

Food allergy after liver transplantation in children: a prospective study

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Food allergy has been increasingly reported in children who had orthotopic liver transplantation (OLT). We aimed to conduct a prospective study to investigate the prevalence of sensitizations and food allergy in pediatric OLT recipients. We also aimed to identify potential risk factors. The study group consisted of 28 children (14 male, 14 female, mean age 4.96 ± 0.76 yrs) who had OLT. Total eosinophil count (TEC), total IgE, and specific IgEs were studied before and 3, 6, 12 months after OLT. Six patients (21%) developed multiple food allergies. Mean age of six patients at OLT who developed food allergy was younger compared to the non-food allergy group (10.2 months vs. 68.9 months, $p < 0.05$). Food allergy has been developed within 1 yr in 5, and in 20 months in one patient after OLT. All six patients had cow's milk and egg allergy after OLT. Five children developed wheat, one children developed lentil and another one developed peach allergy in addition to cow's milk and egg allergy. Out of six food-allergic patients after OLT, four children developed Epstein-Barr virus (EBV) infection prior to food allergy. Before OLT, TECs and total IgE levels were not differed among food allergic and non-food allergic patients ($p > 0.05$). Mean of TECs were significantly higher in food allergic group compared to non-food allergic group at each time point after OLT ($p < 0.05$). Though statistically insignificant, mean of total IgE levels were also higher in the food allergic group ($p > 0.05$). These findings suggest that food allergy should be considered after OLT in patients who are younger than 1 yr of age, who developed hypereosinophilia, high total IgE levels or EBV viremia.

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Life-threatening Type 1 allergic reactions due to common food allergens have been increasingly reported in children who had orthotopic liver-transplantation (OLT). (1–7). The first patient was reported in 1997 who had had anaphylactic reaction after OLT (3). The reaction was due to peanut allergy that was apparently transferred from transplanted liver derived from a 22-yr-old man who had died of anaphylactic reaction after peanut ingestion. However, consequent reports usually failed to disclose a relationship between donor's allergic status and acquired allergy that developed in recipients after OLT. It has been assumed that immunosuppressive

treatment that employed after transplantation facilitates allergic reactions in solid organ recipients. An increased prevalence of food allergy was noted in tacrolimus (Tac)-immunosuppressed young pediatric liver transplant recipients ranging from 10% to 17% in different series (6, 7). However, these reports revealed retrospective or cross-sectional studies on the occurrence of food allergy after OLT. Therefore, we decided to conduct a prospective longitudinal study to investigate the prevalence of sensitizations and food allergy in pediatric OLT recipients. We also aimed to identify potential risk factors.

Materials and methods

Patients

The study group consisted of 28 children (14 male, 14 female) who had OLT between September 2004 and February 2008 at Baskent University Hospital. In order to examine donors' allergic status; we included the patients aged between 6 months-16 yrs and had liver transplantation from living-related donors. We planned to exclude patients who had failed to follow-up for 1 yr. The study was approved by the local ethical committee.

After obtaining informed consent, total eosinophil count (TEC), total immunoglobulin (Ig) E, and specific IgEs were studied before and 3, 6, and 12 months after OLT. At the end of the first year after OLT, follow-up has been continued only in children with symptomatic food allergy by obtaining specific IgEs in every 6 months. Patients completed a structured interview based on the International Study of Asthma and Allergies in Childhood criteria on personal and family history of atopic diseases (8) as well as history of immunosuppressive medication at each time point. This interview has been obtained from their donors only before OLT. We also analyzed specific IgEs for the same food allergy panel in all donors before transplantation. We performed food specific skin prick tests in patients who developed food allergy and also in their donors.

