Original Article

Factors Associated with Development of Food Allergy in Young Children after Liver Transplantation: A Retrospective Analysis of 10 Years' Experience

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What is already known about this topic? The development of food allergy after liver transplantation is increasingly frequent, mainly in young children receiving tacrolimus therapy. However, the infants and young children who are at risk of food allergy remain to be fully characterized.

What does this article add to our knowledge? Eczema at liver transplantation was identified as a significant risk factor for the development of IgE-mediated, but not non−IgE-mediated food allergy after liver transplantation. This implies the involvement of different sensitization pathways in IgE-mediated and non−IgE-mediated food allergy.

How does this study impact current management guidelines? Our findings may contribute to identification of the susceptible subgroup of young children requiring special caution at liver transplantation and to the establishment of an effective strategy for prevention of food allergy after liver transplantation.

BACKGROUND: Although development of food allergy after liver transplantation is most commonly described in young children, little is known about identification of young liver-transplant recipients who are at risk of food allergy.

OBJECTIVE: This study aimed to identify the types of food allergy and the risk factors for the development of food allergy after liver transplantation.

METHODS: This was a retrospective analysis of pediatric liver transplant recipients in our organ transplantation center during 2005-2015. Relevant data of all patients who underwent liver transplantation were extracted from the center's database and the medical records. Differences in patients' characteristics were evaluated for associations between food allergy and potential risk factors. Logistic regression models were used to calculate adjusted odds ratios.

RESULTS: We obtained the data of 206 patients under 36 months of age, 42 (20.4%) of whom developed food allergy after liver transplantation. The allergy was IgE-mediated-only in 30 (71.4%) and non−IgE-mediated-only in 10 (23.8%). Multivariate analysis found eczema at liver transplantation to be a significant risk factor (adjusted odds ratio [aOR] 2.41, 95% confidence interval [CI] 1.14-4.77, $P < .05$). Eczema increased the risk of developing IgE-mediated food allergy after liver transplantation (aOR 3.13, 95% CI 1.41-6.93, $P < .01$), whereas no significant association was observed with non−IgE-mediated food allergy.

CONCLUSIONS: We identified eczema at liver transplantation as a significant risk factor for the development of IgE-mediated food allergy after liver transplantation, but not non−IgE-mediated food allergy. Our findings may contribute to a better understanding of the susceptible subgroup requiring special caution and to the establishment of effective strategies for prevention. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1698-706)

Key words: *Eczema; Epicutaneous sensitization; Food allergy; Liver transplantation; Non−IgE-mediated food allergy*

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Abbreviations used
CI- Confidence interval
EGID- Eosinophilic gastrointestinal disorder
GI- Gastrointestinal
LDLT- Living-donor liver transplantation
LSEC- Liver sinusoidal endothelial cell
NCCHD- National Center for Child Health and Development
OFC- Oral food challenge
OR- Odds ratio
PPV- Positive predictive value

The development of food allergy after solid organ transplantation has been increasing, especially in young children after liver transplantation.[1] Recently, the prevalence of food allergy in young children was estimated at approximately 5% to 10% for IgE-mediated and 0.2% non−IgE-mediated food allergy, respectively.[2,3] Among young children after liver transplantation, the estimated prevalence of food allergy (approximately 6% to 38%) is considered to be higher than in the general population.[4-6] Although the reported prevalence varies because of differences in the diagnostic criteria, study design, and genetic/environmental factors, the apparent recent increase in the prevalence of food allergy after liver transplantation in children is difficult to explain.

Complex mechanisms seem to be involved in the development of food allergy after liver transplantation. A number of mechanisms have been proposed, including passive transfer of donor allergen-specific IgE and/or lymphocytes, use of immunosuppressants, and a special, inherent risk associated with liver transplantation.[7-12] Especially tacrolimus is thought to be one of the main causative factors due to increased intestinal permeability and/or facilitated type 2 inflammation.[13] In addition, studies have highlighted transplant recipient-specific factors, especially younger age.[14] However, little is known about the types of food allergy, the risk factors, and sensitization pathways in young liver transplant recipients.

Currently, tacrolimus immunosuppressive therapy is widely used as first-line therapy in post-liver-transplantation settings. Identification of infants and young children receiving tacrolimus immunosuppressive therapy who are at risk of food allergy after liver transplantation is of particular interest so that their physicians will be on guard. Therefore, our study aimed to identify the types of food allergy and the risk factors for the development of food allergy after liver transplantation in a large cohort from our 10 years of experience in liver transplantation in children.

