De Novo Allergy and Immune-Mediated Disorders Following Solid-Organ Transplantation—Prevalence, Natural History, and Risk Factors

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Objectives To describe the prevalence, natural course, outcome, and risk factors of post-transplant de novo allergy and autoimmunity.

Study design A cross-sectional, cohort study of all children (<18 years) who underwent a solid-organ transplantation, between 2000 and 2012, in a single transplant center, with a follow-up period of 6 months or more post-transplant and without history of allergy or immune-mediated disorder pretransplant.

Results A total of 626 eligible patients were screened, and 273 patients (160 males; 59%) met the inclusion criteria; this included 111 liver, 103 heart, 52 kidney, and 7 multivisceral recipients. Patients were followed for a median period of 3.6 years. A total of 92 (34%) patients (42 males, 46%) developed allergy or autoimmune disease after transplantation, with a high prevalence among liver (41%), heart (40%), and multivisceral (57%) transplant recipients compared with kidney recipients (4%; $P < .001$). Post-transplant allergies included eczema (n = 44), food allergy (22), eosinophilic gastrointestinal disease (11), and asthma (28). Autoimmunity occurred in 18 (6.6%) patients, presenting mainly as autoimmune cytopenia (n = 10). In a multivariate analysis, female sex, young age at transplantation, family history of allergy, Epstein–Barr virus infection, and elevated eosinophil count >6 months post-transplantation were associated with an increased risk for allergy or autoimmunity. Two patients (0.7%) died from autoimmune hemolytic anemia and hemophagocytic lymphohistiocytosis, and 52 episodes of post-transplant allergy, autoimmunity, and immune-mediated disorders (37%) did not improve over time.

Conclusions Allergy and autoimmunity are common in pediatric liver, heart, and multivisceral transplant recipients and pose a significant health burden. Further studies are required to clarify the mechanisms behind this post-transplant immune dysregulation. *(J Pediatr 2017;■■:■■-■■).*

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Allergic and immune-mediated disorders have been reported sporadically in pediatric recipients of solid-organ transplantation (SOT) and are associated with mild-severe morbidity and rarely with mortality. The reported clinical spectrum of SOT-associated allergies is variable, ranging from asymptomatic eosinophilia, through food allergies, eosinophilic gastrointestinal disorders (EGIDs), atopic dermatitis, allergic rhinitis, and asthma to anaphylaxis.[1-6] Likewise, a variety of SOT-associated immune-mediated disorders have been reported, including autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, neutropenia, and pancytopenia.[7-11] These phenomena are attributed to an ongoing exposure of pediatric recipients of SOT to immunosuppressive medications and a unique immune milieu.

The prevalence of post-transplant allergy, autoimmunity, and immune-mediated disorders (PTAA) among pediatric transplant recipients is estimated at 8.5%-45%, with a high prevalence of allergies in liver recipients and low prevalence in kidney recipients; the prevalence of PTAA in heart transplant recipients is unknown.[1-6] PTAA pathophysiology and whether post-transplant allergy and autoimmunity share common triggers and immune pathways also are unknown.

PTAA across all SOT recipients over a long period of follow-up has never been studied systematically, and gaps exist in our knowledge. We studied a large cohort

CNI	Calcineurin inhibitor
EBV	Epstein–Barr virus
EGID	Eosinophilic gastrointestinal disorder
HLH	Hemophagocytic lymphohistiocytosis
IBD	Inflammatory bowel disease
PTAA	Post-transplant allergy, autoimmunity, and immune-mediated disorders
PTLD	Post-transplant lymphoproliferative disease
SOT	Solid-organ transplantation

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of pediatric recipients of liver, heart, kidney, and multivisceral transplants in a single center to assess the clinical spectrum of PTAA, the prevalence among different organs, clinical course, risk factors, and outcomes.

Methods

We conducted a retrospective, cross-sectional, single-center study of all children (<18 years of age) who underwent a primary liver, heart, kidney, intestine, or multivisceral transplantation at the Hospital for Sick Children, Toronto, Canada, between January 2000 and December 2012. Data were retrieved from the patients' prospectively collected electronic charts, available at our center since 2000. Patients were excluded from the study in cases of allergy (excluding drug allergy) and/or immune-mediated disorder before SOT; pretransplant exposure to immunosuppressive medications or chemotherapy; post-transplantation follow-up <6 months; or incomplete data in the patient's chart. Collected data included patient demographics, medical history, and clinical course; immunosuppressive regimens; PTAAs and their treatment; complications; and outcome. Blood test results included eosinophil counts, immunoglobulins, microbiologic studies, and allergy testing. Transplant protocols varied according to organ and year of transplant; however, tacrolimus and steroids were the standard post-transplant immunosuppressive treatment and were used in all cases unless specified. The study was reviewed and approved by the local ethics committee.