Food allergy was diagnosed on the basis of a convincing history of immediate type reactions (flushing, urticaria, pruritis, and angioedema), chronic diarrhea without an evident cause, detectable serum food-specific IgE antibody, and/or resolution of symptoms after food avoidance. History for allergic reactions before OLT and Tac therapy, positive family histories for atopy, and the following data were recorded: indication for OLT, age at OLT, time from OLT to the onset of the first symptoms of food allergy, age at food allergy, concomitant therapy, treatment strategy, and outcome. Laboratory findings recorded at the time of food allergy included serum Tac level, TEC, serum levels of total IgE, and specific IgE antibodies to common food allergens.

Total eosinophil count and percentage have been studied by a hemocytometer (CellDyne 3700; Abbott Diagnostics, Abbott Park, IL, USA) that was calibrated each day. Eosinophilia was considered when the TEC in peripheral blood was over 500/mm³. Serology of Epstein-Barr virus (EBV) has been studied before OLT. Afterwards, viral load was checked by means of PCR when clinically indicated.

Total and specific IgE

Total IgE levels and specific IgE antibodies to a wide panel of food allergens were measured using commercial kits (Immulite 2000 3 g Allergy; Siemens Diagnostic Products Corporation, Los Angeles, CA, USA). Panels tested in all patients comprised cow's milk, hen's egg, beef, lamb, pork, chicken meat, codfish, shrimp, blue mussel, tuna, salmon, wheat, oat, corn, sesame seed, buckwheat, peanut, hazelnut, Brazil nut, almond, and coconut allergens. Specific IgE levels over 0.35 kUA/L were considered positive. When indicated by history, other food sensitizations that were not included in the panel were tested by skin prick test.

Statistics

Statistical calculations were performed using spss software (Statistical Package for the Social Sciences, version 13.0; SSPS Inc, Chicago, IL, USA). Distributions of the variables were analyzed by Shapiro-Wilk normality test. Within group comparisons and the change in TECs and serum total IgE levels were analyzed by the Friedman test. Between group (food allergic and non-food allergic) comparisons of TECs and serum total IgE levels were analyzed by Mann-Whitney *U*-test. Results for all measurements are expressed as mean $\pm$ s.d., median and quartiles (IQR). A *p*-value of 0.05 or less was considered statistically significant.

Results

Patient data

All 28 patients included in the study completed the 1 yr follow-up. The indication for liver transplantation was as follows; biliary atresia in five, progressive familial intrahepatic cholestasis (PFIC)-II in five, PFIC-III in one, tyrosinemia in four, fulminant liver failure due to hepatitis A in two, non-A-non-E hepatitis in two, Crigler-Najar syndrome type I in two, Wilson disease in two, cryptogenic cirrhosis in two, autoimmune hepatitis in one, alpha-1 antitrypsin deficiency in one, and neuroblastoma in one patient. Immunosuppressive therapy was based on Tac in 24 patients, Cyclosporin A (CsA) + mycophenolate mofetil in three, and sirolimus in one patient. Treatment was changed from Tac to CsA in two patients, and to sirolimus in one patient during follow-up in food allergy group. In all transplanted patients, the Tac and CsA serum blood levels were monitored and their levels were

maintained at 5–13 ng/ml and 100–300 ng/ml respectively. All six food allergic patients received Tac and two of them were switched to CsA after 3 and 6 months of Tac treatment. In the food allergic children, Tac, and CsA were adjusted to achieve a serum level of 10.43 ng/ml and 243.9 ng/ml, respectively. One patient who had food allergy and post-transplant lymphoproliferative disorder (PTLD) (Patient 3) was switched from Tac to sirolimus.

None of their donors had history of food allergy. Food specific IgE or skin prick tests were negative in all 28 donors including children who developed food allergy. Out of 28, three children had evidence for a positive family history of allergic disorders (allergic rhinitis, and asthma). Among these three children, only one developed food allergy. His father, also his donor, had allergic rhinitis (Patient 2). All patients were on a regular diet for their age group.