METHODS

Study design and setting

This study was approved by the Ethics Committee of the National Center for Child Health and Development (NCCHD) (Acceptance Number #59). It was a retrospective analysis of pediatric liver transplant recipients in our organ transplantation center from November 2005 through June 2015, using the transplantation center's database. The medical records of all children who underwent liver transplantation were reviewed independently by 2 board-certified pediatricians (MM, ON) and confirmed by 2 board-certified allergy specialists (TS, IN). Analysis was restricted to young children under 36 months of age to evaluate this high-risk patient group.

NCCHD's transplantation center has performed living-donor liver transplants (LDLT) for patients with severe liver disease since 2005. Including cadaveric liver transplantations, we perform 45 to 50 liver transplant operations per year, which is the largest number in the world. Our LDLT graft survival rate is one of the highest in the world, and the 5-year survival rate is approximately 90%. All patients undergo LDLT by a standard procedure, as previously reported.[15] No venovenous bypass is used, because total clamping of the inferior vena cava is not necessary. Tacrolimus and low-dose steroids are used for initial immunosuppression. Tacrolimus administration is started on the day after transplantation. The target whole blood trough level of tacrolimus is 10 to 12 ng/mL for the first 2 weeks, approximately 10 ng/mL for the following 2 weeks, and 8 to 10 ng/mL thereafter. Treatment with steroids is initiated at the time of graft reperfusion at a dose of 10 mg/kg, which is then reduced by 1.0 to 0.3 mg/kg/day during the first month and withdrawn within the first 3 months.

Definition of food allergy

The development of food allergy is evaluated after liver transplantation. Specific food allergies are diagnosed when a patient has a clear history of reaction after ingestion of the food, along with a positive reaction in an oral food challenge (OFC) test. If an OFC cannot be performed (as was the case in many of the children included in this study), then the diagnosis is supported by a positive food-specific IgE test, represented by a serum IgE level greater than the established specific IgE cutoff,[16] for example, a 95% positive predictive value (PPV) for egg, milk, peanut, and fish, or 70% PPV for soy and wheat. The test is performed using an ImmunoCAP Specific IgE kit (CAP-FEIA; Thermo Scientific, Uppsala, Sweden). For foods other than the above, a specific IgE level of greater than 0.35 kUA/L is considered as positive. Based on the time course, food allergy is generally roughly divided into immediate-type and non−immediate-type reactions. In this study, these 2 types of reactions are defined as follows: immediate reactions, manifesting within 2 hours (IgE-mediated), and non−immediate-type reactions, manifesting within 2 to 24 hours (non−IgE-mediated). Non−IgE-mediated food allergy is also diagnosed based on Powell's criteria[17] and a recent modification by Leonard et al:[18] (1) repeated exposure to the causative food elicits gastrointestinal (GI) symptoms without any alternative cause, (2) absence of symptoms that may suggest an IgE-mediated reaction, (3) removal of the causative food results in resolution of the symptoms, and (4) re-exposure or OFC elicits typical symptoms.

Data collection

The following factors, known to be associated with food allergy after liver transplantation, were extracted from the medical record database and used as potential confounders: gender, age at liver transplantation, eczema at liver transplantation (based on the physician's diagnosis), season of birth, parental history of food allergies, donor's age, indication of liver transplantation, previous history of intestinal surgery before the liver transplantation, past infection with Epstein-Barr virus and/or cytomegalovirus, and laboratory data before transplantation, such as the white blood cell count, peripheral eosinophil count, transaminases, total bilirubin, and tacrolimus trough levels.

