

## Letter to the Editor

### Manifestations and long-term outcome of food allergy in children after solid organ transplantation

#### To the Editor:

The development of food allergy in children after organ transplantation has been increasingly recognized, with reported incidences from 6% to 57%.<sup>1-3</sup> Most cases have occurred after liver transplantation, but food allergy after small bowel, heart, and kidney transplantations have also been described.<sup>4,5</sup> Recognition of posttransplantation food allergy is important because it can lead to significant morbidity, and immunosuppressive drugs can sometimes be reduced when appropriate diets are instituted.<sup>6</sup> We retrospectively reviewed 25 children given diagnoses of food allergy after organ transplantation to achieve a better understanding of the manifestations and long-term outcome of food allergy in this population (see this article's Methods section in the Online Repository at [www.jacionline.org](http://www.jacionline.org)).

A detailed description of the participants (11 girls and 14 boys) is presented in Table I. All received tacrolimus immunosuppression, and 23 of 25 received additional immunosuppressive therapies, including mycophenolate mofetil (11/25) and corticosteroids (20/25). Tacrolimus was generally started 48 hours after transplantation and was dosed to maintain trough levels between 7 and 10 ng/mL. The median age of transplantation was 8.7 months (interquartile range [IQR], 5.8-13.3 months), the median time from transplantation to the first suspected food reaction was 6.0 months (IQR, 4.4-10.4 months), and the median time until allergy confirmation was 10.1 months (IQR, 8.3-17.5 months). All patients had allergic symptoms, including angioedema in 15, urticaria in 15, eczema in 6, lower respiratory tract symptoms in 10, upper respiratory tract symptoms in 3, and gastrointestinal symptoms in 20. Fifteen of the 25 patients had biopsy-confirmed eosinophilic gastrointestinal disease, and 14 had persistent gastrointestinal symptoms that resolved with food avoidance. Of the 15 patients with eosinophilic gastroenteropathy, 12 also experienced acute food reactions.

Specific food sensitivities were diagnosed based on positive skin and ImmunoCAP test results in 11 patients, positive ImmunoCAP results only in 12 patients, and positive skin test results only in 2 patients. Patients were sensitized to a median of 5 foods (IQR, 3-8 foods) and had clinical reactions to a median of 4.5 foods (IQR, 2-6 foods). One child was sensitized to 28 different foods. Specific foods causing acute allergic reactions included egg (n = 19), milk (n = 19), peanut (n = 10), soy (n = 9), wheat (n = 9), and "other" (n = 14). Seventeen of the 25 patients had other atopic disease, including eczema (n = 11), allergic rhinitis (n = 11), and/or asthma (n = 4). No patients had a history of food allergy or other allergic disease before surgical intervention, except 1 patient with eczema. Information regarding allergy in the donor was available in 11 cases; 3 had a history of atopy, but none had a history of food allergy. Sixteen of the 25 patients had a family history of allergic respiratory disease, including 3 with a history of food allergy.

The median duration of follow-up was 2.4 years (IQR, 1.4-4.7 years) in the clinic and 6.1 years (IQR, 3.9-7.5 years) by telephone. Only 3 of 25 patients followed unrestricted diets at the time of last follow-up. Of the 163 foods avoided

collectively, 52 have been successfully reintroduced, and 17 of 25 children were able to reintroduce at least 1 food at a median of 30.6 months (IQR, 18.0-47.7 months) after transplantation. Of the foods still being avoided, specific IgE levels, where available, decreased from initial testing to last follow-up for 30 of 47 foods, worsened for 12 of 47 foods, and were unchanged for 5 of 47 foods. Patient 4 died 22 months after transplantation from EBV-related lymphoproliferative disease. Patient 14 also had lymphoproliferative disease and discontinued tacrolimus 3 years before our last follow-up. He continues on an elemental formula and eats no foods except fish, but his IgE levels for most foods have decreased. All other patients continued to take tacrolimus at our last follow-up.

The pathogenesis of allergic disease after organ transplantation is poorly understood and likely involves several factors. The immunomodulatory effects of tacrolimus, including its propensity to skew toward a T<sub>H</sub>2 phenotype by inhibiting production of IL-2, as well as its effects on intestinal permeability, are potentially important.<sup>7</sup> Other proposed mechanisms include passive transfer of food-specific IgE or lymphocytes with specificity for particular food antigens from donors,<sup>8,9</sup> although this appears unlikely here because none of the known donors had a history of food allergy. Most of the children were less than 1 year of age at the time of transplantation, and the appearance of allergy might be explained by their limited exposure to dietary antigens. However, several reacted to foods that they tolerated before transplantation. The majority of patients had a family history of atopy, which might be another risk factor for food allergy after transplantation.<sup>1</sup>

These data suggest that children with food allergy after transplantation typically present within the first year after surgery and are typically allergic to multiple foods. Eosinophilic gastroenteropathy is common after transplantation and should be considered in all children with gastrointestinal symptoms undergoing transplantation. This study is the first to describe the long-term outcome of food allergy in this population, demonstrating that although a substantial number of food sensitivities are lost, most children remain sensitized to at least a subset of foods for an extended period.