Prevalence and clinical features of transplant associated food allergy;

Twenty-eight children who had living-related OLT were included in the study. Mean follow-up time was 25.4 months (range 12–40 months). Six patients (21%) developed multiple food allergies. All children who developed food allergy were sensitized to more than one food. One patient who had cow's milk allergy before OLT developed multiple food allergies after transplantation (Patient 6). All six patients had cow's milk and egg allergy after OLT. Five children developed wheat, one children developed lentil and another one developed peach allergy in addition to cow's milk and egg (Tables 1 and 2). Skin

prick tests of these patients were consistent with specific IgE results.

The allergic symptoms were shown on Table 1. In the group of allergic children, a dietetic regimen that avoids the allergenic food was prescribed. Their symptoms resolved with appropriate elimination diets. Reproducibility of the reaction was confirmed by recurrence of clinical episodes after consumption of bread despite elimination in three children. We performed upper and lower endoscopic examinations in three of five patients who developed diarrhea. Endoscopic examinations were visually normal, however duodenal and colonic biopsies revealed eosinophilic colitis in two patients and eosinophilic duodenitis and colitis in one patient.

During follow-up, one children experienced recurrent flushing and pruritis after ingestion of peach (patient 5) and another one developed angioedema after ingestion of lentil (patient 4). In two patients, egg specific IgE and skin prick tests became negative 7 months (patient 4) and 18 months (patient 6) after the development of food allergy. Egg elimination has been ended after obtaining negative oral challenge test. Among non-food allergic patients, two developed asthma and another one developed atopic dermatitis. Inhalant and food allergen specific IgEs and skin prick tests were all negative. We are still following them with the same diagnosis for the last 2 yrs.

Timing of transplant associated food allergy

Mean age of whole study group at OLT was 4.96 ± 0.76 yrs. However, mean age of six patients at OLT who developed food allergy

Table 1. Characteristics of patients with food allergy

Patient no.	1	2	3	4	5	6
Sex	Male	Male	Male	Female	Female	Male
Primary diagnosis	Criggler Najjar typel	Tyrosinemia	Biliary atresia	Biliary atresia	PFIC II	PFIC II+ MA
Age at OLT (months)	9	8	10	12	6	16
Immunosuppressive treatment	Tac	Tac	Tac	Tac	Tac	Tac
Time from OLT to food allergy (months)	20	3	12	11	6	6
Age at food allergy (months)	29	13	22	23	12	22
Recurrent diarrhea	—	+	+	+	+	+
Flushing and pruritis	+	—	—	+	+	—
Angioedema	+	—	—	+	—	—
Time from OLT to EBV infection	18 months	—	10 months	—	3 months	4 months
Time from OLT to development of PTLD	—	—	10 months	—	3 months	—
Specific IgE + to food allergens positive	M, E, W	M, E, W	M, E, W	M, E, W	M, E	M, E, W
Skin tests to food allergens	M, E, W	M, E, W	M, E, W	M, E, W, L	M, E, P	M, E, W
Endoscopy	—	+	—	—	+	+
Histology (prior to diet change)	—	Eosinophilic duodenitis, colitis	—	—	Eosinophilic colitis	Eosinophilic colitis

PFIC, progressive familial intrahepatic cholestasis; OLT, orthotopic liver-transplantation; EBV, Epstein-Barr virus; PTLD, post-transplant lymphoproliferative disorder; MA, milk allergy; M, milk; W, wheat; E, egg; L, lentil; p, peach.

Table 2. Eosinophilia and total IgE levels before, and 3, 6, 12 months after OLT in patients with food allergy