Statistical analysis

For statistical analysis, differences in the children's characteristics were tested as follows to evaluate for associations of food allergy with other potential risk factors. Univariate analysis was performed using

TABLE I. Clinical characteristics of the patients

	Total (N = 206)	
	n	%
Gender		
Male	88	42.7
Female	118	57.3
Age at liver transplantation		
Median months	9	
Interquartile range (IQR)	6.0-14.3	
<12 mo	135	65.5
≥12 mo	71	34.5
Eczema at liver transplantation		
No	141	68.4
Yes	65	31.6
Season of birth		
Spring-Summer	117	56.8
Fall-Winter	89	43.2
Parental history of food allergies		
No	187	90.8
Yes	19	9.2
Donor's age		
Median (y)	33.0	
IQR	30.0-38.0	
Indication for liver transplantation		
Biliary atresia	111	53.9
Others	95	46.1
Fulminant hepatic failure	35	17.0
Congenital metabolic disease	41	20.0
Liver cirrhosis	2	1.0
Liver fibrosis	1	0.5
Congenital absence of portal vein	2	1.0
Hepatoblastoma	10	4.9
Alagille	3	1.5
Caroli disease	1	0.5
Previous history of intestinal surgery		
No	65	31.6
Yes	141	68.4
Past infection		
Epstein-Barr virus		
No	80	38.8
Yes	126	61.2
Cytomegalovirus		
No	63	30.6
Yes	143	69.4
Laboratory data at liver transplantation		
WBC (/μL)		
Median	7,220	
IQR	5,127-10,297	
Peripheral eosinophil count (/μL)		
Median	188	
IQR	78.1-367	
Aspartate aminotransferase (IU/L)		
Median	115	
IQR	49.8-189	
Alanine aminotransferase (IU/L)		
Median	69.0	
IQR	29.8-135	
Total bilirubin (mg/dL)		
Median	6.3	
IQR	1.0-13.3	
Tacrolimus trough level after liver transplantation (ng/mL)		
At 7 d		
Median	9.9	
IQR	7.5-12.5	
At 14 d		
Median	9.2	
IQR	7.3-11.8	
Development of food allergy after liver transplantation		
No	164	79.6
Yes	42	20.4
IgE-mediated-only	30	71.4
Non−IgE-mediated-only	10	23.8
Changed from non−IgE-mediated to IgE-mediated	2	4.8

the chi-square test with Fisher's exact test and Mann-Whitney *U* test for categorical variables and continuous variables, respectively. In addition, a multivariate logistic regression model was applied for all the potential risk/confounding factors described in a recent review article.[6] Goodness-of-fit was assessed by Hosmer-Lemeshow tests. Multiple logistic regression was performed to estimate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs). All statistical analyses were performed using SPSS version 19 (IBM, Armonk, NY) with a 2-sided 5% significance level.

RESULTS

Characteristics of the patients

We obtained the data of 206 patients under 36 months of age. Table I summarizes their clinical characteristics. The most common indication for liver transplantation was biliary atresia (111 patients, 53.9%). The median age at transplantation was 9 months, and infants accounted for 65.5%. Nineteen children had a family or donor history of food allergy.

Development of food allergy after liver transplantation

Forty-two patients developed food allergy after liver transplantation, and the cumulative incidence was 20.4% (Table I). Among the 42 patients, the food allergy was diagnosed as IgE-mediated-only in 30 (71.4%) patients and non−IgE-mediated-only in 10 (23.8%) patients. The other 2 patients changed from the non−IgE-mediated to the IgE-mediated phenotype during treatment. The patients' median age at transplantation was 8 months (IgE-mediated, 8.5 months; non−IgE-mediated, 6 months). The median duration from transplantation to the recognition of food allergy was 3.0 months (interquartile range, 1-8 months). Six patients were diagnosed by OFC, whereas the other patients were diagnosed on the basis of a 95% PPV of

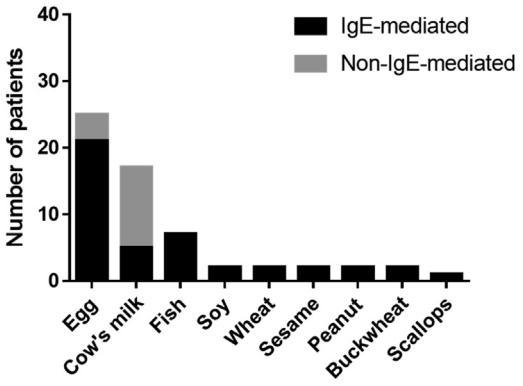

FIGURE 1. Causative foods of food allergy after liver transplantation.

serum specific IgE level. The main allergic manifestations were urticaria and angioedema (86.7%), and GI symptoms (63.3%).

Figure 1 shows the causative foods. The most common allergens were egg and cow's milk (59.5% and 40.5%, respectively), with 21 patients reacting to more than 2 allergens. Egg was more likely to cause IgE-mediated food allergy: IgE-mediated, 21 patients (65.6%), versus non−IgE-mediated, 4 patients (33.3%). Conversely, cow's milk was more likely to cause non−IgE-mediated allergy: IgE-mediated, 5 (15.6%), versus non−IgE-mediated, 12 (100%).

