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Clinical Predictors of Autoimmune and Severe Atopic Disease in Pediatric Heart Transplant Recipients

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Abstract

Autoimmune and allergic diseases cause morbidity and diminished quality of life in pediatric organ transplant recipients. We hypothesize that younger age at transplantation and immunosuppression regimen play a role in the development of immune mediated disease following heart transplant. A single institution retrospective review identified all patients undergoing heart transplant at ≤18 years of age from 1987-2010 who survived ≥1 year. Using medical record and database review, patients were evaluated for development of autoimmune or severe allergic disease. Of 129 patients who met criteria, seven patients (5.4%) with autoimmune or severe atopic disease were identified. Immune mediated diseases included inflammatory bowel disease (n = 3), eosinophilic esophagitis/colitis (n=4), and chronic bullous disease of childhood (n=1). Patients <1 year at transplant were at greater risk of developing autoimmune disease than patients 1-18 years at transplant (OR = 9.3, 95% CI 1.1-79.2, p=0.02). All affected patients underwent thymectomy at < 1 year of age (7/71 vs. 0/58, p=0.02). In our experience heart transplantation in infancy is associated with the development of immune mediated gastrointestinal and dermatologic diseases. Further study is needed to determine risk factors for the development of immune mediated disease to identify best practices to decrease incidence.

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Keywords

Pediatric heart transplantation; autoimmune disease; atopic disease; infant heart transplantation; thymectomy; immunosuppression

Introduction

Heart transplantation is now a proven and accepted therapy for infants and children with end-stage cardiac failure secondary to cardiomyopathy and inoperable congenital heart disease.(1, 2) With increased survival and improved outcomes post transplantation, focus has shifted to prevention and treatment of long-term complications of organ transplantation and immunosuppression.

Among these complications, autoimmune and allergic diseases are an important cause of morbidity in pediatric organ transplant recipients. A range of autoimmune diseases following solid organ transplantation have been reported including immune cytopenias, inflammatory bowel disease, autoimmune hepatitis, and chronic bullous disease.(3) Clinically important atopic diseases including multiple food allergies, eczema, and eosinophilic gastrointestinal disease have been reported as well.(4-6) Development of immune mediated complications in pediatric heart transplant recipients is likely multifactorial, related in part to the unique features of both pediatric and thoracic organ transplantation. For example, incidental partial or total thymectomy to increase exposure to the heart and great vessels is a routine practice in children undergoing corrective or palliative cardiothoracic surgery. Thymectomy results in important immuno-modulatory changes not encountered in other solid organ transplants. Several studies in patients with congenital heart disease have demonstrated decreased T cell number and diversity post thymectomy.(7-11) Similar alterations in the T cell compartment have been noted in pediatric heart transplant recipients in whom chronic immunosuppression further modifies T cell function. These differences are particularly striking in those undergoing heart transplantation at less than one year of age, likely due to the immaturity of the immune system.(12, 13)

Although limited studies have demonstrated alterations of the immune system secondary to thymectomy and immunosuppression in pediatric heart transplant recipients, clinical factors that modify risk of immune mediated disease are not known. We tested the hypothesis that younger age at transplantation, and thus at thymectomy, increases risk for development of immune mediated disease following heart transplantation.

Material and Methods

Patient Selection & Study Variables

We performed a retrospective cohort study of patients who underwent primary heart transplantation from 1987 to 2011 at Vanderbilt Children's Hospital. Patients who were transplanted at less than 18 years of age and survived a minimum of 1 year post transplantation were included in the analysis. The endpoint of data collection was at patient death or last follow-up ending April 2012. Study data were collected and managed using

