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Impact of age on incidence and prevalence of moderate-to-severe cellular rejection detected by routine surveillance biopsy in pediatric heart transplantation

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pediatric heart transplantation;
rejection;
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BACKGROUND: The effect of age at transplant on rejection detected by routine surveillance biopsy (RSB) in pediatric heart transplant (HT) recipients is unknown. We hypothesized there would be low diagnostic yield and decreased prevalence of rejection detected on RSB in infants (age <1 year) when compared with children (age 1 to 9 years) and adolescents (age 10 to 18 years).

METHODS: We utilized Pediatric Heart Transplant Study (PHTS) data from 2010 to 2013 to analyze moderate-to-severe (ISHLT Grade 2R/3R) cellular rejection (MSR) detected only on RSB (RSBMSR).

RESULTS: RSB detected 280 of 343 (81.6%) episodes of MSR. RSBMSR was detected in all age groups even >5 years after HT. Infant RSBMSR had a greater proportion ($p = 0.0025$) occurring >5 years after HT (39.2 vs 18.4 vs 10.8%) and a lower proportion ($p = 0.0009$) occurring in the first year after HT (25.5 vs 60.6 vs 51.7%) compared with children and adolescents, respectively. Freedom from RSBMSR was 87 ± 7% in infants, 76 ± 6% in children and 73 ± 7% in adolescents 4 years after HT. In 1-year survivors who had RSBMSR in the first year after HT, the risk of RSBMSR occurring in Years 2 to 4 was significantly ($p < 0.0001$) greater than patients without RSBMSR in the first year (hazard ratio 21.28, 95% confidence interval 10.87 to 41.66), regardless of recipient age.

CONCLUSIONS: RSBMSR exists in all age groups after pediatric HT with long-term follow-up. The prevalence in infant recipients is highest >5 years after HT. Those with RSBMSR in the first year after HT are at a high risk for recurrent rejection regardless of age at HT.

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One of the major complications after solid-organ transplant is graft rejection. The bulk of management decisions revolve around rejection prevention, monitoring and treatment. Fortunately, the incidence of acute cellular rejection (ACR) after pediatric heart transplantation (HT) has

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decreased in recent years secondary to advancements in immunosuppression, identification and human leukocyte antigen (HLA) matching.[1,2] The first year after transplant remains the time of greatest risk, with decreasing incidence in later years.[1–4] Age at transplant plays a role as well, with the lowest risk reported in infant recipients, whereas older recipients carry a higher risk of rejection.[1,2,5]

Diagnosing rejection can be relatively straightforward in a symptomatic patient. Acute graft dysfunction from ACR often presents with signs and symptoms of heart failure, such as dyspnea, tachycardia and peripheral edema. Conversely, ACR may be present in a completely asymptomatic patient, making early identification extremely difficult. Non-invasive imaging has shown promise in differentiating rejection from non-rejection, but results lack the degree of consistency needed to replace endomyocardial biopsy (EMB) as the diagnostic standard in ACR.[6,7]

Beyond obtaining biopsies for episodes of symptomatic rejection, multiple routine surveillance biopsies (RSB) are performed for ACR monitoring in asymptomatic patients, especially during the first year post-transplant. In 2000, a large, single-center study reported the incidence of moderate-to-severe ACR (i.e., ISHLT Grade 2R/3R) diagnosed on RSB as 18% in the first year, 12% between Years 1 to 5 and 2.9% at >5 years after HT.[8] In Years 1 to 5, infants and those without rejection in the first year after HT showed a decreased incidence of RSBMSR, but the data did not reach statistical significance. Current data are lacking on the diagnostic yield of RSB, including whether or not the age at transplant and time from transplant-dependent prevalence follows the same pattern as previous reports. For this study, we proposed 2 hypotheses: (1) routine surveillance biopsy will have a low diagnostic yield compared with symptomatic indications for biopsy; and (2) RSBMSR will show a decreasing prevalence over time, with the lowest prevalence seen in infants compared with children and adolescents.

Methods

Data were acquired from the Pediatric Heart Transplant Study Group (PHTS). This prospectively collected database is managed at the University of Alabama at Birmingham. PHTS membership currently includes 52 centers across 3 continents.

This retrospective database review included all enrolled individuals ≤18 years of age with at least 1 episode of moderate-to-severe rejection (MSR) between 2010 and 2013. This time frame was chosen because the database began collecting data on biopsy indication in 2010. Rejection was defined as a biopsy-driven clinical episode that resulted in an augmentation of immunosuppression. Only MSR rejection (ISHLT 2R/3R) was included in the study to eliminate the interpretive variability surrounding Grade 1R classification. Patients who received a multiple-organ transplant were excluded from the analysis. Recipient age groups were defined as infants (age <1 year), children (age 1 to 9 years) and adolescents (age 10 to 18 years). Post-transplant time periods included the first year, Years 2 to 5 and >5 years.

Data obtained from PHTS included date of birth, gender, race, date of transplant, panel-reactive antibody (PRA) percentage at transplant, date of rejection episode, baseline immunosuppression at transplant, biopsy score, indication for biopsy, rejection therapy and degree of hemodynamic compromise at the time of rejection.

Statistical analysis

All analyses were performed at the School of Medicine, Washington University of St. Louis. Study-specific variables were extracted from the PHTS limited data set to create a unique data set for analysis. Proportions were estimated with contingency tables and tested for differences with Pearson's chi-square test. Survival and time to rejection were estimated with product-limit survival curves. Group hazard rates were estimated and compared with Cox proportional hazard regression. All analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

A total of 797 rejection episodes were reported to PHTS from 2010 to 2013 (Figure 1). The indication for biopsy was missing for 101 rejection episodes, requiring exclusion from analysis. Another 68 were excluded for failing to produce a change in immunosuppression. Of the remaining 628 rejection episodes, 476 (76%) listed "routine protocol" as the biopsy indication. One additional episode listed the biopsy indication as "routine protocol" and "symptoms." Additional biopsy indications included "symptoms" in 106 (16.9%) and "objective evidence of graft dysfunction" in 45 (7.1%). Patients' demographics based on biopsy indication are presented in Table 1.

Prevalence of MSR diagnosed on routine surveillance biopsy

The data set contained 343 episodes of MSR. Routine biopsy was responsible for identifying 280 (81.6%) episodes of MSR. RSBMSR was detected in all age groups during the 3 study time periods after HT, and was the primary indication for biopsy for all patients (Table 2). The greatest prevalence of RSBMSR in infants was found >5 years after HT (39.2%), with the lowest prevalence occurring in the first year after HT (25.5%). The opposite pattern was seen in children and adolescents. Most RSBMSR was found in the first year after HT (children 60.6%, adolescents 51.7%), with a steady reduction over time to the lowest prevalence found beyond Year 5. There was a significant difference between the prevalence of RSBMSR during the 3 time periods when analyzed by age group. The total percentage of MSR diagnosed by RSB did not differ significantly among age groups (infants 89.5%, children 82%, adolescents 78.4%).

Incidence of MSR diagnosed on routine surveillance biopsy

Freedom from RSBMSR was significantly ($p < 0.001$) greater in infants compared with children and adolescents (87 ± 7% in infants, 76 ± 6% in children, 73 ± 7% in adolescents) at 4 years post-HT (Figure 2). The hazard of RSBMSR was significantly lower ($p < 0.0001$) in infants