Multiple logistic regression analysis of the development of food allergy in young children after liver transplantation

Univariate analysis found that eczema at liver transplantation and the peripheral eosinophil count were associated with a higher risk of development of food allergy after liver transplantation (Table II). Multiple logistic regression analysis was performed to identify variables that represented an independent risk for the development of food allergy. Among the confounding factors, eczema at liver transplantation remained a significant risk factor in multivariate analysis (adjusted odds ratio [aOR] 2.41, 95% CI 1.14-4.77, $P < .05$) (Table III).

Comparison of patients with IgE-mediated food allergy and non−IgE-mediated food allergy after liver transplantation

Based on the results of logistic regression analysis, eczema at liver transplantation was a significant risk factor for food allergy. To further clarify the contribution of eczema, we performed subgroup analysis stratified for IgE mediation. Interestingly, patients with eczema at liver transplantation were more likely to develop IgE-mediated food allergy after liver transplantation (aOR 3.13, 95% CI 1.41-6.93, $P < .01$), whereas no statistically significant association was observed in patients with non−IgE-mediated food allergy (Figure 2). Table IV compares patients with IgE-mediated and non−IgE-mediated food allergy after liver transplantation. The groups showed no significant differences except for age at liver transplantation and eczema at liver transplantation ($P = .048$, $P = .041$, respectively) (Table IV).

DISCUSSION

Our analyses demonstrated 2 important clinical findings. First, eczema at liver transplantation was a significant risk factor for the development of food allergy, especially IgE-mediated food allergy, after liver transplantation. This finding is of particular interest to physicians because it could help to identify those children who require caution for possible food allergy at transplantation. Moreover, eczema may be a modifiable risk factor for food allergy, even if we cannot rule out the possibility that patients who developed IgE-mediated food allergy have already become atopic and are progressing down the "atopic march." Second, the development of non−IgE-mediated food allergy was more frequent after liver transplantation. Moreover, various factors such as genetic/environmental factors might be involved, and because eczema was not significantly associated with non−IgE-mediated food allergy, there may be different sensitization pathways for IgE-mediated and non−IgE-mediated food allergy after liver transplantation.

Our findings suggest that eczema at liver transplantation became a significant risk factor for the development of food allergy after liver transplantation. To date, a few studies have examined for such an association. Shroff et al[4] investigated atopic manifestations in children who had undergone solid organ liver transplant (N = 175) and found a correlation of food allergy with eczema ($P = .058$). Wisniewski et al[19] also examined for risk factors for the development of food allergy and eosinophilic gastrointestinal disorder (EGID) in 352 pediatric liver transplantation recipients (30 patients with food allergies and 60 selected patients without food allergies as controls), and similarly found an association of food allergy with lifetime eczema ($P < .001$). There is thus agreement among these studies, but our research has several distinguishing features and strengths, such as using a large cohort of this high-risk group, investigating potential risk factors using the information recorded at transplantation and performing multivariate logistic regression analysis to adjust for relevant confounders. Thus, our findings in this large cohort clearly confirm in more detail the association of eczema with food allergy and have great potential for identification of small children who are at risk of food allergy after liver transplantation.

It is of note that significantly higher odds ratios of eczema were seen for IgE-mediated food allergy, suggesting that the transepicutaneous pathway may be a major sensitization pathway involved in this form of food allergy in this population. Recent evidence has begun to highlight the critical role of the skin in the pathogenesis of IgE-mediated food allergy. Several clinical and experimental studies suggest that sensitization to food allergens can occur by environmental allergen exposure through eczematous skin.[20] A recent study demonstrated that Langerhans cells extend dendrites that vertically penetrate tight junctions to the skin surface in patients with atopic dermatitis, suggesting that eczema is important in the development of sensitization.[21] Thus, if food sensitization and/or allergy are in part due to damage to the skin barrier, it may be important to use topical ointments to repair the barrier and restore epidermal integrity. Indeed, we recently reported that the daily application of a moisturizer to neonates with a family history of atopic dermatitis during the first 32 weeks of life can significantly reduce the risk of atopic dermatitis/eczema.[22] Therefore, skin barrier repair might play an important role in preventing food allergy after liver transplantation.