REDCap (Research Electronic Data Capture), a secure, web-based application designed to support data capture for research studies, hosted at Vanderbilt Medical Center.(14) Data collected included demographics, initial diagnosis, indication for transplantation, operative details, immunosuppression regimen, development of immune mediated disease, rejection and post-transplant lymphoproliferative disorder, and survival at time of study endpoint. Per routine cardiothoracic surgical practice at our institution, all patients underwent at least partial thymectomy at the time of transplantation or at the time of prior surgery for congenital heart disease. Thymic tissue obstructing view of the operative area is routinely excised; however, operative reports do not comment upon the extent of thymectomy and thmyic tissue is not routinely sent for pathologic evaluation. To identify patients with immune mediated disease, the medical record was queried for gastroenterology, dermatology, and rheumatology consultations as well as procedures including esophagogastroduodenoscopy (EGD), colonoscopy, or other biopsy. Severe atopic or autoimmune disease was defined by positive biopsy and subspecialist diagnosis. Prior to establishing a diagnosis of inflammatory bowel disease or eosinophilic bowel disease, extensive evaluation in cooperation with the gastroenterology service ensued to exclude alternative etiologies. Patients were evaluated by stool and serum studies to exclude infectious causes, elimination diets and/or medication changes were performed to exclude food or medication intolerance, and all patients underwent endoscopy with pathologic specimens demonstrating inflammatory or eosinophilic disease. Eczema, allergic rhinitis, and asthma were not included in the case definition given high prevalence in the general pediatric population and varied diagnostic criteria. The study was performed with approval of the Vanderbilt Institutional Review Board.

Immunosuppression by era

Subject era of transplantation was defined according to immunosuppressive regimen. Those transplanted before or during 1999 most commonly received Nashville rabbit anti-thymocyte serum for induction therapy and cyclosporine and azathioprine for chronic immunosuppression. Those transplanted after 1999 predominantly received commercially produced anti-thymocyte globulin for induction therapy and tacrolimus and mycophenolate mofetil for chronic immunosuppression.

Initially, Nashville rabbit anti-thymocyte serum was used with dosing of 1-4 mL/kg/day for 14 days early in our experience with duration later decreased to 7 days. After FDA approval in 1998, commercially produced anti-thymocyte globulin (ATG) was used with dosing of 5-15 mg/kg total over 5 days.

Steroids were given at high dose post-operatively for 4 days. After the initial steroid pulse, steroids were stopped for those <6 months, or weaned off by 1 month for those <10 years. Adolescents in the cyclosporine era were continued on maintenance steroids indefinitely, while in the tacrolimus era they were weaned off over 1-6 months.

Cyclosporine and azathioprine were routinely used until the introduction of tacrolimus and mycophenolate mofetil in the late 1990s. Goal immunosuppressant trough levels were 100-250 ng/mL for cyclosporine, 4-12 ng/mL for tacrolimus, and 2-4 μg/mL for mycophenolate mofetil. Since 2000, sirolimus has been used in place of mycophenolate

mofetil or azathioprine in patients with refractory rejection, coronary vascular disease, or renal dysfunction. Sirolimus goal levels were 2-10 ng/mL.

Statistical analysis

Descriptive data are presented for all study patients and are stratified by age at transplant (<1 year at transplantation versus those > 1 year at transplantation). Categorical study variables are presented as proportions or percentages and continuous variables are presented as medians with interquartile range and/or total range. Demographic continuous variables were compared with the Mann-Whitney U test and categorical variables were compared with the chi-square or Fisher's exact tests, where appropriate. The primary outcome was development of immune mediated disease. The relationships between the binary outcome of autoimmune status and age at transplant as well as age at thymectomy (<1 year vs. 1-18 years) were evaluated with Fisher's exact test. The secondary outcome of graft rejection was evaluated as the number of rejection episodes per 10 years of patient follow-up. In the group transplanted at less than one year of age the incidence rate of rejection was compared in those with and without autoimmune disease via the Mann Whitney U test as well as with Poisson regression. R version 2.15.0 (2012-03-30) and IBM SPSS Statistics version 20 were used in data analysis.