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TABLE I. Patient characteristics

| Patient no. | Age [mo (sex)] at xplant | Type of xplant | Indication   | First sx of FA/first test confirm FA (mo post xplant) | Manifestations |            |            | Food allergies and sensitivities | Outgrow first food (mo post) | Foods outgrown    | Other atopy | Clinic/ phone FU (y post) |
|-------------|--------------------------|----------------|--------------|-------------------------------------------------------|----------------|------------|------------|----------------------------------|------------------------------|-------------------|-------------|---------------------------|
|             |                          |                |              |                                                       | GI             | EGID       | Other      |                                  |                              |                   |             |                           |
| 1           | 4.8 (F)                  | LR/OLT         | BA/FK        | 10.4/17.5*                                            | AP, V          | EE, EG, EC | A          | <b>E, M, P, S, W, O (6)</b>      | 79.2*                        | E, S, W, O (4)    | E, R        | 2.3/10.6                  |
| 2           | 6.6 (M)                  | Heart          | PA           | 5.4/34.8                                              | AP, BS, D, V   | EE, EG, EC |            | <b>E, M, P, S, W, O (9, 23)</b>  | 35.1                         | W, O (11)         |             | 6.2/6.9                   |
| 3           | 6.0 (F)                  | OLT            | BA           | 0.8/7.1                                               | BS, D, V       | EE, EG, EC | U, A, E    | <b>E, M, P</b>                   | 24.8                         | M                 | E, A, R     | 1.2/3.3                   |
| 4           | 8.3 (M)                  | LR             | BA/FK        | 0.3/3.8                                               | BS, D          | EE, EG, EC | U, W, E    | <b>E, M, P, O (1)</b>            | NA                           | None              |             | 1.9/                      |
| 5           | 22.8 (F)                 | OLT            | Citrulinemia | 1.1/33.28                                             | D              | EE, EG, EC |            | <b>E, M, P, S, W, O (4, 5)</b>   | NA                           | None              |             | 4.8/5.1                   |
| 6           | 7.8 (F)                  | L-SB           | SGS          | 9.2/10.0                                              | BS, V          | EE, EG     | U, A, W, N | <b>E, M, S, P, O (2, 3)</b>      | NA                           | None              |             | 1.4/3.9                   |
| 7           | 9.8 (F)                  | LR             | BA/FK        | 4.2/6.4                                               | D              | EE, EG     | U, A, W, N | <b>E, M, P</b>                   | 30.6                         | E, M              | E, A, R     | 7.1/7.7                   |
| 8           | 1.4 (M)                  | LR             | LF           | 2.0/9.9                                               | V              | EE, EG     | U          | <b>M</b>                         | NA                           | None              | E, A        | 1.1/                      |
| 9           | 2.7 (F)                  | SB             | SBO          | 64.0/79.5                                             |                | EE, EC     | A, U, W, E | <b>E, P, O (5)</b>               | 132.0                        | None              | E, R        | 7.3/12.3                  |
| 10          | 13.3 (F)                 | LR             | BA/FK        | 4.4/6.0                                               | AP, BS, V      | EG, EC     | A, W       | <b>E, M, P, S, W, O (1)</b>      | 13.1                         | E, M, S, W, O (1) | R           | 4.7/7.5                   |
| 11          | 10.9 (M)                 | L-SB           | SGS          | 58.1/69.1                                             | D              | EE         |            | <b>E, M, P, S, W, O (2, 3)</b>   | NA                           | None              |             | 7.1/                      |
| 12          | 8.7 (M)                  | LR             | BA/FK        | 11.0/11.6                                             | AP, BS, D, V   | EE         | U, A, W    | <b>E, M, P, S, W, O (6, 8)</b>   | 14.5                         | O (3)             |             | 1.8/2.2                   |
| 13          | 11.3 (M)                 | LR             | BA/FK        | 13.7/14.0                                             | V              | EG         | A          | <b>E, P</b>                      | NA                           | None              | E, A        | 4.7/11.1                  |
| 14          | 9.6 (F)                  | LR             | CC           | 6.0/7.3                                               | BS             | EG         | A, U, W, E | <b>E, M, S, P, O (3)</b>         | 36.2                         | Other (1)         | E, R        | 3.0/5.3                   |
| 15          | 16.4 (M)                 | OLT            | BA/FK        | 4.5/10.1                                              | BS, V          | EC         | U          | <b>E, M, P</b>                   | 12.0                         | M                 | R           | 0.8/3.1                   |
| 16          | 7.2 (M)                  | LR             | Hepatitis    | 4.8/8.9                                               | V              |            | A          | <b>E</b>                         | 55.2                         | E                 | A, R        | 4.6/4.6                   |
| 17          | 13.3 (M)                 | OLT            | TPN          | 0.1/9.9                                               | D              |            | A, U       | <b>E, M, P, W, O (8, 10)</b>     | NA                           | None              | E, R        | 1.0/                      |
| 18          | 9.0 (F)                  | LR             | BA/FK        | 5.5/10.8                                              | BS, D          |            |            | <b>E, M, S</b>                   | 47.7                         | M                 | R           | 1.4/6.0                   |
| 19          | 4.0 (M)                  | OLT            | BA/FK        | 39.9/42.0                                             | V              |            | E          | <b>E, M, P</b>                   | NA                           | P                 | E           | 3.5/6.1                   |
| 20          | 5.8 (M)                  | LR             | BA/FK        | 6.2/17.0                                              | V              |            | U, A, W, N | <b>E, M, P, O (2)</b>            | 19.0                         | None              | A           | 1.9/2.0                   |
| 21          | 24.6 (M)                 | L-SB           | SGS          | 8.2/8.3                                               | V              |            | A, U, W    | <b>E, M, P, S, W, O (2)</b>      | 59.0                         | E, M, W           | E, A        | 0.7/6.9                   |
| 22          | 101.9 (M)                | SB             | Dysmotility  | 6.0/6.0                                               |                |            | U          | <b>P</b>                         | 18.0                         | P                 |             | 0.5/7.5                   |
| 23          | 1.4 (F)                  | OLT            | Hemochrom    | 7.2/11.5                                              |                |            | U, A, E, W | <b>E, M, P, S, W, O (2, 8)</b>   | 26.1                         | S, O (6)          | E, A        | 5.8/6.1                   |
| 24          | 14.6 (F)                 | LR             | BA/FK        | 21.4/24.0                                             |                |            | A          | <b>E, P</b>                      | 31.4                         | E, P              | R           | 2.4/9.1                   |
| 25          | 5.6 (M)                  | OLT            | BA/FK        | 6.4/8.4                                               |                |            | U          | <b>M, S</b>                      | 13.9                         | S                 |             | 2.6/3.5                   |