In this study, a majority of the food allergy cases that manifested after liver transplantation were IgE-mediated, but its prevalence was not significantly higher than in the general population.[2,23] By contrast, the prevalence of non−IgE-mediated allergy was significantly higher than in the general population.[3] "Non−IgE-mediated GI food allergy," which might be the

TABLE II. Comparison of clinical characteristics between the study population (N = 206) stratified for children who developed food allergy (cases) and those who did not develop food allergy (controls) after liver transplantation

	Did not develop food allergy (n = 164)		Developed food allergy (n = 42)		
	n	%	n	%	*P* value
Gender					
Male	96	58.5	22	52.4	.47
Female	68	41.5	20	47.6	
Age at liver transplantation					
Median months	9		8		.44
Interquartile range (IQR)	6.0-16.0		6.0-13.0		
<12 mo	105	64.0	30	71.4	.37
≥12 mo	59	36.0	12	28.6	
Eczema at liver transplantation					
No	119	72.6	18	42.9	.01
Yes	45	27.4	24	57.1	
Season of birth					
Spring-Summer	91	55.5	26	61.9	.45
Fall-Winter	73	44.5	16	38.1	
Parental history of food allergies					
No	151	92.1	36	85.7	.20
Yes	13	7.9	6	14.3	
Donor's age					
Median (y)	33		35		.49
IQR	33.0-37.8		29.8-38.3		
Indication of liver transplantation					
Biliary atresia	92	52.0	24	57.1	.64
Others	85	48.0	18	42.9	
Fulminant hepatic failure	29	16.4	10	23.8	
Congenital metabolic disease	39	22.0	5	11.9	
Liver cirrhosis	2	1.1	1	2.4	
Liver fibrosis	1	0.6	0	0.0	
Congenital absence of portal vein	2	1.1	0	0.0	
Hepatoblastoma	10	5.6	0	0.0	
Alagille	1	0.6	2	4.8	
Caroli disease	1	0.6	0	0.0	
Previous history of intestinal surgery					
No	51	31.1	14	33.3	.78
Yes	113	68.9	28	66.7	
Past infection					
Epstein-Barr virus					
No	60	36.6	20	47.6	.22
Yes	104	63.4	22	52.4	
Cytomegalovirus					
No	52	31.7	11	26.2	.58
Yes	112	68.3	31	73.8	
Laboratory data at liver transplantation					
WBC (/μL)					
Median	7,095		7,700		.15
IQR	4,780-10,187		6,147-10,872		
Peripheral eosinophil count (/μL)					
Median	171		273		.02
IQR	67.4-360		153-412		
Aspartate aminotransferase (IU/L)					
Median	114		122		.79
IQR	46.5-187		66.5-191		

(continued)

TABLE II. *(Continued)*

	Did not develop food allergy (n = 164)		Developed food allergy (n = 42)		
	n	%	n	%	*P* value
Alanine aminotransferase (IU/L)					
Median	64.0		79.0		.63
IQR	27.3-131		50.0-153		
Total bilirubin (mg/dL)					
Median	6.3		6.4		.16
IQR	0.8-13.3		2.5-13.3		
Tacrolimus trough level after liver transplantation (ng/mL)					
At 7 d					
Median	9.9		10.0		.88
IQR	7.8-12.4		7.5-12.6		
At 14 d					
Median	9.3		9.1		.53
IQR	7.3-11.9		7.3-10.7		

TABLE III. Multiple logistic regression analysis of the development of food allergy in young children after liver transplantation

	Crude OR	95% CI	*P* value	Adjusted OR*	95% CI	*P* value
Age at liver transplantation (mo)	0.97	0.93-1.01	.20	0.98	0.93-1.03	.44
Gender (female vs male)	1.28	0.65-2.53	.47	1.40	0.66-2.69	.35
Eczema at liver transplantation (yes vs no)	2.40	1.20-4.82	.01	2.41	1.14-4.77	.02
Donor's age (y)	1.03	0.98-1.08	.25	1.03	0.98-1.09	.20
Parental history of food allergies (yes vs no)	1.94	0.69-5.44	.21	1.79	0.60-4.99	.29
Peripheral eosinophil count (/μL)	1.20	1.00-1.43	.05	1.00	0.99-1.00	.28

CI, Confidence interval; *OR*, odds ratio.
*Adjusted for all variables shown.