Results

Patient population

Between 1987 and April 2011, 157 patients <18 years of age received primary transplantation and 10 patients received repeat transplantation at our institution. Of the patients receiving primary transplantation, 129 (82%) survived at least one year post transplantation and were included in the study group. Of those included, 54 (42%) were <1 year of age at primary transplantation. A total of 28 patients (22%) died during the data collection period. Of those transplanted at < 1 year of age, there were 6 deaths between 1 and 5 years post transplantation and 4 deaths from 6 to 11 years post transplantation. Follow-up time post transplantation in the infant group was a median of 7.7 years (range 1-22.6 years). Within the 1-18 year old age group, there were 11 deaths between 1 and 5 years post transplantation and 7 deaths within 6 and 20 years post transplantation. Follow-up time post transplantation in the older group was a median of 5.4 years (range 1-21 years). Four patients were followed at other institutions at the time of the study, for whom 3 had records available for review. Only one patient was lost to follow-up.

Patient demographics and clinical characteristics were compared among those transplanted at < 1year and those transplanted at 1-18 years of age (Table 1). The groups were not significantly different in proportions of male and females. The older group, transplanted at 1-18 years of age, had a higher proportion of those with black race ($p = 0.042$). Infant recipients were more likely to have congenital heart disease than older recipients ($p = 0.05$). A total of 38 patients were transplanted before 1999 (the cyclosporine era), 18 of which were < 1year at the time of transplantation. Era of transplantation was defined by alteration in immunosuppression regimens after the introduction of commercially produced ATG, tacrolimus, and mycophenolate mofetil (1987-1999 versus 2000-2011) (Table 2). The

proportion of patients transplanted in each age group was similar among eras (p = 0.41). The median age at thymectomy and transplantation was significantly higher in the older group (p = 0.001).

Immune mediated disease

Autoimmune or severe atopic disease was identified in seven patients (5.4%). All patients with disease were <1 year of age at thymectomy, 7/71 vs. 0/58 at 1-18 years of age at thymectomy, (p = 0.02; Table 3). Patients transplanted at less than 1 year of age were more likely to develop disease (odds ratio of 9.3, 95% CI 1.1-79.2, p = 0.02; Table 3). Although not statistically significant (p-value = 0.2), 6/36 infants (17%) transplanted from 2000-2010 developed disease versus 0/18 infants transplanted from 1987-1999.

Immune mediated diseases included inflammatory bowel disease (n = 3), eosinophilic esophagitis/colitis (n = 4), and chronic bullous disease of childhood (n = 1). The median time from transplantation to diagnosis was 4.8 years (range 0.6-7.9). Clinical details of the patients with immune mediated disease are summarized in Table 4. Cases 1, 2, and 3 required treatment with steroids as well as monoclonal antibody therapy. Colectomy was required for case 1 and is being considered for case 2. Cases 4 and 5 required treatment with oral agents, developed recurrent symptoms, and required frequent gastroenterology follow-up. Case 6 had significant inflammation in the esophagus and upper airway requiring laser excision of airway lesions due to respiratory compromise. It is notable that immune mediated disease caused significant morbidity in all affected infant transplant recipients; however, the affected patient who underwent thymectomy <1 year of age but was not transplanted until 5 years of age (case 7) is relatively asymptomatic.

Additional post-transplant morbidities

During the study period, nine patients (6%) in the cohort developed post-transplant lymphoproliferative disease, 6 of which were transplanted at <1 year of age. None of the patients with immune mediated disease have developed post-transplant lymphoproliferative disease (0/7 vs. 9/122, p-value =1). Of those transplanted at < 1 year of age, there were 36 episodes of rejection in 22 patients with a total follow-up time of 517 years. In the six patients with immune mediated disease transplanted at less than 1 year, there were 4 episodes of rejection in three patients during a total of 50 years of follow-up. Using Poisson regression, the mean predicted number of rejection episodes per patient over a 10 year follow-up period is 0.7 in those transplanted at <1 year of age without immune mediated disease and 0.8 in those with immune mediated disease. In the <1 year age group, the occurrence rate of graft rejection was not significantly different between those with and without autoimmune disease (p=0.7).