Patient no.	1	2	3	4	5	6
Before OLT						
Eos. mm ³ (%)	141 (0.4)	1 (0.1)	51 (1)	423 (4)	685 (5)	12(1)
T. IgE (UI/ml)	20	28.5	15	55.9	86.7	63.2
Specific IgE	—	—	—	—	—	M
After OLT						
3 months						
Eos. mm ³ (%)	202 (1.8)	1575 (15)	251 (3.8)	576 (4)	226 (3)	117 (2)
T. IgE (UI/ml)	25	498.7	36.2	52.5	28.7	58.7
Specific IgE	—	M, W, E	—	—	—	M
6 months						
Eos. mm ³ (%)	169 (1.4)	628 (9)	349 (5.2)	373 (3.6)	1404 (18)	1250 (20)
T. IgE (UI/ml)	42.8	17	120.8	146.5	27	236.3
Specific IgE	—	M, W, E	—	—	M, E	M, W, E
12 months						
Eos. mm ³ (%)	173 (1.1)	350 (4)	1880 (13)	2010 (11)	734 (7)	594 (7)
T. IgE (UI/ml)	36.4	48	1120	477	157	96.2
Specific IgE	—	M, W, E	M, W, E	M, W, E, L	M, E, P	M, W, E

OLT, orthotopic liver-transplantation; Eos., eosinophil; T. IgE, total IgE; M, milk; W, wheat; E, egg; L, lentil; P, peach.

was younger compared to the non-food allergy group (Table 3). After OLT, food allergy developed within 1 yr in five, and 20 months in one patient (Patient 1). The time between transplantation and onset of food allergy was 3, 6 (in two patients), 11, 12, and 20 months (mean 9.7 months).

Risk factors for transplant associated food allergy

Total eosinophil counts are shown on Table 4. Before OLT, TECs and total IgE levels were not differed among food allergic and non-food allergic patients ($p > 0.05$). Mean of TECs were significantly higher in the food allergic group compared to non-food allergic group at each time point after OLT ($p < 0.05$). Though statistically insignificant, mean of total IgE levels were also higher in the food allergic group. Among non-food allergic group, two patients had eosin-

ophilia, five patients had high IgE levels for their age and one had both before OLT. Their IgE levels were within normal limits during follow-up after OLT. Only two patients who developed food allergy had high IgE levels for their age before OLT. In patients with food allergy, TECs and total IgE levels reached to a maximum at the time when they developed allergic symptoms. After introducing elimination diets, both TECs and total IgE levels decreased during the following 6–12 months.

There were nine patients who developed EBV infection after OLT. Among food allergic group, two children developed EBV infection and another two developed an EBV-associated PTLN prior to food allergy (Table 3). They all had hypereosinophilia and increased IgE levels. In non-food allergic group, there were five patients who developed EBV infection. None of them had hypereosinophilia, increased IgE levels or PTLN.

Table 3. Comparison of patients with or without food allergy

	Food allergy group n = 6 Mean $\pm$ s.d. Median, (IQR)	Non-food allergy group n = 22 Mean $\pm$ s.d. Median, (IQR)	p
Age at transplant (month)	10.2 $\pm$ 3.48 9.5 (7.5–13)	68.9 $\pm$ 10.1 73.5 (15–108)	<0.05
Sex (male/female)	4/2	10/12	NS
Presence of allergic disease in donor/recipient	1/1	2/3	NS
EBV infection after OLT	4	5	NS
Time from OLT to EBV infection (month)	8.75 $\pm$ 6.9 7 (3.25–16)	9.25 $\pm$ 7.1 8 (3.25–16.5)	NS
Age at EBV infection (month)	10.25 $\pm$ 4.2 9.5 (6.75–14.5)	60.0 $\pm$ 67.6 15 (11–131)	NS

s.d., standard deviation; IQR, inter-quartile range; OLT, orthotopic liver-transplantation; EBV, Epstein-Barr virus; NS: non-significant.