PTAAs were identified according to the reported diagnoses in the patient's electronic chart based on compatible clinical and laboratory findings. Charts of all patients diagnosed with PTAA were reviewed by 3 physicians to avoid over- or incorrect diagnoses. Cases of disagreement were discussed, and patients were diagnosed with PTAA only on mutual agreement. Patients were determined allergic only if symptoms persisted, were followed by the relevant subspecialty service (eg, immunology, dermatology, pulmonology), or received ongoing treatment for their allergy. Food allergy was diagnosed clinically by an allergist or a gastroenterologist. IgE-mediated reactions were defined by the combination of clinical symptoms including anaphylaxis, urticaria, or angioedema and a positive skin prick testing, the presence of food-specific IgE antibodies, or a positive oral challenge test. Non–IgE-mediated reactions were diagnosed clinically, ie, the presence of vomiting or diarrhea that responded to elimination diet. Allergic rhinitis, asthma, eczema, and atopic dermatitis were all diagnosed clinically. EGIDs were diagnosed by compatible clinical and histologic findings.[12,13] Peripheral blood eosinophilia was analyzed by patient ages according to reference ranges provided by the SickKids laboratory service in Toronto, Canada (0-3 months $>1 \times 10^9$, 3-12 months $>0.7 \times 10^9$, >1 year $>0.5 \times 10^9$ eosinophils/L, respectively), and recorded categorically as normal/abnormal at 3, 6, and 12 months post-transplant. Autoimmune and immune-related disorders were diagnosed according to accepted criteria for each of these pathologies.

Statistical analysis was computed with SPSS (V. 21.0; IBM Corp, Armonk, New York). Student *t* test and Fisher exact tests (for $n < 10$) were used for continuous variables, and the χ^2 test was used for categorical variables; all tests were performed with 2-sided tails with a CI of 95%. Kendall tau-B test was used to assess categorical trends. Survival was calculated with the Mantel–Cox test and logistic regression was used for multivariate analysis with a CI of 95%.

Results

A total of 626 patients who underwent their first SOT at our center during the study period were screened. Of those, 353 patients were excluded: 47 due to an immune-mediated etiology of their original disorder (31 kidney, 10 liver, and 6 heart transplant recipients); 61 due to a previous state of allergy (49 kidney and 12 heart transplant recipients), and 5 patients who underwent liver transplant were excluded due to pretransplant chemotherapy; the remaining 240 patients were excluded for short (<6 months) follow-up and were either transferred to another institution or lost to follow-up.

A total of 273 patients were included in the study cohort: 111 liver recipients, 103 heart, 52 kidney, and 7 patients who underwent multivisceral transplantation. Male subjects (160, 59%) predominated with a male/female ratio of 1.4 ($P < .01$); primarily because of male predominance among kidney transplant recipients (**Table I**). The overall median age at transplantation was 2.9 (IQR 0.7-10.3) years, with median ages for liver (1.7 year) and heart (1.2 year) recipients significantly lower than kidney recipients (10.8 years, $P < .001$). The median post-

Table I. Patient demographics by organ

	Organ				
Characertistics	**Liver**	**Heart**	**Kidney**	**Multivisceral**	**Total**
Patients, n (%)	111 (40)	103 (38)	52 (19)	7 (2.6)	273 (100)
Male, n (%)	63 (57)	56 (54)	37 (71)*	4 (57)	160 (59)
Age at transplantation, y, median (IQR)	1.7 (0.8-6.9)	1.2 (0.4-9.2)	10.8 (6.3-15.5)*	1.2 (0.9-1.6)	2.9 (0.7-10.3)
Length of follow-up, y, median (IQR)	3.2 (1.6-5.8)	4.5 (2.8-6.8)	2.4 (1.2-6.0)	4.8 (1.6-5.5)	3.6 (1.7-6.3)
Age at last follow-up, y, median (IQR)	7.0 (3.7-12.0)	9.0 (5.7-15.1)	17.5 (11.3-18.0)*	7.0 (4.5-7.3)	9.2 (5.2-15.6)

*$P < .05$.

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