Discussion

In our single center experience, heart transplantation (with thymectomy) in infancy is associated with the development of immune mediated gastrointestinal and dermatologic diseases. Previous case reports have described inflammatory bowel disease, eosinophilic gastroenteritis, and bullous disease after solid organ transplant. In this study, we have begun

to assess the relationship between clinical factors and development of immune mediated disease in pediatric heart transplant recipients. The association between heart transplantation in infancy and immune mediated diseases is likely multifactorial. The immaturity of the infant immune system may be the sole etiology; however, the multiple hits inflicted by thymectomy and immunosuppression further increase risk of immune derangement.

The effects of thymectomy are more profound in infants than in older children. The composition of T cell populations in children with congenital heart disease post-surgical thymectomy has been previously described. Prior partial or total thymectomy resulted in a decrease in total lymphocyte count, CD4+ and CD8+ T cells as well as naïve T cells. In addition, thymectomy also diminishes thymic maturation of naïve T cells demonstrated by measurement of T cell receptor excision circles (TREC).(7) Neonatal thymectomy has also produced long-term alterations in thymic function with persistent reduction of naïve T cells and TRECs as well as skewed T cell receptor diversity, reflecting peripheral expansion of pre-existing lymphocytes.(8, 9) These studies suggest that removal of the thymus for anatomic exposure of the heart may prevent heart transplant recipients from generating mature T cells, thus altering the T cell repertoire; it may further influence the balance of effector and regulatory T cells as described in murine models of thymectomy which would also drive autoimmune disease. (15)

Autoimmunity is also common in primary immunodeficiency diseases.(16, 17) Patients with thymic hypoplasia secondary to partial DiGeorge syndrome have variable T cell immunodeficiency with increased prevalence of atopic and autoimmune disease.(18, 19)

In addition to the direct effects of thymectomy in infancy, immunosuppression of the immature immune system further depletes mature T cells and depresses T cell proliferation. Commonly used immunosuppressants including azathioprine and mycophenolate interfere with DNA synthesis and are cytotoxic to dividing lymphocytes. Cyclosporine, tacrolimus, and sirolimus interfere with T cell signaling and inhibit T cell proliferation. T cell and thymic function deficiencies with reduced TRECs and significant decrease in T cell receptor diversity have been demonstrated in patients who underwent cardiac transplantation at less than one year of age.(12) Although the relative contributions of thymectomy and immunosuppression are not well defined, it is clear that the resultant lymphopenia encourages homeostatic proliferation of peripheral T cells demonstrated by decreased diversity of the T cell compartment and defective cell mediated immune function.(13) The combination of thymectomy and immunosuppression may result in a partial T cell immunodeficiency increasing risk for immune mediated disease, similar to that seen in patients with partial DiGeorge syndrome.

The risk of immune mediated disease may not be equal across all immunosuppressive regimens. All of the patients in our cohort who developed immune mediated disease received ATG for induction therapy and tacrolimus as the initial calcineurin inhibitor. Our study is underpowered to evaluate the effects of specific drug regimens; however, it is notable that the frequency of immune mediated disease appears to be increasing in the current era. This trend may be secondary to the different mechanism of action of newer agents and, therefore, altered effects on the various immune cells types. Particularly,

tacrolimus use has been associated with immune mediated cytopenias and development of significant food allergies in solid organ transplantation recipients.(4, 6, 20)

Over-immunosuppression is a postulated etiology of immune mediated disease development; however, none of the affected patients in our cohort developed post-transplant lymphoproliferative disease. In addition, the occurrence rates of rejection were similar between those with and without immune mediated disease. The absence of significant differences in the incidence of post-transplant lymphoproliferative disease or rejection suggests that the level of functional immunosuppression was not different in those developing autoimmune disease versus those without.

Limitations

This retrospective cohort study is primarily limited by small sample size with insufficient numbers to adequately evaluate the individual effect of thymectomy and specific immunosuppression regimens on the primary study outcome of immune mediated disease. The evaluation of the contribution of thymectomy on development of immune mediated disease is limited by the possibility of differing extents of thymic tissue removal. Although at least partial thymectomy is routinely performed at the time of heart transplantation or at a prior surgery for congenital heart disease, the extent of thymic tissue removal is not detailed in operative reports. In addition, no standard evaluation was performed to evaluate for the persistence of or re-growth of thymic tissue.

