

Development of multiple food allergies in children taking tacrolimus after heart and liver transplantation

Özdemir Ö, Arrey-Mensah A, Sorensen RU. Development of multiple food allergies in children taking tacrolimus after heart and liver transplantation.

Pediatr Transplantation 2006; 10: 380–383. © 2006 Blackwell Munksgaard

Abstract: Angioedema and chronic diarrhea in patients taking immunosuppressants are not always because of side effects and could be a new onset of food allergy. Our aim is to discuss the pathogenesis and treatment of the post-transplant development of food allergies. The first patient was receiving tacrolimus subsequent to heart transplantation and developed angioedema after consumption of dairy products at 12 months after transplantation. He was found to be allergic to multiple foods by both RAST and ImmunoCAP tests. The second patient with argininosuccinic aciduria, post-liver transplant, also received tacrolimus and developed chronic non-mucoid/bloody diarrhea at seven months following transplantation. ImmunoCAP test was positive only for egg white and peanuts. Biopsy showed eosinophilic infiltration of the mucosa from the stomach to the rectum. Elimination diets in both patients resolved the symptoms. These cases suggest a direct relationship between tacrolimus and development of food allergy.

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Key words: tacrolimus – macrocyclic lactone – transplant-acquired food allergy – pediatric transplantation – immunosuppressant

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Accepted for publication 2 November 2005

The acquisition of new food allergy after transplantation or transplant-acquired food allergy (TAFA) is now a well-described phenomenon, mainly reported in children. The transfer of allergy from a food-allergic liver donor to a previously non-allergic recipient (passive transfer) was first reported in 1997 (1). The phenomenon is consistent with previous findings of allergy transfer via bone marrow transplantation, and the finding that donor-derived stem cells present in a transplanted liver can sustain long-term hematopoiesis in a recipient (2). The picture is complicated by numerous case reports of TAFA after the receipt of liver grafts from donors with no history of food allergy. Later, some authors have suggested that immunosuppressive therapy, especially tacrolimus, may lead to TAFA.

Tacrolimus (FK506) is a macrocyclic lactone used extensively for immunosuppression in pe-

diatric transplant recipients. Tacrolimus-induced TAFA has been widely reported in young children despite wide use of tacrolimus in adults, in whom it occurs mostly via passive transfer. This suggests that the effects of tacrolimus might be more prominent in less mature immune and gastrointestinal systems (3). The estimated prevalence ranges from 10 to 17% in young children and 1.5% in adults (4). Although tacrolimus and cyclosporine-A (CsA) are calcineurin inhibitors and studies have demonstrated recovery of delayed-type hypersensitivity after transplantation, to date, there are only a few reports of food allergies in CsA-immunosuppressed patients despite its widespread use since 1984 (5). Here, we describe two cases presenting with different manifestations of food allergy despite use of the same immunosuppressive agent tacrolimus after different solid organ transplantation.

Case reports

The first patient is a two-yr-old Caucasian male who received heart transplantation at one month

Abbreviations: CsA, cyclosporine-A; immunoCAP, immunoCAP-specific IgE; RAST, radioallergosorbent test; TAFA, transplant-acquired food allergy

of age because of hypoplastic left heart from a cadaveric donor with no known history of atopy. He was receiving orally an immunosuppressive regimen of prednisone (0.1 mg/kg/day) and tacrolimus (Prograf[®], Fujisawa Healthcare, Deerfield, IL, USA) at 0.2 mg/kg/day for the last two yr. He was brought to us with a new onset of multiple food allergies.

He was breastfed until six months with age-appropriate supplemental formulas before and after transplantation. Personal history prior to transplantation and family history were negative for any allergic diseases/symptoms. Solid foods were started at the age of four months and continued till the age of 12 months without any problem. Then, he developed multiple episodes of acute urticarial rashes on his cheeks, trunk, and facial swelling (angioedema) after eating dairy products. Laboratory investigations revealed significant eosinophilia (23%) and total IgE of 4998 IU/mL. C3, C4, CH50, and plasma protein C1 esterase inhibitor (C1INH) levels were normal. Repeated IgE levels were 3025 and 1229 IU/mL. Radioallergosorbent test (RAST) and ImmunoCAP-specific IgE (ImmunoCAP) test results were positive for multiple foods (see Table 1) but negative for rice and corn. A strict elimination of dairy products, seafood, peanuts, tree nuts, soy, oat, wheat, and eggs was implemented. In the beginning of the avoidance diet when he accidentally ate foods including dairy products, similar symptoms occurred again a couple of times. The patient has been symptom free on diet since then.

