

high homology with proteins belonging to the lipid transfer protein (LTP) family, especially with those from wheat (100% identity, 100% similarity), barley (53% identity, 93% similarity), rice (66% identity, 86% similarity), maize (53.3% identity), and peach (46.6% identity).

We may conclude that in this patient the massive exposure to spelt caused sensitization to it, clinically expressed as cutaneous contact reaction; sensitization to spelt likely also conditioned allergy to several foods immunochemically related to spelt, clinically expressed as generalized urticaria and angioedema. A main point was that the avoidance of the contact with spelt led to a complete resolution not only, as expected, of the symptoms to spelt but also of the symptoms and sensitization to the other foods. A possible explanation may be based on the well-known IL-4-dependent modulation of the IgE synthesis through a T_H1/T_H2 shift, the " T_H2 hypothesis."¹ A continuous antigenic stimulation may give rise to a polyclonal rather than antigen-specific increase in the IgE synthesis; allergen avoidance in this patient, who was previously not atopic, might have caused a return to a low IL-4 content in the microenvironment, turning off the IgE synthesis.

Moreover, in this study we have identified a 9-kd allergen as a newly discovered relevant IgE binding protein of spelt, which is an LTP highly homologous to wheat LTP (never demonstrated to be allergenic) and to other LTPs of maize and peach, identified as major allergens.^{2,3} The structural similarity could thus explain the reactions of this patient to Rosaceae fruits and the IgE cross-reactivity between spelt and peach LTP, demonstrated by immunoblotting inhibition.

Elide A. Pastorello, MD^a

Laura Farioli, BSc^b

Anna M. Robino, MD^a

Chiara Trambaioli, BSc^a

Amedeo Conti, BSc^c

Valerio Pravettoni, MD^a

^aAllergy Center

3rd Division of General Medicine

Ospedale Maggiore IRCCS

Milan, Italy

^bICP Hospital, CEMOC

Milan, Italy

^cNational Research Council

Turin, Italy

REFERENCES

1. Romagnani S. The role of lymphocytes in allergic disease. *J Allergy Clin Immunol* 2000;105:399-408.
2. Pastorello EA, Farioli L, Pravettoni V, Ispano M, Scibola E, Trambaioli C, et al. The maize major allergen, which is responsible for food-induced allergic reactions, is a lipid transfer protein. *J Allergy Clin Immunol* 2000;106:744-51.
3. Pastorello EA, Farioli L, Pravettoni V, Ortolani C, Ispano M, Monza M, et al. The major allergen of peach (*Prunus persica*) is a lipid transfer protein. *J Allergy Clin Immunol* 1999;103:520-6.

1/8/114988

doi:10.1067/mai.2001.114988

Food allergy after pediatric organ transplantation with tacrolimus immunosuppression

To the Editor:

We report 7 pediatric organ transplant recipients diagnosed with food allergy while receiving systemic tacrolimus immunosuppression. Food allergy was diagnosed on the basis of a convincing history of reactions, positive skin testing to the causal food, detectable serum food-specific IgE antibody, and/or resolution of symptoms after food avoidance.

Patients 1-6 received liver transplants at a median age of 9 months, and patient 7 received small bowel transplant at 8.6 years (Table I). All patients received primary tacrolimus immunosuppression, serum tacrolimus levels being maintained at 7-10 ng/mL. Three donors had

histories of asthma and/or allergic rhinitis, but none were food-allergic. None of the patients had a history suggesting food allergy before transplantation, at which time all infants were on Pregestimil and age-appropriate solid foods and patient 7 was on regular diet. Five patients had family histories of atopy. The median time between transplantation and onset of food allergy was 5 months (range, 5 days to 12 months). All patients presented with hives and/or angioedema, and 3 patients had persistent gastrointestinal symptoms and biopsy-proven eosinophilic gastroenteritis. In all patients, symptoms resolved with appropriate elimination diets or elemental formula. One patient developed eczema 6 months after liver transplantation and 2 patients developed allergic rhinitis, but none have developed asthma.

Food allergy has previously been reported in transplant recipients receiving tacrolimus. A long-term follow-up of 49 heart transplant recipients on primary (38) or conversion (11) tacrolimus revealed that 22% manifested allergic disease.¹ Thirty-nine percent had eosinophilia, 10% had elevated IgE levels, 20% had gastrointestinal symptoms, and 4% were diagnosed with allergic eosinophilic gastroenteritis. Lacaille et al² reported a child who developed anaphylaxis to milk, and Inui et al³ described 2 children with fish allergy after liver transplantation with tacrolimus immunosuppression. An abstract describing experience with 64 pediatric liver transplant recipients reported 11 patients (17%) with food allergy,⁴ though no details of the allergy evaluations were provided.

These reports and our current series implicate an association of transplantation with the development of allergic disease, particularly food allergy. Although there are several alternative explanations, it is most likely that the specific risk factor for the development of allergy is the tacrolimus immunosuppression. For example, food allergy could be transferred through transplantation from a food-allergic donor,⁵ but none of the donors in our series were food-allergic. Delayed manifestation of food allergy could also be attributed to limited exposure to dietary antigens before transplant, especially in the context of anergy caused by chronic liver disease, with liver transplantation re-establishing immune competence with the subsequent manifestation of allergy.⁶ Interestingly, patients on cyclosporin A have been shown to recover their delayed-type hypersensitivity after transplantation, but there are no reports of food allergies in cyclosporin A-immunosuppressed patients despite its availability since 1984.

