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The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Outcome, incidence and risk factors for stroke after pediatric heart transplantation: An analysis of the International Society for Heart and Lung Transplantation registry

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KEYWORDS:
heart transplantation;
mortality;
pediatric;
stroke;
congenital heart disease;
outcome;
mechanical support

BACKGROUND: In the registry of the International Society for Heart and Lung Transplantation (ISHLT), cerebrovascular accidents are the fifth most common cause for mortality after pediatric heart transplantation (PHTx), but details are lacking in the literature. The purpose of this analysis of the ISHLT registry was to determine the prevalence, risk factors and outcomes of stroke after PHTx.

METHODS: Data from the ISHLT registry (1998 to 2010) were used to identify all patients whose primary transplantation was performed at <18 years of age. Of the 10,441 transplants reviewed, 9,837 primary transplants and 604 retransplants were analyzed.

RESULTS: Three hundred thirty-three (3%) patients had a stroke after PHTx; 54% were male, median age at PHTx was 6 years (0 to 17 years), and 44% had a diagnosis of congenital heart disease (CHD). Freedom from stroke was 99% at 1 month, 97% at 5 years, 95% at 10 years and 91% at 20 years post-PHTx. After a stroke, survival at 1 month, 1 year and 5 years was 83%, 69% and 55%, respectively. Multivariable independent risk factors for stroke included a primary diagnosis of congenital heart disease [hazard ratio (HR) 1.4 (1.1 to 1.7), $p = 0.01$], previous stroke [HR 4.5 (3.2 to 6.2), $p < 0.001$], history of aborted sudden death [HR 1.5 (1.1 to 2), $p = 0.01$], ventricular assist device [HR 1.5 (1.1 to 2.2), $p = 0.03$] or extracorporeal membrane oxygenation [HR 1.7 (1.2 to 2.2), $p = 0.01$], post-operative dialysis [HR 3.3 (2.3 to 4.7), $p < 0.001$], infection requiring antibiotics before discharge [HR 1.9 (1.4 to 2.5), $p < 0.001$], pacemaker implantation [HR 1.6 (1 to 2.5), $p = 0.04$] or drug-treated hypertension [HR 1.4 (1.1 to 1.8), $p = 0.003$] during follow-up.

CONCLUSIONS: Stroke after pediatric heart transplantation is associated with increased mortality. Congenital heart disease and mechanical support both portend greater risk, in addition to markers of increased pre- and post-transplant medical acuity.

J Heart Lung Transplant ▮▮▮▮;▮:▮▮▮–▮▮▮

Pediatric heart transplantation continues to grow worldwide since the first transplantation in 1967. Congenital heart disease (CHD) represents the most common indication for transplantation, followed closely by cardiomyopathy.[1] The first year after transplantation has the highest risk of mortality, with graft failure and technical issues being the

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1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2016.01.1226

most common cause of death (30%), followed by multi-organ failure (16%), infection (14%) and rejection (12%).[1] Importantly, cerebrovascular events represent the fifth most common cause of mortality in the early post-operative period (10%).[1]

The incidence of stroke in children is estimated at 2.6 per 100,000 per year.[2] Patients with CHD are at higher risk for acute ischemic stroke.[3] Almost one third of pediatric patients with acute ischemic stroke have CHD.[4] Risk factors for stroke in this group include a prothrombotic condition, a mechanical valve and an acute illness at the time of the stroke.[5] The risk of peri-operative stroke increases in those patients with CHD who are older at the time of surgery and in those who undergo reoperation or have a longer duration of cardiopulmonary bypass.[4] Overall, the frequency of stroke after surgery for CHD is low, occurring in just over 0.5% of cases,[4] but has been reported to be as high as 3%.[6] In those patients who have had a stroke, 25% occur after a surgical or catheter-based procedure.[7] Recurrence of acute ischemic stroke in patients with CHD occurs in up to 30%.[5,8,9] Although approximately one third of pediatric patients after stroke remain asymptomatic, it is a major source of morbidity and mortality, with just over a third having a seizure disorder or a persistent neurologic deficit and 20% dying after acute ischemic stroke.[9]

The burden of stroke in the pediatric heart transplant population is not well known. According to the registry of the International Society for Heart and Lung Transplantation (ISHLT), cerebrovascular accidents represent the fifth most common cause of death after pediatric heart transplantation (PHTx). The purpose of this analysis of the ISHLT registry was to determine the prevalence, risk factors and outcomes of stroke after PHTx.