The retrospective nature of the study is associated with inability to randomize and prospectively determine immunosuppression regimens and clinical management of transplant morbidities. Dividing immunosuppression regimens by era was an attempt to best characterize a time period of significant change in post-transplantation immunosuppression; however, this division is limited by imperfect separation of immunosuppression regimes. In addition, the overall trend in decreased immunosuppression is difficult to quantify and thus account for in our analysis. Despite these limitations, immunosuppression at our institution has been standardized in regards to dosing and goal drugs levels with minimal variability between patients due to primary transplant care provided almost exclusively by one provider throughout the study period. Changes in immunosuppression regimen during the study were primarily related to new drug availability and experience with dosing ranges over time.

Finally, because the median follow-up time in patients without disease (6.8 years) is less than the time from transplant to disease in two of the reported cases, it is possible that additional cases of immune mediated disease will develop with a longer follow-up period. An underestimation of disease occurrence may particularly affect patients greater than one year of age at the time of transplant, as the median follow-up time for these patients is shorter than that of the infant transplant recipients (5.4 vs. 7.7 years, p-value 0.017, as noted in Table 1).

Conclusion

Heart transplantation in infancy is associated with development of immune mediated gastrointestinal and dermatologic diseases. Thymectomy and immunosuppression with resultant T cell immunodeficiencies may contribute to increased risk of atopic and

autoimmune disease by alteration of delicate immature immune systems. Further investigation is needed to define the T-cell compartment deficiencies in pediatric heart transplant recipients and to further evaluate how age at thymectomy and immunosuppressive regimen impacts cell mediated immunity. Multicenter participation and correlation of immune derangements to disease will be required to determine how the altered immune system contributes to development of autoimmune and atopic disease. Definition of specific immune derangements would enable proactive evaluation and screening of the T cell compartment before and after heart transplantation allowing modification of immunosuppression regimens in attempts to decrease risk.

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Table 1
Demographics by Age Group at Transplant

	<1 year(n=54)	1-18 years (n=75)	p-value
Sex			0.17[1]
Female	29 (54%)	31 (41%)	
Male	25 (46%)	44 (59%)	
Race			0.04[1]
White	45 (83%)	47 (63%)	
Black	6 (11%)	24 (32%)	
Hispanic	2 (4%)	3 (4%)	
Other	1 (2%)	1 (1%)	
Diagnosis			0.05[1]
Congenital heart disease	36 (67%)	37 (49%)	
Cardiomyopathy/cardiac tumor	18 (33%)	38 (51%)	
Era of Transplantation*			0.41[1]
1987-1999	18 (33%)	20 (27%)	
2000-2010	36 (67%)	55 (73%)	
Age at thymectomy, median years (range)	0.19 (0.01-0.96)	2.6 (0.01 - 16.11)	<0.001[2]
Age at transplant, median years (range)	0.25 (0.04-0.96)	5.91 (1.08 - 17.27)	<0.001[2]
Living			0.23[1]
Alive	45 (83%)	57 (76%)	
Dead	8 (15%)	18 (24%)	
Lost to follow-up	1 (2%)	0 (0%)	
Follow-up duration, median years (range)	7.7 (1-22.6)	5.4 (1-21)	0.017[2]

*Era of transplantation as defined by immunosupression regimen,

[1]chi-square test,

[2]Mann-Whitney U test

Table 2
Initial Immunosupression Regimen by Era

	1987-1999 (n = 38)	2000-2011 (n = 91)
Induction therapy		
Anti-thymocyte serum	28 (74%)	0 (0%)
Anti-thymocyte globulin*	5 (13%)	88 (97%)
Muromonab-CD3 (OKT 3)	1 (3%)	1 (1%)
None	4 (10%)	2 (2%)
Calcineurin Inhibitor		
Cyclosporine	36 (95%)	1 (1%)
Tacrolimus	2 (5%)	90 (99%)
Anti-proliferative		
Azathioprine	37 (97%)	5 (5%)
Mycophenolate mofetil	1 (3%)	86 (95%)

