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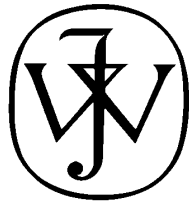
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The Development of Food Allergy After Liver Transplantation

Robert J. Boyle,¹ Winita Hardikar,² and Mimi L.K. Tang^{1,3}

The acquisition of new food allergy after orthotopic liver transplantation is now a well described phenomenon, mainly reported in children. The etiology of this phenomenon is at present unclear, but has been ascribed by some to tacrolimus treatment. Here we report a case of liver transplant acquired food allergy (LTFA) in a child who received a split liver graft. The case is remarkable for the absence of new food allergy in the adult recipient of the same graft. This suggests that host-specific factors play an important role in the development of food allergy after liver transplantation, and emphasizes the predisposition that children have toward this phenomenon. Possible mechanisms underlying the development of food allergy after liver transplantation are discussed. In conclusion, tacrolimus treatment alone cannot account for LTFA. Host factors such as the maturity of immune regulatory mechanisms are likely to play a critical role in the development of new food allergy after a liver transplant. (*Liver Transpl* 2005;11:000–000.)

The transfer of allergy from a food allergic liver donor to a previously nonallergic liver transplant recipient was 1st reported in 1997, and has subsequently been reported in 1 further case.^{1,2} 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.^{3,4} The picture is complicated by numerous case reports of liver transplant acquired food allergy (LTFA) after the receipt of liver grafts from donors with no documented history of food allergy.^{5–11} These latter cases have exclusively been reported in children, and all but 2 cases have been in patients receiving tacrolimus rather than cyclosporine treatment. This has led some authors to suggest that tacrolimus therapy may lead to LTFA due to its effects on intestinal mucosal barrier integrity and on T cell cytokine response profiles. We present a recent case of LTFA with the unique feature of differential LTFA development in 2 recipients of the same liver, which leads us to question the role of tacrolimus in the development of LTFA.

Case Report

Biliary atresia was diagnosed in a male infant presenting at 3 weeks age with conjugated hyperbilirubinemia. Kasai procedure was performed at 6 weeks age and produced partial drainage. He developed moderately severe eczema

during infancy. Deteriorating liver function from 17 months age led to orthotopic liver transplantation at 19 months with a split graft. Methylprednisolone, azathioprine and tacrolimus immunosuppression were used for the transplant, and tacrolimus therapy was continued at a dose of .2–.6 mg/kg/day for prophylaxis of chronic rejection, achieving a serum level of 6–17 $\mu\text{g/L}$. Prior to liver transplantation the boy ate a mixed diet including peanut and egg with no history of adverse food reaction. After transplantation he had a number of adverse reactions to foods. At 1 month posttransplant, he ate a peanut butter sandwich, his 1st exposure to peanut after the transplant. Within minutes, he developed facial and then truncal urticaria. He was treated with an antihistamine, and symptoms resolved within 2 hours. There was no associated angioedema, respiratory, or intestinal symptoms. At 15 months posttransplant, he ate a small quantity of cooked chicken egg in egg fried rice and within 1 minute developed a similar urticarial rash. Symptoms resolved within 2 hours, and again there was only cutaneous involvement. He had no history of exposure to other nuts, and had not otherwise ingested egg or peanut since transplantation. Investigation results 18 months after transplantation are shown in Table 1, and support a diagnosis of immunoglobulin E-mediated nut and egg allergy.

The remaining right lobe of the same liver was used to transplant a 35-year-old woman with fulminant hepatic failure of unknown cause. She was also treated with tacrolimus and methylprednisolone at the time of liver transplantation and continues tacrolimus at a dose of 4 mg/day, achieving a serum level of 9.5 $\mu\text{g/L}$. She had no prior history of allergic disease, and both before and after liver

Abbreviations: LTFA, liver transplant acquired food allergy.

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Table 1. Investigation Results of Child With LTAFa After Transplantation

Test	Allergen	Result
Skin prick test	Egg white	12 mm wheal
	Peanut	15 mm wheal
	Cashew	12 mm wheal
RAST test	Egg	13.00 kUA/L
	Peanut	8.86 kUA/L
Abbreviation: RAST, radioallergosorbent.		

transplantation ate a mixed diet including peanut and egg with no history of adverse reactions to food. Her investigation results 1 year after liver transplantation are shown in Table 2, and do not support a diagnosis of immunoglobulin E-mediated food allergy.

The liver donor was not recorded as having a history of allergic disease, but direct questioning of the donor's family revealed that she had suffered severe eczema in infancy which persisted to her death at 15 years of age. She also had a history of reactions to a number of foods in infancy, had been evaluated by an allergist during childhood, and was thought to be allergic to peanut. Further details of food reactions in infancy were not clearly recalled. The majority of these infant food reactions did not persist at the time of death, but the donor did complain of an itchy throat and abdominal discomfort when exposed to peanuts, and avoided nuts in general. There was no history of exposure to cashew nuts, and at 15 years the donor tolerated cooked egg in large quantities.