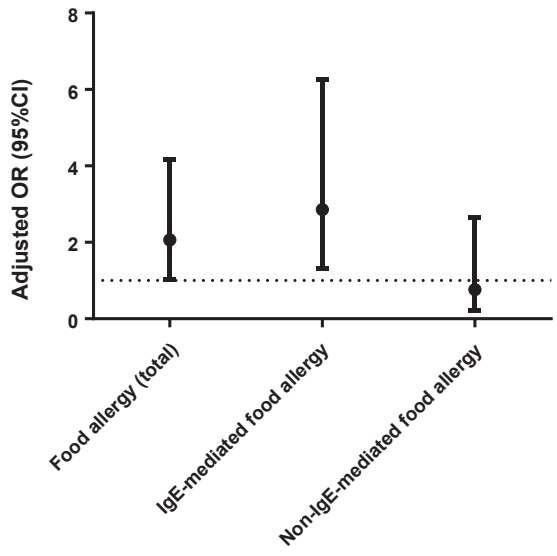

FIGURE 2. Associations between eczema at liver transplantation and food allergy stratified by IgE-mediated food allergy or non−IgE-mediated food allergy. *CI*, Confidence interval; *OR*, odds ratio.

proper diagnosis for our patients, collectively refers to several diseases such as food protein-induced enterocolitis/enteropathy/proctocolitis and/or EGID.[3,24] We could not perform GI endoscopy or histological evaluation because of safety concerns, and this might have resulted in overestimation of the prevalence of non−IgE-mediated food allergy. However, the Brisbane experience reported by Noble et al suggested that the prevalence of EGID in liver transplant children is up to 100 times greater than in nontransplant children.[19,25-27] Based on these observations, the development of non−IgE-mediated food allergy after liver transplantation is more frequent than previously thought and should be considered in all children with GI symptoms after undergoing liver transplantation.

Our study revealed that the presence of eczema in non−IgE-mediated allergy cases was significantly lower than in IgE-mediated cases. This suggests that different sensitization pathways might be involved in IgE-mediated and non−IgE-mediated food allergy after liver transplantation. Although the exact sensitization pathways remain unknown, 2 mechanisms of breaking oral tolerance have been hypothesized to account for alternative sensitization pathways. The first mechanism is increased intestinal permeability, which might favor transport of antigens from the intestinal lumen and contact with the immature intestinal mucosal system of children, leading to oral antigen sensitization and development of food allergy.[28] This hypothesis is supported by reports of an association between increased intestinal permeability and non−IgE-mediated food allergy.[29,30] Indeed, the age at transplantation in non−IgE-mediated allergy cases was significantly lower than in IgE-mediated cases. The second mechanism is breaking hepatic regulatory systems that prevent induction of immunity against gut-derived food allergens.[31] In the liver, naïve T cells recirculating within the sinusoids make direct contact with sinusoidal cells, such as liver sinusoidal endothelial cells (LSECs) or Kupffer cells. Gut-

TABLE IV. Comparison of patients with IgE-mediated food allergy and non–IgE-mediated food allergy after liver transplantation*

	IgE-mediated (n = 30)		Non–IgE-mediated (n = 10)		
	n	%	n	%	*P* value
Gender					
Male	16	53.3	3	30.0	.20
Female	14	46.7	7	70.0	
Age at liver transplantation					
Median months	8.5		6.0		.048
Interquartile range (IQR)	7.0-13.0		5.0-9.3		
<12 mo	21	70.0	8	80.0	.48
≥12 mo	9	30.0	2	20.0	
Eczema at liver transplantation					
No	10	33.3	7	70.0	.041
Yes	20	66.7	3	30.0	
Season of birth					
Spring-Summer	18	60.0	7	70.0	.57
Fall-Winter	12	40.0	3	30.0	
Parental history of food allergies					
No	25	83.3	9	90.0	.61
Yes	5	16.7	1	10.0	
Donor's age					
Median (y)	35.5		31.5		.80
IQR	30.0-38.3		29.5-39.3		
Indication of liver transplantation					
Biliary atresia	16	53.3	7	70.0	.36
Others	14	46.7	3	30.0	
Fulminant hepatic failure	7	23.3	3	30.0	
Congenital metabolic disease	5	16.7	0	0.0	
Liver cirrhosis	1	3.3	0	0.0	
Liver fibrosis	0	0.0	0	0.0	
Congenital absence of portal vein	0	0.0	0	0.0	
Hepatoblastoma	0	0.0	0	0.0	
Alagille	1	3.3	0	0.0	
Caroli disease	0	0.0	0	0.0	
Previous history of intestinal surgery					
No	11	36.7	3	30.0	.70
Yes	19	63.3	7	70.0	
Past infection					
Epstein-Barr virus					
No	15	50.0	4	40.0	.58
Yes	15	50.0	6	60.0	
Cytomegalovirus					
No	9	30.0	1	10.0	.21
Yes	21	70.0	9	90.0	
Laboratory data at liver transplantation					
WBC (/μL)					
Median	7,790		6,195		.09
IQR	6,440-10,712		4,917-9,132		
Peripheral eosinophil count (/μL)					
Median	273		262		.88
IQR	141-491		159-389		
Aspartate aminotransferase (IU/L)					
Median	122		122		1.00
IQR	49.8-212		91.0-162		
Alanine aminotransferase (IU/L)					
Median	84.5		76.5		.78
IQR	51.8-153		40.5-171		