Table 4. Eosinophilia during OLT

Eosinophilia	Food allergy group n = 6	Non-food allergy group n = 22	All patients n = 28
	Mean $\pm$ s.d. mm ³ (%) Median, [IQR]	Mean $\pm$ s.d. mm ³ (%) Median, [IQR]	Mean $\pm$ s.d. mm ³ (%) Median, [IQR]
Before OLT	220 $\pm$ 275 (1.7 $\pm$ 1.8)† 96 [11.5–488.5]	184 $\pm$ 202 (2.4 $\pm$ 2) 93.4 [37.2–272.5]	191 $\pm$ 214 (2.3 $\pm$ 2) 93.4 [31.7–340.5]
After OLT 3 months	762 $\pm$ 769 (6.28 $\pm$ 6.1)** 401.3 [179.3–1651.3]	120 $\pm$ 118 (1.7 $\pm$ 1.8) 64.8 [24.3–209.0]	258 $\pm$ 458 (2.74 $\pm$ 3.6) 125.8 [36.3–237.2]
After OLT 6 months	1399 $\pm$ 926 (12.8 $\pm$ 7.35)***,† 1327.0 [671.3–2125.3]	153 $\pm$ 161 (2.4 $\pm$ 2) 121.4 [27.02–191.0]	420 $\pm$ 670 (4.66 $\pm$ 5.7) 143.0 [48.7–473.4]
After OLT 12 months	549 $\pm$ 205 (5.6 $\pm$ 1.3)* 594.0 [347.0–730.0]	214 $\pm$ 280 (3.1 $\pm$ 3.2) 94.6 [55.6–222.5]	290 $\pm$ 297 (3.5 $\pm$ 3.1) 157.5 [64.1–545.5]

s.d., standard deviation; IQR, inter-quartile range; OLT, orthotopic liver-transplantation.

*p < 0.05 between food allergy and non-food allergy groups.

**p < 0.01 between food allergy and non-food allergy groups.

***p < 0.001 between food allergy and non-food allergy groups.

†p < 0.01 among OLT groups.

Only one of the non-food allergic patients was below 1 yr of age and the rest of them were 5–10 yrs of age at the time of OLT.

Discussion

Transplant-acquired food allergy (TAFA) is frequently reported in children with no history of food allergy. This is the first prospective study concerning TAFA in children who had OLT. The estimated prevalence of TAFA in retrospective and cross-sectional studies revealed ranges from 10 to 17% in young children and 1.5% in adults (7). In our study, six patients (21%) developed multiple food allergies within approximately 2 yrs of follow up, that was compatible with recent studies. History of allergic disorders and a panel of food specific IgEs were negative before transplantation in our patients, except milk allergy in one child who developed multiple food allergies after OLT. Since most of the studies rely on retrospective reports, our finding is the first objective data supporting that food allergy in these patients is an acquired event. As all the transplantations were performed from live donors, we were able to evaluate food allergy in donors and possible transmission of allergy to recipients. Some previous reports suggested transmittable allergy from donors to recipients. Passive transfer of food-antigen-specific IgE or food-antigen-specific lymphocytes from a sensitized donor has been accused in this phenomenon (3, 5). However, none of the donors in our study had specific IgE or positive skin prick test against food antigens that caused allergy in their recipients. Furthermore, panel of food-specific IgEs were also negative in all our donors. These

results suggest that food allergy in our patients was not transmitted from their donors.

Age at transplant had previously been noted to be a risk factor for development of TAFA. In our study, food allergy has been developed mostly in children younger than 1 yr of age (mean age 0.84 yrs) that was compatible with most of the reports in literature (6, 7, 9, 10). We observed food allergy in five of 10 patients who were younger than 1 yr of age. Only one patient who had previous milk allergy was 1.5-yr-old at transplant (Patient 6), nevertheless younger than the mean age of non-food allergic patients. It is well known that due to immaturity of oral tolerance, food allergy is more prevalent in infants. Oral tolerance refers to ignorance of antigenic food proteins by systemic immune system. Under normal circumstances, immunologic and functional barriers are capable of distinguish between food and pathogenic organisms (11). Breakdown of oral tolerance that leads to food allergy occurs mostly in young children as a consequence of different mechanisms. These mechanisms include lack of protective factors such as IgA or suppressive CD8+ lymphocytes, increased antigen resorption caused by increased intestinal permeability, and loss of mucosal integrity attributable to intestinal infections or drugs (11). Tacrolimus, the most frequently used immunosuppressive drug in our patients, may increase intestinal permeability and cause immunodysregulation with Th2 skewing (12). Transplant-acquired food allergy has not been reported in kidney transplant recipients reflecting the role of the liver in immune tolerance induction to food antigens during childhood. In conclusion, young age, immune suppressive drugs, gastrointestinal infections, and EBV

infection may be the reasons for development of food allergy due to breakdown of oral tolerance in our patients.

