clinical symptoms of type 1 allergy. No statistically significant association of sensitization or allergy prevalence with patient age, kind of immunosuppressive therapy, and time since transplantation was found.
Conclusions. The phenomenon of transplantation-associated allergy is not age-restricted and thus should be assessed more thoroughly in all age groups.

Keywords: Organ transplantation, IgE, Allergy, Immunosuppression, Adults.

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The immunosuppressive therapy used to suppress the rejection of the allograft targets mainly the cell-mediated immune response, in particular, T and B lymphocytes (*1*). These cells play a basic role in type 1 hypersensitivity reactions; therefore, some immunosuppressive drugs also are applied in the treatment of severe allergic disease (*2*, *3*). Consequently, it should be expected that transplanted patients receiving long-term immunosuppressive therapy would not develop sensitization or at least not show clinical signs of allergy.

Surprisingly, various forms of atopic disease have been reported in organ-transplant recipients (*4–18*). The phenomenon of transplantation-associated allergy has been reported after kidney, liver, lung, intestinal, and heart transplantation and is estimated to affect 10% of transplanted children (*5*, *14*). The underlying cause for this paradoxon is at present unknown but has been connected to different factors, such as young recipient age, liver transplantation, or tacrolimus immunosuppression (*6*, *9*, *14*).

With the exception of two case reports describing passive transfer of food allergy via the transplanted liver (*9*, *12*), literature about type 1 allergy after organ transplantation is restricted to children. This led to the suggestion that the maturity of the immune system, in particular the presence of regulatory mechanisms, prevents the occurrence of transplantation-associated allergy in adults (*9*, *14*, *15*).

We previously performed a cross-sectional study evaluating organ-transplanted children, which showed a high rate of posttransplant allergic disease irrespective of patient age (*5*). This led us to question the influence of age on transplantation-associated allergy. The following study was therefore designed to characterize the occurrence of sensitization and allergy in lung-transplanted adults.

Between December 2004 and July 2005, 42 lung-transplanted patients (17 male, 25 female) were assessed for type 1 allergy by standardized interviews, skin prick tests, and total and specific serum IgE measurements. Inclusion criteria were age at enrolment between 25 and 50 years, age at transplantation at greater than 18 years, and time since transplantation of at least 6 months. All participants underwent the interview and IgE measurement, whereas two subjects (2 of 42, 4.76%) denied skin prick testing. Mean age at enrolment was 38.91 years (±7.31 SD, range 25 to 50 years), mean age at transplantation was 34.81 years (±8.18 SD, range 18 to 49 years). Time since transplantation varied between 6 and 157 months (mean 48.69±41.2 SD). Immunosuppressive therapy consisted of different combinations of corticosteroids, azathioprin, mycophenolate mofetil, cyclosporin A (CsA), tacrolimus, and rapamycin. Immunosuppression at time of evaluation and transplantation, total time of exposure to different immunosuppressive drugs, and underlying diseases leading to transplantation (Supplementary Tables 1 and 2 online only).

Data on atopic diseases, that is, allergic rhinoconjunctivitis, allergic bronchial asthma, atopic dermatitis, and food allergy, were collected by a detailed questionnaire using core questions from the International Study of Asthma and Allergies in Childhood (ISAAC) (*19*). In addition, underlying disease leading to organ transplantation, personal and family history of atopic disease, and immunosuppressive medication since transplantation were assessed.

Skin prick tests with eight common allergen extracts (ALK-Scherax, Hamburg, Germany) as well as specific IgE

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TABLE 1. Characteristics of sensitized and allergic patients

	1	9	13	15	17	22	33	36	39	44
Primary diagnosis	HSD	PPH	CF	CF	PPH	CTEPH	COPD	HSD	CF	COPD
Sex (m/f)	f	f	f	f	m	m	f	f	m	f
Age (yrs)	39	46	26	30	44	38	42	38	29	44
Age at tx (yrs)	38	42	18	29	43	36	39	28	26	41
Time since tx (months)	6	39	108	11	10	22	28	117	36	32
Total IgE (kU/L)	16.8	34.3	8.72	61.1	145	79	17.1	5.55	25.2	24.7
Specific IgE (CAP class)	Inh: tg 2, rp 2	Nut: ep 2	Inh: tg 2, rp 2	Inh: tg 3, rp 3, bp 2	Inh: mw 4, rp 2, bp 2, dd 2, tg 1, cd 1	Inh: dp 1	neg	Inh: tg 1, rp 1	Inh: tg 2, dp 2, rp 1,	neg
Skin prick test	Inh: b, gm	neg	Inh: gm	Inh: gm, bp, dd	Inh: gm, bp, dd, cd	Inh: gm	Inh: gm, bp, dp	Inh: gm	Inh: gm, bp, dp, cd	Inh: gm, bp, al, dp
Allergic symptoms	neg	neg	rc	sr, rc	neg[a]	ur	neg	neg	rc	rh
Allergic symptoms before tx	neg	neg	neg	pos	pos	pos	neg	pos	pos	neg
IS at transplantation	CS, MMF, tac	CS, MMF, tac	CS, MMF, CsA	CS, MMF, tac	CS, MMF, tac	CS, MMF, tac	CS, MMF, CsA	CS, MMF, CsA	CS, MMF, tac	CS, MMF, tac
IS at evaluation	CS, MMF, tac	CS, MMF, tac	CS, MMF, tac, rapa	CS, MMF, tac	CS, MMF, tac	CS, MMF, tac	CS, MMF, CsA	CS, MMF, CsA	CS, MMF, tac	CS, MMF, tac
Family history	pos	neg	pos	neg	neg	pos	neg	pos	neg	neg