Table 1. RAST and ImmunoCAP test results of our first patient are shown

ALLERGENS	First RAST	Second RAST	ImmunoCAP
<i>Pediatric foods</i>			
Egg whites	Class II	Class V	Class IV
Cow's milk	Class V	Class VI	Class V
Cheese	ND	ND	Class IV
Oats	ND	ND	Class IV
Wheat	ND	Class IV	Class III
Soybeans	ND	Class IV	Class III
Peanuts	Class III	Class VI	Class V
<i>Others</i>			
Shrimp	Negative	Class VI	Class IV
Crab and lobster	ND	ND	Class IV
Catfish	Negative	Negative	ND
Tuna	ND	ND	Class I
Pecans	Negative	Class II	Class I
Cashews	ND	Class III	Class II
Sesame seeds	ND	ND	Class III
Tomatoes	ND	ND	Class III

Class I = 0.35–0.70 kU/mL, Class II = 0.71–3.50 kU/mL, Class III = 3.51–17.50 kU/mL, Class IV = 17.51–50.00 kU/mL, Class V = 50.01–100 kU/mL, Class VI = > 100 kU/mL.

ND, not done; RAST, radioallergosorbent test; ImmunoCAP, ImmunoCAP Specific IgE test.

The second patient is a 3½-yr-old Caucasian female with argininosuccinic aciduria, status-post-liver transplant from a living-related, non-food-allergic donor, referred to us for evaluation and management of chronic diarrhea. She had undergone transplantation at 18 months of age and received the following immunosuppressive medications: tacrolimus at 0.2 mg/kg/day, mycophenolate mofetil (Cellcept[®], Hoffman-La Roche, Nutley, NJ, USA) at 20 mg/kg/day, and prednisone at 0.1 mg/kg/day. At seven months post-transplant, she developed chronic diarrhea, about 15 watery, non-mucoid, non-bloody stools daily for two months prior to evaluation. The diarrhea persisted despite rehydration, BRAT diet, and trial of Flagyl for two wk. In addition to a negative personal history prior to transplantation and a negative family history for any allergic diseases/symptoms, the patient had a clear history of ability to eat implicated foods before transplantation. Significant normal-negative laboratory results included the following: liver function studies, blood–urine culture, stool examinations for bacteria, viruses, ova, parasites, and occult blood. Significant abnormal results included the following: peripheral eosinophilia was 10% (800 cells/ μ L) and serum IgE level was 900 IU/mL. ImmunoCAP test was positive for egg white and peanuts (19, 28 kU/L, respectively). Tacrolimus level was elevated to 22 ng/mL on admission from her baseline of 12 ng/mL. Gastrointestinal biopsy showed eosinophilic infiltration of the mucosae (stomach to rectum). The patient was placed on a complete table diet excluding foods containing eggs and peanuts. Once she inadvertently ate foods including eggs and peanut traces, severe diarrhea episode recurred. She has been diarrhea free for over 24 months since then. Her tacrolimus level (12.8 ng/mL) also normalized after dietary intervention.

Discussion

Our patients developed food allergies at 12 and seven months post-transplant demonstrated by biopsy-proven eosinophilic gastroenteritis and elevated specific IgEs. Although we are aware of the less than perfect reliability of negative atopic history alone, especially in our first patient, as far as we know our patients were not predestined to develop food allergy as they did not have a positive family and personal history prior to transplantation. Elimination diet completely resolved their symptoms, consistent with the literature (6). To the best of our knowledge, multiple food allergies have not been reported in children taking tacrolimus after heart transplantation (1). Although

Asante-Korang et al. (7) reported eosinophilia, anemia, renal toxicity, hyperkalemia, and chronic diarrhea after heart transplantation, they did not mention the development of food allergy at all and held side effects of tacrolimus responsible for some of the symptoms suggesting allergy.

An elevated tacrolimus level in the second patient was because of chronic diarrhea secondary to food allergies, indicating that the etiology of the diarrhea is not always a side effect of tacrolimus. Tacrolimus is metabolized by the cytochrome P 450-CYP3A4 enzyme system, a substrate for multi-drug transporter P-glycoprotein. Both CYP3A4 and P-glycoprotein are present throughout the small intestine and colon. Studies have documented decreasing concentration of CYP3A4 enzymes from the duodenum to the colon, resulting in higher serum levels if the drug is given into the colon rather than the stomach (8). Diarrhea resulted in decreased gastrointestinal transit time, downregulation of CYP3A4, and diminished activity of P-gp, which enhanced oral availability by shunting tacrolimus to areas of lower intestinal metabolism. It is also noteworthy that the diarrhea subsided on elimination diet and the tacrolimus levels returned to baseline.