The time to clinical symptoms of food allergy after OLT varies in different reports. In two recent studies, this interval in patients with food-induced angioedema and eosinophilic gastroenterocolitis was 3.75 yrs and 20 months, respectively (6, 13). These results were longer than those observed in our patients (mean 9.7 months). Since angioedema and chronic diarrhea are dramatic and easily recognizable symptoms of food allergy, the reason for discrepancy between our study and these two studies may be due to underestimation of less severe symptoms of food allergy. Also, retrospective design of these studies may be another reason for loss of relevant data. In our longitudinal study, we detected food allergy in some patients with milder symptoms such as pruritis, and flushing.

In most of our patients timing of food related allergic reactions was consistent with an IgE-mediated process and they have manifested high eosinophil counts and elevated total and specific IgE levels compatible with recent studies (6, 9, 13). However, hypereosinophilia and elevated serum IgE levels may also occur due to acute rejection and immune suppressive drugs such as Tac and CsA after OLT (14, 15). In our study group, TECs and total IgE levels were not differed among patients with food allergy and non-food allergy before OLT. After OLT, TECs were significantly higher in all six patients with food allergy compared to those without food allergy. Furthermore, TECs reached to a maximum at the time of allergic manifestations and decreased after elimination of food that caused allergy. We did not observe such an increase in TECs in our non-food allergic patients. These findings imply that hypereosinophilia observed in our patients was not caused by the immunosuppressive drugs or acute rejection. Therefore we suggest that acute increase in the TECs together with relevant symptoms may be an indicator for food allergy in patients after OLT, especially in young infants.

Our patients developed allergy to most frequently consumed foods in their age group such as milk, egg, and wheat. Although the most frequent symptom of food allergy is skin findings in children, our five patients who developed food allergy exhibited vomiting and diarrhea as initial symptoms. These patients also had hypereosinophilia and elevated IgE levels. Endoscopic examinations in three of them revealed eosinophilic gastroenteritis. Another report of eosinophilic gastroenteritis in pediatric liver transplant

recipients noted the development of peripheral eosinophilia in 28% of patients and evidence of eosinophilic gastroenteritis in 26% (16). Although the number of patients who developed food allergy after OLT is limited in most of the reports as well as our study, it seems that gastrointestinal symptoms are more frequently observed symptoms of food allergy in patients after OLT.

One of our interesting findings was development of EBV infection in four food-allergic patients prior to the development of food allergy. There are a few studies addressing relationship between EBV infection and following occurrence of allergic disorders. There are reports advocating that Th2 immune response could be triggered after EBV infection. Mechanisms causing this reaction include induction of IL-10 in infected cells, production of IL-10 analogue, induction of B-cell proliferation, and polyclonal antibody production (17, 18). It has been suggested that EBV infection can result in atopic disease (19). A recent retrospective study suggested that after OLT, patients with peripheral eosinophilia experienced more frequent episodes of detectable EBV viral load (16). Our patients also had peripheral hypereosinophilia when they developed EBV infection or PTLT. However, none of the non-food allergic patients with EBV infection had hypereosinophilia. Although the number of patients in our study is limited, we suggest patients who developed increased EBV load and peripheral eosinophilia should be evaluated for possible allergic reactions including food allergy.

In conclusion, our study suggests that TAFA should be considered after OLT in patients who are younger than 1 yr of age, who developed hypereosinophilia, high total IgE levels or EBV viremia.

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