Type of transplant (*xplant*): LR, living related liver; OLT, orthotopic liver; L-SB, liver–small bowel; SB, small bowel.

Indication: BA, biliary atresia; FK, failed Kasai; PA, pulmonary atresia; SGS, short gut syndrome; LF, liver failure; SBO, small bowel obstruction; CC, choledochal cyst; TPN, TPN cholestasis; Hemochrom, hemochromatosis.

First symptom (*sx*) of food allergy (FA)/first test that confirmed food allergy: months post transplantation.

Gastrointestinal (GI) manifestations: AP, abdominal pain; V, vomiting; BS, bloody stool; D, diarrhea.

Eosinophilic gastrointestinal disease (EGID): EE, eosinophilic esophagitis; EG, eosinophilic gastroenteritis; EC, eosinophilic colitis.

Other manifestations: A, angioedema; U, urticaria; E, eczema after ingestion of specific food; W, wheezing; N, nasal symptoms.

Food allergies and sensitivities: E, egg; M, milk; P, peanut; S, soy; W, wheat; O, other foods (number of other foods); foods provoking reactions are listed in bold, and sensitivities are shown in normal type.

Months after transplantation (*post*): first food allergy was outgrown (number of other food allergies outgrown).

Other atopic diseases (*atopy*) post transplantation: E, eczema; R, allergic rhinitis; A, asthma.

Follow-up (FU) in clinic or by telephone in years after transplantation (*post*).

\*Months from first transplantation.

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## METHODS

Patients were recruited from the Johns Hopkins University and Mount Sinai Pediatric Allergy Clinics between 1995 and 2007. Specific food allergies were diagnosed if a patient had a clear history of reaction after ingestion of the food along with a positive skin prick test response (wheal diameter,  $>3$  mm), a food-specific IgE level of greater than 0.35 kUA/L (UniCAP; Phadia, Portage, Mich), or both. They were considered to be sensitized to a food if they had a positive skin test response or specific IgE result and no known tolerance to that food. Patients were defined as having outgrown a food allergy when they were able to ingest the food without reaction after either clinic or home introductions. Challenges were offered when, in the judgment of the principal investigators, the patient had at least a 50% chance of passing the challenge. Patients with milk allergy, egg allergy, or both who are currently eating it in baked goods but not in a direct or concentrated form were considered to still be allergic for this analysis. The current status of the patients' food allergies, details of their reactions, family histories, and diagnoses of allergic rhinitis, eczema, and asthma were obtained from review of their medical records and confirmed by means of a telephone interview. Specific details of the transplantation and immunosuppression protocols were obtained from the patients' records. The study was approved by the Internal Review Boards of the Johns Hopkins and Mount Sinai Schools of Medicine.