Discussion

LTAFa has been widely reported now, and is estimated to affect 10% of children who receive a liver transplant.⁷ The majority of cases reported have been in young children receiving tacrolimus immunosuppression, and in only 2 cases has passive transfer of food allergy from an allergic donor been documented. The case presented here is remarkable for the discordant development of LTAFa in 2 recipients of the same liver. This highlights the importance of transplant recipient specific factors in this condition. The only reports of LTAFa in adults have occurred via passive transfer from a food allergic liver donor, whereas LTAFa has been commonly reported in children receiving liver transplants from donors with no known food allergy. Those who develop LTAFa may also have greater background risk of allergic disease than those who fail to develop LTAFa. For example, in 1 series 50% of

those developing LTAFa had a family history of asthma and / or allergic rhinitis.⁷ So it seems that children, and possibly atopic children, are predisposed to develop LTAFa. *De novo* autoimmune hepatitis has also been reported in children after liver transplant, and it may be that children have a predisposition to autoimmune as well as to allergic disease in this context.^{12,13}

It is of interest to discuss the development of both peanut allergy and egg allergy in the case presented. The liver donor had a history consistent with peanut allergy, so peanut allergy may have been passively acquired as previously described. The etiology of the acquired egg allergy is more complex. There was a history of outgrown food allergies in the liver donor, who suffered severe eczema in infancy. Egg allergy is the most common food allergy in infants with severe eczema and affects over 70% of such infants.^{14,15} So the liver donor is likely to have outgrown a previous egg allergy. This suggests that immune factors in the donor that were suppressing their egg allergy were absent or insufficient in the child recipient, and this allowed the clinical manifestation of egg allergy in the child.

Food allergies are predominantly seen in young children and the reasons for this are still not well understood.¹⁶ Differences have been observed in both intestinal mucosal permeability and in lymphocyte responses between infants, young children, and adults.^{17–20} Altered maturation of lymphocyte responses has also been shown in children with allergic diseases.^{20–22} These studies suggest that immature infant immune responses play an important part in their predisposition to allergic disease. However, the normal maturation of many immune responses through childhood has not been elucidated. Of particular importance in the context of LTAFa, the evolution of allergen-specific regulatory T cell activity in childhood has not been well studied. Such activity is likely to account for the outgrowing of specific allergies.^{23–26} Those who lose a specific allergy through outgrowing it or through immunotherapy often do so by developing an active population

Table 2. Investigation Results of Adult Recipient of Liver Graft From the Same Donor

Test	Allergen	Result
Skin prick test	Egg white	Negative
	Peanut	Negative
	Cashew	Negative
RAST test	Egg	<.35 kUA/L
	Peanut	<.35 kUA/L
Abbreviation: RAST, radioallergosorbent.		

Table 3. Reported Cases of LTAFAs					
Case*	Primary diagnosis	Age at transplant	Months to food reaction	Food allergens	Donor allergic status
1	Biliary atresia	11 months	13	Peanut, egg	Nil
2	Biliary atresia	8 months	.5	Milk	Nil
3	Biliary atresia	9 months	2	Peanut	Nil
4	Biliary atresia	15 months	21	Peanut	Nil
5	Biliary atresia	4 months	12	Milk, egg, peanut	Nil
6	Biliary atresia	13 months	5	Peanut, egg, soy	Nil
7	OTC	30 months	31	Fish	Nil
8	OTC	36 months	3	Fish	Nil
9	Biliary atresia	7 months	5	Milk	Nil
10	Mitochondrial cytopathy	6 months	24	Egg†	Nil
11	Biliary atresia	14 months	30	Egg	Nil
12	Biliary atresia	14 months	21	Egg†	Nil
13	Alagille	36 months	30	Egg, soy, wheat, peanut, fish	Nil
14	Biliary atresia	15 months	13	Egg, kiwi	Nil
15	Biliary atresia	15 months	28	Egg, fish, nuts, milk	Nil
16	Biliary atresia	24 months	29	Nil‡	Nil
17	Biliary atresia	12 months	19	Lentil, mustard, almond	Nil
18	Biliary atresia	11 months	34	Multiple	Nil
19	Biliary atresia	12 months	18	Lentil,† pea†	Nil
20	Biliary atresia	9 months	45	Milk,† peanut,† soy†	Nil
21	Biliary atresia	18 months	41	Tuna	Nil
22	Hepatitis B/cirrhosis	60 years	1	Cashew, peanut	Peanut allergy
23	Hepatitis C/cirrhosis	35 years	3	Peanut	Peanut allergy
24	Fulminant hepatitis	13 years	6	Egg†	Nil
25	Cryptogenic cirrhosis	9 years	4	Peanut, egg	Nil
26	GSD-1	5 years	9	Egg, peanut, chicken	Nil
27	Biliary atresia	6 months	2	Milk	Nil
28	Biliary atresia	19 months	1	Peanut, egg	Peanut allergy