There are several mechanisms by which tacrolimus could contribute to the development of allergy. It exerts a unique effect on intestinal mucosa by inhibiting cellular energy production with increased intestinal permeability,⁷ which might impair the intestinal barrier against antigen uptake and increase the risk of food allergy. In addition, as a potent IL-2 inhibitor, tacrolimus might cause a shift toward T_H2 -type immune responses. Despite the wide use of tacrolimus in adults, all food allergy reports concern children, suggesting that effects of tacrolimus might be most prominent in the setting of less mature immune and gastrointestinal systems.

In summary, our report suggests a potential association between transplantation and food hypersensitivity. Further studies are necessary to determine whether there is a true causal relationship between tacrolimus or whether other factors are involved.

Anna H. Nowak-Węgrzyn, MD^a

Scott H. Sicherer, MD^a

Mary Kay Conover-Walker, MSN, RN, CRNP^b

Robert A. Wood, MD^b

^aThe Mount Sinai School of Medicine

Department of Pediatrics, Division of Allergy & Immunology

The Jaffe Food Allergy Institute

New York, NY 10029-6574

^bThe Eudowood Division of Allergy & Immunology

Department of Pediatrics

Johns Hopkins University School of Medicine

Baltimore, MD

TABLE I. Characteristics of patients

	Patient no.						
	1	2	3	4	5	6*	7†
Primary diagnosis	Biliary atresia	Biliary atresia	Biliary atresia	Biliary atresia	Biliary atresia	Biliary atresia	Multiple anomalies
Age at transplantation (mo)	11	8	9.6	15.5	4.8	13	8.6 years
Transplant type	Living related liver	Living related liver	Living related liver	Living related liver	Living related liver	Living related liver	Small bowel
Immunosuppression	FK 506, CC, Pred	FK 506, CC, Pred	FK 506, Pred	FK 506, CC, Pred	FK 506, CC, Pred	FK 506, CC, Pred	FK 506, CC, Pred
Diet before transplantation	Pregestimil, solids	Pregestimil, solids	Pregestimil, breast milk	Pregestimil	Pregestimil	Pregestimil, solids	Regular, including Pn
Diet after transplantation	Table foods	Pregestimil, solids	Cow's milk formula, table foods	Pediasure, whole milk, table foods	Alimentum, table foods	Whole milk, table foods	Regular
Food allergy after transplantation	Pn, E-angioedema, anaphylaxis	M-anaphylaxis, chronic diarrhea, reflux, AEG	Pn-angioedema	Pn-angioedema	M, E, C, Pn-facial swelling, V&D; AEG	Pn-rash, E-vomiting, S-diarrhea; AEG	Pn-anaphylaxis
Age at onset of food allergy	2 y	8.5 mo	1.1 y	3 y	1.4 y	1.5 y	8.9 y
Time from transplantation to diagnosis of food allergy (mo)	13	0.5	2	21	12	5	4
Positive skin prick test‡	E, Pn, C	M	Pn	Not done	Not done	M, E, Pn, S, W	Not done
Allergen-specific IgE (kIU/L)§	E-40, Pn-25	E-2, M-1, Pn-1	Pn-40	E-0.8, Pn-0.5	E-6, M-14, O-16, Pn-3.5, R-0.5, S-3, W-24	E-73, M-9, Pn-38, S-32, W-21	Not done
Peripheral eosinophilia (%)	9	4-10	16	15	25	10	10

CC, CellCept (mycophenylate mofetil); *Pred*, prednisone; *Pn*, peanut; *E*, egg; *M*, milk; *C*, chicken; *V&D*, vomiting and diarrhea; *AEG*, allergic eosinophilic gastroenteritis; *S*, soy; *W*, wheat; *O*, oat; *R*, rice.

*This patient was transfused at 18 months because of symptomatic anemia resulting from gastrointestinal bleeding associated with AEG.

†This patient experienced 2 severe anaphylactic reactions to peanut, one under physician observation.

‡Skin prick test with bifurcated needle (Allergy Labs of Ohio, Columbus, Ohio) and food allergen extracts (Greer Laboratories, Lenoir, NC), considered positive if wheal was at least 3 mm greater in mean diameter than mean saline-induced wheal.

§Serum food-specific IgE measured by CAP System FEIA, Pharmacia Diagnostics, Uppsala, Sweden.

Supported by the Eudowood Foundation for the Consumptives of Maryland (RA Wood).

REFERENCES

- Asante-Korang A, Boyle GJ, Webber SA, Miller FA, Fricker FJ. Experience of FK 506 immunosuppression in pediatric heart transplantation: a study of long-term adverse effects. *J Heart Lung Transplant* 1996;15:415-22.
- Lacaille F, Laurent J, Bousquet J. Life-threatening food allergy in a child treated with FK 506. *J Pediatr Gastroenterol Nutr* 1997;25:228-9.
- Inui A, Komatsu H, Fujisawa T, Matsumoto H, Miyagawa Y. Food allergy and Tacrolimus. *J Pediatr Gastroenterol Nutr* 1999;28:355-6.
- Prabhakaran K, Lau HT, Wise B, Schwarz K, Colombani PM. Incidence of allergic symptoms in pediatric liver transplant recipients treated with tacrolimus based immunosuppression. *Pediatrics* 1999;104:786-7.
- Legendre C, Caillat-Zucman S, Samuel D, et al. Transfer of symptomatic peanut allergy to the recipient of a combined liver-and-kidney transplant. *N Engl J Med* 1997;337:822-4.
- O'Rourke M, Post J, Fernandez M, et al. Recovery of delayed-type hypersensitivity following liver transplantation. *Transplant Proc* 1995;27:1150-1.
- Gabe SM, Bjarnason I, Tolou-Ghamari Z, et al. The effect of tacrolimus (FK 506) on intestinal barrier function and cellular energy production in humans. *Gastroenterology* 1998;115:67-74.

1/8/116571

doi:10.1067/mai.2001.116571