Methods

Study design

This study was a retrospective cohort analysis of ISHLT registry transplants performed from 1988 to 2010. The ISHLT registry is an international longitudinal voluntary database that collects data from the time of transplant and throughout follow-up.

Study population

Heart transplant recipients whose primary transplant was performed at <18 years of age were included in our study data. Those patients who had any stroke, irrespective of etiology, were the focus of our analysis. The comparison group included all transplantations, both primary and retransplantations, within the registry over the same time period. Patients who underwent multi-organ transplantation were excluded from the analysis.

Data collection

Risk factors for stroke were divided into patients' characteristics, pre-transplant characteristics, transplant characteristics, post-transplant complications and complications during follow-up. Outcomes were evaluated at the time of yearly follow-up.

Statistical analysis

Data are described as mean with standard deviation or as median with the 5th and 95th percentiles and frequencies. Variables were excluded when there were no events in the patient population, when there was a high level of missing data (>70%), and wherever rates were <1% or variables were considered not relevant to the analysis. Time-related events (morbid events and survival) were modeled in multiphase parametric hazard models that decompose risk over time in up to 3 additive, overlapping phases of risk (descriptively labeled as early, constant and late, but actually representing different mathematical functions to model specific patterns of event distribution over time). The analysis was performed using the HAZARD procedure for SAS available from http://www.clevelandclinic.org/heartcenter/hazard. A complete mathematical description and validation of the procedure has been published.[10] Associations between patients' characteristics and hazard of stroke were first tested at the univariable level. Associations with $p < 0.10$ were then included in a multivariable regression model with backward selection of variables to obtain a final model. Bootstrap bagging resampling (500 random samples) was used to determine the internal validity of the multivariable risk models using a reliability threshold of 50% (i.e., variable selected in at least 50% of the random samples). Mean imputation was used to account for missing variables. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Patients' characteristics

Patients' characteristics are summarized in Table 1. Univariable risk factors for stroke are summarized in Table 2 and multivariable risk factors are summarized in Table 3. Patients with stroke were more likely to have had: CHD [hazard ratio (HR) 1.31 (1.05 to 1.62), $p = 0.02$], although the proportion with cardiomyopathy vs CHD was similar in the stroke cohort (46% vs 44%); a pre-transplant history of aborted sudden death [HR 1.63 (1.25 to 2.13), $p < 0.001$]; previous stroke [HR 6.12 (4.13 to 9.06), $p < 0.001$]; hospitalization before transplantation [HR 1.52 (1.17 to 1.97), $p = 0.002$]; been hospitalized for >31 days (38% vs 29%, $p = 0.04$); an infection requiring antibiotics before transplantation [HR 2.08 (1.57 to 2.74), $p < 0.001$]; a need for dialysis before transplantation [HR 2.46 (1.15 to 5.24), $p = 0.02$]; and received a blood transfusion before transplantation [HR 2.88 (1.06 to 1.46), $p = 0.007$]. At the time of transplantation, patients with stroke were more likely to require inotropes [HR 1.26 (1.00 to 1.59), $p = 0.05$], mechanical ventilation [HR 2.00 (1.56 to 2.56), $p < 0.001$] or mechanical circulatory support in the form of a ventricular assist device (VAD) [HR 2.17 (1.55 to 3.04), $p < 0.001$] or extracorporeal membrane oxygenation (ECMO) [HR 2.84 (1.96 to 4.11), $p < 0.001$]. Retransplantation [HR 1.76 (1.17 to 2.66), $p = 0.007$] and later year of transplantation was also associated with stroke [HR 1.11 (1.08 to 1.13)].

Risk factors that remained significant for stroke on multivariable analyses included CHD [HR 1.35 (1.08 to 1.69), $p = 0.009$], a history of aborted sudden death [HR 1.48 (1.11 to 1.97), $p = 0.007$], later transplant year