Abbreviations: OTC, ornithine transcarbamylase deficiency; GSD-1, glycogen storage disease type 1; IgE, immunoglobulin E.
 *References: Cases 1–6 (6); Cases 7, 8 (9); Case 9 (8); Cases 10–21 (7); Case 22 (2); Case 23 (1); Cases 24–26 (10); Case 27 (11); Case 28—this paper.
 †Insufficient information published to confirm IgE mediated food allergy.
 ‡History suggestive of food allergy but no food allergen identified.

of allergen-specific regulatory T cells rather than by clonal deletion of their allergen-specific Th2 cells.^{23,24,27} So one might hypothesize that liver transplantation from a donor who has outgrown a food allergy to a young recipient with immature regulatory T cell development can lead to reactivation of that food allergy in the graft recipient. Likewise the failure of an adult recipient of the same graft to develop food allergy might reflect the presence of mature allergen-

specific regulatory T cells capable of suppressing the clinical manifestation of food allergy.

This represents a new hypothesis for the etiology of LTAFAs, and should be discussed in the context of current hypotheses. Table 3 summarizes the clinical and immunological features of all reported cases of LTAFAs, and provides useful data to inform a discussion of the etiology of LTAFAs.

Tacrolimus as a Cause of LTAFa

Several authors have suggested that LTAFa represents an adverse effect of tacrolimus therapy.^{6–9} Tacrolimus is known to increase intestinal permeability, and inhibits interleukin 2 production; these effects in turn may lead to increased systemic exposure to allergenic peptides, and to a shift in T helper cell cytokine expression to a Th2 phenotype.²⁸ Some authors have reported a resolution of food allergic symptoms in patients with LTAFa who are subsequently switched from tacrolimus to cyclosporine immune suppression.⁷ However, transplant acquired food allergy has not been reported in renal or heart transplant patients treated with tacrolimus, nor to our knowledge has newly acquired food allergy been reported in those treated with tacrolimus for other indications. Moreover, 2 cases of LTAFa have been reported in patients taking cyclosporine as rejection prophylaxis.^{7,10} Tacrolimus is used more frequently than cyclosporine in liver transplant recipients, and the increased reporting of LTAFa in connection with tacrolimus may reflect this, rather than a causal relationship. Tacrolimus certainly does cause increased intestinal permeability in liver transplant recipients, but nonsteroidal antiinflammatory drugs increase intestinal permeability by a similar mechanism and have not been associated with the development of new food allergies.^{28,29} So while the immune and intestinal effects of tacrolimus and cyclosporine may play a part in the development of LTAFa, they are unlikely to be the sole explanation for this phenomenon.

The Immune Anergy of Liver Failure and LTAFa

Acute and chronic liver disease particularly cirrhosis have long been recognized to be associated with absent delayed cutaneous hypersensitivity responses.³⁰ So an alternative explanation for LTAFa development in children is that some food allergic children fail to manifest their food allergy due to the immune anergy caused by their liver failure. When this liver failure is corrected, the symptomatic food allergy may manifest itself. Children with biliary atresia are known to have a decrease in circulating naïve CD4⁺ / CD45RA⁺ T cells.^{31,32} However, it has recently been shown that the abnormal distribution of lymphocyte subsets seen in biliary atresia is unchanged after liver transplantation.³³ So these specific immune changes are unlikely to account for an unmasking of food allergy after liver transplantation. Moreover, the immune function abnormalities seen in biliary atresia and other childhood liver disorders are

not severe or specific enough to make this a likely explanation for the phenomenon of LTAFa.

The Immune Competence of the Liver

New food allergy has also rarely been reported after small bowel transplant.⁶ The fact that only liver, bone marrow, and small bowel transplants have been associated with newly acquired food allergy suggests a role for hematopoietic tissue in this phenomenon. These organs are all rich in lymphocytes and antigen-presenting cells, and their immunological competence is reflected in their well-recognized ability to cause graft vs. host disease.^{34,35} It seems that an interplay between hematopoietic cells from the transplanted organ and recipient-specific factors underlies the development of LTAFa.

Conclusions

To our knowledge, this is the 1st report of the discrepant development of food allergy in 2 recipients of a split liver graft. A review of published cases of LTAFa emphasizes the predominance of children and the absence of transplant acquired food allergy in cardiac, pulmonary, and renal transplant recipients. While immunosuppressive agents may play a part in the development of LTAFa, and direct transfer of allergy from an allergic donor is occasionally implicated, our case demonstrates that neither of these mechanisms is sufficient to explain the occurrence of most LTAFa. The case highlights the importance of transplant recipient-specific factors in the etiology of this condition. We suggest that LTAFa occurs when patients with immature immunoregulatory responses undergo liver transplantation and fail to suppress the clinical expression of new food allergies.

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