[a]no pollen season since transplantation.

al, alternaria; bp, birch pollen; cd, cat dander; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CS, corticosteroids; CsA, cyclosporin A; CTEPH, chronic thromboembolic pulmonary hypertension; dp, dermatophagoides pteronyssinus; dd, dog dander; ep, egg protein; gm, grass mix; HSD, heart septal defect; Inh, inhalant allergens; MMF, mycophenolate mofetil, mw, mugwort; Nut, nutritional allergens; PPH, primary pulmonary hypertension; rapa, rapamycin; rp, rye pollen; rc, rhinoconjunctivitis; rh, rhinitis; sr, skin rash; tac, tacrolimus; tg, timothy grass pollen; u, urticaria.

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measurements enquiring eight common inhalant and 10 common nutritional allergens were conducted with all serum samples. Additional allergens were included if indicated by the patient's history. Specific and total IgE levels in peripheral blood were determined using the CAP-fluoroenzyme immunoassay by Phadia AB (Uppsala, Sweden).

Descriptive statistical analyses were performed using SPSS for Windows, version 11.0 (SPSS Inc, Chicago, IL). Univariate analysis was performed to detect an association of potential risk factors with sensitization, allergy, or total IgE. Tested determinants included gender, time since transplantation, immunosuppressive medication taken at time of transplantation, current immunosuppressive medication, total time of exposure to distinct immunosuppressive drugs, age of patients at evaluation, and age of patients at transplantation. Chi-square test or when indicated Fisher's exact test was used to compare categorical variables, whereas numeric variables were analyzed by Wilcoxon rank sum test. To investigate independent risk factors for sensitization and allergy, conventional multivariate logistic regression (Enter-method) was applied. The study protocol was approved by the Ethics Committee of the Medical University of Vienna, and informed consent was obtained from all patients.

Ten patients (10 of 42, 23.81%) were found to be sensitized to one or more allergens, reflected by elevated specific serum IgE in nine patients (9 of 40, 21.43%) or positive prick test results in eight patients (8 of 42, 19.05%). Total serum IgE levels ranged from <2 to 150 kU/L (mean 22.1, SD 33.98), exceeding the threshold value of 100 kU/L in two patients (2 of 42, 4.76%). Five of the sensitized individuals (5 of 42, 11.9%) additionally reported corresponding clinical symptoms upon exposure to the respective allergen and thus were classified as "allergic."

Nine patients (9 of 10, 90%) were sensitized against inhalant allergens and two (2 of 10, 20%) against nutritive allergens. Symptoms reported most frequently were seasonal or perennial rhinitis, rhinoconjunctivitis, and conjunctivitis of variable degree. One patient reported urticaria on both arms annually during hay harvest, and one patient experienced four episodes of skin rash accompanied by intense pruritus upon peanut ingestion. Mostly, symptoms were of low intensity, and only one of the symptomatic individuals required regular antiallergic treatment. Table 1 gives baseline characteristics and putative risk factors of sensitized and allergic patients.

Two of the allergic patients could not recall having allergic symptoms before transplantation. One patient, who had a history of severe seasonal rhinoconjunctivitis since childhood, reported improvement of nasal symptoms but developed de novo peanut allergy after transplantation. Two subjects dated allergy onset before transplantation.

Both sensitization and allergic disease occurred irrespective of gender, age, immunosuppressive medication, and time since transplantation. Differences in prevalence rates could not be statistically explained by any single variable or by combination of variables in multivariate logistic regression. However, the small sample size certainly limited statistical analysis. A summary of the outcomes on the comparison of non-sensitized, sensitized, and allergic patients is displayed in Table 2.

To our knowledge, this is the first study to characterize allergic disease in transplanted adults. Our results show that adult lung transplant recipients display a prevalence of specific sensitization and clinical manifest allergy, which is similar to that described in unselected Austrian adults (*20*, *21*). The predominant symptoms reported by allergic subjects (allergic rhinitis or conjunctivitis) also are in line with the general population of similar age. The results of the present study

TABLE 2. Baseline characteristics and results of the univariate analysis comparing nonsensitized, sensitized, and allergic lung transplant recipients