TAFAs may be caused by several mechanisms (1, 7, 9) in children after transplantation: (I) the recovery of delayed-type hypersensitivity in patients who could have been in a state of relative immune deficiency, e.g. cirrhosis before transplantation; (II) delayed manifestation of food allergy may be because of limited exposure to dietary allergens prior to transplant, which occurs especially in the context of anergy caused by chronic liver disease; (III) atopic background could be a contributing factor; (IV) intestinal injury as well as inhibition of cellular energy production by tacrolimus in the intestine plays a significant role allowing penetration of protein antigens (3) and skewing the immune response toward TH2 via induction of cytokines like IL-10; and (V) tacrolimus is a potent IL-2 inhibitor that may cause a TH2 shift with the development of allergy/atopy (10).

Although differing structurally, CsA and tacrolimus share a similar mechanism of action involving the inhibition of calcineurin, which results in repression of an early step of T-/B-cell activation and differentiation as well as T-cell cytokine production. Both agents are similar in that they bind to cytosolic proteins termed immunophilins, the resulting complex acting to inhibit the activity of calcineurin (11), but differ in that CsA binds to cyclophilins (CsA-binding protein) while tacrolimus binds to FKBP-12. Although their administration usual-

ly produces a therapeutic immunosuppression, the paradoxical marked elevation of IgE in patients has been reported, with FK506 exhibiting a greater effect than CsA (12). They both block the calcium-dependent signal transduction pathway by inhibiting the calcineurin and nuclear translocation of the nuclear factor of activated T cells (NFAT) necessary for gene activation by IL-2 and secondary TH1 cells facilitating the IgE response. IL-2 is crucial to the recruitment and activation of CD4 T cells and also, via the induction of other cytokines, orchestrates the actions of cytotoxic CD8 cells and natural killer cells, and also stimulates B-cell activation. IL-2 is produced by a subset of T lymphocytes, called TH1, which also produce IFN- γ , whereas IL-4, IL-5, IL-10, and IL-13 are produced by the subset of lymphocytes TH2, which do not secrete IL-2 and IFN- γ . Interleukin-4 and IL-13 induce secretion of IgE by promoting the switch of isotypes from immunoglobulin M to IgE on resting B cells, whereas IFN- γ inhibits both IL-4-induced and spontaneous IgE synthesis. Tacrolimus-induced imbalance between the TH1/TH2 subsets, or in IFN- γ and IL-4 production, results in a loss of control of the synthesis of IgE antibodies.

However, none of the hypotheses would clearly explain why food allergy develops specifically in tacrolimus- but not CsA-immunosuppressed children if the mechanism was only the TH1/TH2 imbalance and immunosuppression. We can hypothesize some reasons for this large difference: firstly, tacrolimus was found to be more potent between 10 and 100 times more than CsA in inhibiting IL-2 synthesis and in other functions (13). This is probably the reason why FK506-related food allergy resolves or occurs less in humans treated with CsA. Secondly, ubiquitously distributed cyclophilins and a slight difference in mode of action may also contribute this (11). Thirdly, one interesting finding is that tacrolimus exerts a unique effect on intestinal mucosa (3). Fourthly, there could also be something specific about the tacrolimus/FKBP12 interaction that affects atopy differently than does the CsA/cyclophilin interaction. For instance, CsA was demonstrated to have an anti-inflammatory effect and was also shown to inhibit IgE activation-induced cytokine transcripts and mediator release from human Fc epsilon R1+ cells (14).

In our patients, recovery of delayed-type hypersensitivity, delayed manifestations, as well as atopic background from personal past medical and family history appeared unlikely and cannot explain the picture. And we can speculate that tacrolimus-induced imbalance between the TH1/TH2 subsets,

or in IFN- γ and IL-4 production, with a loss of control of the synthesis of IgE antibodies as well as its probable effects on immature immune and intestinal system played a major role in the development of TAFA.

In conclusion, physicians need to be aware of a new onset atopy in symptomatic patients who are on immunosuppressive medications. The avoidance of the offending allergen can result in symptom resolution, improved quality of life, and even prevention of anaphylaxis.

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