

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.

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;■:■–■)

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

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 criteria¹⁷ 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

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