* 2 patients received Nashville rabbit anti-thymocyte globulin prior to FDA approval of commercially available anti-thymocyte globulin

Table 3

Demographics and Clinical Characteristics Comparing Patients With and Without Autoimmune or Severe Atopic Disease

	Autoimmune or Atopic Disease (n=7)	No Disease (n = 122)	p-value
Sex			0.25[1]
Female	5 (71%)	55 (45%)	
Male	2 (29%)	67 (55%)	
Race			0.56[1]
White	7 (100%)	85 (70%)	
Black	0	30 (25%)	
Hispanic	0	5 (4%)	
Other	0	2 (1%)	
Diagnosis			0.24[1]
Congenital heart disease	2 (29%)	70 (58%)	
Cardiomyopathy/cardiac tumor	5 (71%)	52 (42%)	
Age at thymectomy			0.02[1]
<1 year	7 (100%)	64 (53%)	
1-18 years	0	58 (47%)	
Age at transplant			0.02[1]
<1 year	6 (86%)	48 (39%)	
1-18 years	1 (14%)	74 (61%)	
Follow-up duration, median years (range)	8.2 (4.8-10.6)	6.8 (1-22.6)	0.41[2]

[1] chi-square or Fisher's exact test,

[2] Mann-Whitney U test

Table 4

Clinical details of patients with autoimmune or severe atopic disease

Case	Cardiac diagnosis	Autoimmune/Atopic disease	Transplant year	Transplant age (years)	Time transplant to symptoms (years)	ATG dose (mg/kg)	Immunosuppression Regimen			Tac level* (ng/ml), Median (IQR)		Rejection
							Initial	At diagnosis	Current	Year one	After year one	
1	Dilated cardiomyopathy	Inflammatory bowel disease	2002	0.4	5.5	10.5	Tac, Aza	Tac, Aza	Tac, Aza	10.3 (7.9-13.2)	7 (4.8-10.7)	Yes
2	Dilated cardiomyopathy	Inflammatory bowel disease	2004	0.4	4.8	12	Tac, Aza	Tac, Aza	Tac, Aza	9.6 (6.3-13.8)	6.9 (5.6-8.9)	No
2	Cardiac fibroma	Chronic bullous disease of childhood & Inflammatory bowel disease	2002	0.1	7.9	14	Tac, MMF	Tac, MMF	Tac, Aza	8.5 (7.1-11.5)	6.3 (4.6-8.4)	No
4	Dilated cardiomyopathy	Eosinophilic colitis	2001	0.3	4	13.7	Tac, MMF	Tac, Aza	Tac, MMF	12.4 (8.8-14.9)	7.7 (5.8-10.3)	Yes
5	Dilated cardiomyopathy	Eosinophilic colitis & esophagitis	2007	0.6	1.6	11.8	Tac, MMF	Tac, MMF	Tac, Sir	8 (6.1-10.9)	7.5 (6.2-9.2)	Yes
6	Pulmonary atresia	Eosinophilic esophagitis	2005	0.1	0.6	13.3	Tac, MMF	Tac, MMF	Tac, MMF	8 (6.4-9.3)	5.7 (4.6-7.8)	No
7	Complex single ventricle	Eosinophilic esophagitis	2004	5.1	7.3	3.8	Tac, MMF	Tac, MMF	Tac, Sir	8.7 (6-11.3)	9.1 (6.7-12.5)	Yes

*Tacrolimus level divided from initial discharge until the end of the first year post-transplant and subsequent to the first year post-transplant, ATG - anti-thymocyte globulin, Aza - azathioprine, IQR - interquartile range, MMF - mycophenolate mofetil, Sir - sirolimus, Tac - tacrolimus