(continued)

TABLE IV. *(Continued)*

	IgE-mediated (n = 30)		Non−IgE-mediated (n = 10)		
	n	%	n	%	*P* value
Total bilirubin (mg/dL)					
Median	6.1		8.4		.44
IQR	2.1-13.2		3.7-20.4		
Tacrolimus trough level after liver transplantation (ng/mL)					
At 7 d					
Median	10.4		10.0		.99
IQR	7.4-12.6		6.9-14.5		
At 14 d					
Median	9.1		8.1		.54
IQR	7.0-10.4		7.1-10.6		
Development of food allergy after liver transplantation					
Total IgE (IU/mL)					
Median	129		52.7		.42
IQR	15.6-1048		22.4-131		
Egg-specific IgE					
Median	37.1		3.9		.24
IQR	8.0-60.7		1.2-10.3		
Milk-specific IgE					.67
Median	5.6		5.7		
IQR	0.8-23.4		3.5-39.2		

*Two overlapping patients were excluded from the analysis.

derived food antigens are taken up by Kupffer cells, LSECs, and liver dendritic cells and presented to naïve T cells, leading to immune tolerance of both CD8+ T cells and CD4+ T cells.[32] Therefore, transplantation-associated damage to the liver, especially to these cells that are involved in immune tolerance induction, might have suppressed oral tolerance to food allergens and promoted the development of food allergy. Interestingly, some case reports described non−IgE-mediated allergy that were accompanied by severe liver damage, suggesting the validity of this mechanism.[33,34]

In the current study, the peripheral eosinophil count at transplantation and the development of food allergy showed no significant association. Similar to our results, an earlier prospective study (N = 28) reported that the total eosinophil count before liver transplantation did not differ in patients who subsequently developed food allergy compared with those who did not develop food allergy, although elevated levels could be detected in the blood at the time when they developed food allergy.[35] Notably, another study investigated the immune response using patients' peripheral blood mononuclear cells, and posttransplant allergic patients showed a significantly higher level of IL-5 secretion, associated with eosinophil maturation and differentiation, in comparison with nonallergic transplant patients.[36] Although the optimal predictive biomarker has not yet been identified, biomarkers using blood could be very beneficial in clinical practice to improving prediction of food allergy development. Further assessment of the mechanisms, as well as prospective studies, is needed in consideration of their phenotypes, such as IgE-mediated and non−IgE-mediated food allergy.

Some limitations of this study that may have affected our results need to be pointed out. First, OFC was not conducted in most of the children. Although food allergy should ideally be confirmed by OFC, this test could not be routinely performed in this population, because of the high-risk nature of the test. Therefore, an acceptable substitute was employed: assay of specific IgE levels to foods, based on the established specific IgE cutoffs. Second, because this was a retrospective study, we had no data on the donor livers and no data regarding the parents', donors', or patients' immunologic status and status of allergic sensitization before the liver transplantation.

In conclusion, we found that eczema at liver transplantation became a significant risk factor for the development of IgE-mediated food allergy in young children after liver transplantation, but not non−IgE-mediated food allergy. Our findings may contribute to a better understanding of the susceptible subgroup of children requiring special caution and to establishing an effective strategy for prevention of food allergy after liver transplantation.

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