	Sensitization		Allergy	
	No	Yes	No	Yes
N	32 (76.19%)	10 (23.81%)	37 (88.1%)	5 (11.9%)
Sex (m/f)	14/18 (43.8%/56.3%)	3/7 (30%/70%)	15/22 (40.5%/59.5%)	2/3 (40%/60%)
Age, yrs (mean± SD)	39.38±7.44	37.4±7.01	39.7±7.05	33±7.14
Age at tx, yrs (mean± SD)	35±8.25	34.2±8.38	35.41±7.97	30.4±9.29
Positive family history	8 (25%)	4 (40%)	10 (27%)	2 (40%)
Total IgE, z-units (median, range)	6.15 (1.9−150)	24.95 (5.55−145)	7.51 (1.9−150)	25.2 (8.72−79)
Positive prick test (n=58)	0	9 (90%)	0	5 (100%)
Positive specific IgE	0	8 (80%)	4 (10.8%)	4 (80%)
Time since tx, months (median, range)	36 (7–157)	30 (6–117)	34 (6–157)	32 (11–108)
Immunosuppressive therapy, months (median, range)				
Aprednisolone	37.5 (7–157)	30 (6–117)	34 (6–157)	32 (11–108)
Azathioprine	0 (0–50)	—	0 (0–50)	—
Mycophenolate mofetil	32 (3–111)	30 (6–117)	31 (3–117)	32 (11–108)
Cyclosporin A	3 (0–152)	0 (0–110)	0 (0–152)	0 (0–69)
Tacrolimus	12 (0–157)	16.5 (0–39)	12 (0–157)	32 (11–39)
Rapamycin	0 (0–21)	0 (0–29)	0 (0–21)	0 (0–29)

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are thus in accordance with previous publications in that they confirm that allergic disease does occur in organ-transplanted patients. However, contradicting previous hypotheses we did not find that adult age at time of transplantation protects from allergic disease. The rates of sensitization and allergy in adult patients were actually analog to the results we found in transplanted children and adolescents (23.8% and 11.9% in comparison to 24.4% and 10.3% in pediatric patients) (*5*).

Moreover, we could not confirm an association of sensitization or allergy prevalence with kind of immunosuppressive therapy. Because tacrolimus was suggested to be the specific risk factor for transplantation-associated allergy by several authors (*6*, *14*, *15*), a higher prevalence in the tacrolimus-treated patients compared with those treated with CsA could have been expected. In our collective, we did indeed find a slightly increased sensitization and allergy prevalence in patients receiving tacrolimus both at time of transplantation and at evaluation (Table 3). At time of investigation, each of the five allergic individuals was treated with tacrolimus. Furthermore, median time of total exposure to tacrolimus showed a trend to be higher in the sensitized and allergic patients, whereas total CsA exposure tended to be higher in nonsensitized patients (Table 3). However, none of these results showed statistical significance. Therefore, we question the exclusive role of tacrolimus in the development of allergic disease in this particular population. No association with any other immunosuppressive drug was found.

Another remarkable finding was the predominance of inhalant allergies in our patient group. This is in contrast to literature, as most authors report occurrence of food allergy after organ transplantation. Most likely, this difference can be ascribed to the very young age of patients in the majority of previous reports, which is known to be associated with a high prevalence of IgE-mediated food allergy (6–8% in comparison to 1–2% in the unselected adult population) (*22*).

The exact underlying immune mechanism by which transplantation could contribute to the development of type 1 allergy still needs to be elucidated. The complex interactions of immunosuppressive medication with the immune system led to the assumption that immunosuppression is the specific risk factor for allergy development after transplantation. However, more than one factor might be involved. Moreover, because of the cross-sectional design of the present study, patients' atopic history was obtained retrospectively. Thus, we cannot exclude that allergic disease already existed before transplantation. To verify a de novo development of allergic disease as a consequence of transplantation, prospective studies evaluating the pretransplant atopic status and the sequential development of allergy are required.

In summary, our results confirm that therapeutic immunosuppression does not control sensitization or clinical manifestation of type 1 allergy in lung transplant recipients and demonstrate that the phenomenon of transplantation-associated allergy is not restricted to the pediatric age.

TABLE 3. Allergy and sensitization prevalence in the patient subsets defined by immunosuppressants taken at transplantation and at evaluation (%)

		Sensitization		Allergy	
Corticosteroids					
At tx	(n=42)	23.81	(n=10)	11.9	(n=5)
At eval	(n=42)	23.81	(n=10)	11.9	(n=5)
Azathioprin					
At tx	(n=2)	0	(n=0)	0	(n=0)
At eval	(n=0)	—			
Mycofenolate mofetil					
At tx	(n=38)	26.32	(n=10)	13.16	(n=5)
At eval	(n=37)	27.03	(n=10)	13.51	(n=5)
Cyclosporin A					
At tx	(n=21)	14.29	(n=3)	4.76	(n=1)
At eval	(n=15)	13.33	(n=2)	0	(n=0)
Tacrolimus					
At tx	(n=21)	33.33	(n=7)	19.05	(n=4)
At eval	(n=27)	29.63	(n=8)	18.52	(n=5)
Rapamycin					
At tx	(n=0)	—		—	
At eval	(n=5)	20	(n=1)	20	(n=1)

eval, evaluation.

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