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Fontan-associated protein-losing enteropathy and heart transplant: A Pediatric Heart Transplant Study analysis

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BACKGROUND: Post-Fontan protein-losing enteropathy (PLE) is associated with significant morbidity and mortality. Although heart transplantation (HTx) can be curative, PLE may increase the risk of morbidity before and after HTx. This study analyzed the influence of PLE influence on waiting list and post-HTx outcomes in a pediatric cohort.

METHODS: Fontan patients listed for HTx and enrolled in the Pediatric Heart Transplant Study from 1999 to 2012 were stratified by a diagnosis of PLE, and the association of PLE with waiting list and post-HTx mortality, rejection, and infection was analyzed.

RESULTS: Compared with non-PLE Fontan patients ($n = 260$), PLE patients listed for HTx ($n = 96$) were older (11.9 years vs 7.6 years; $p = 0.003$), had a larger body surface area (1.1 m^2 vs 0.9 m^2; $p = 0.0001$), had lower serum bilirubin (0.5 vs 0.9 mg/dl; $p = 0.01$), lower B-type natriuretic peptide (59 vs 227 pg/ml; $p = 0.006$), and were less likely to be on a ventilator (3% vs 13%; $p = 0.006$). PLE patients had lower waiting list mortality than non-PLE Fontan patients ($p < 0.0001$). There were no intergroup differences for post-HTx survival or times to the first infection or rejection. PLE was not independently associated with increased post-HTx mortality at any time point.

CONCLUSIONS: In this multicenter cohort, the diagnosis of PLE alone was not associated with increased waiting list mortality or post-HTx morbidity or mortality. Given the limitations of our data, this analysis suggests that PLE patients in the pediatric age group have outcomes similar to their non-PLE counterparts. Additional multicenter studies of PLE patients with targeted collection of PLE-specific information will be necessary to fully delineate the risks conferred by PLE for HTx.

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Staged palliation to Fontan circulation is the current standard of care for patients with single-ventricle physiology. Unfortunately, severe and life-threatening complications may occur after the Fontan palliation, including protein-losing

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enteropathy (PLE). PLE is characterized by the abnormal loss of protein into the enteral lumen, which results in hypoproteinemia and hypoalbuminemia,[1] and although it has been reported in 1% to 11% of Fontan patients,[1,2] the true prevalence is unknown. The consequences of enteral protein loss are numerous, including loss of intravascular oncotic pressure leading to diffuse edema, disturbed calcium regulation, enhanced coagulation, quantitative immune abnormalities with probable immune dysregulation, poor bone density, and growth failure[1,3]; these morbidities cumulatively contribute to marked morbidity and mortality in this patient group.[4]

PLE is frequently characterized by a waxing and waning course punctuated by flares in protein loss and resulting symptoms. Further, the severity of protein loss and resulting sequelae may vary significantly between patients. This heterogeneity in the disease often makes evaluating the response to therapy challenging. Thus, although multiple pharmacotherapeutic options and anatomic interventions have demonstrated some efficacy in temporizing PLE symptoms, no available therapy has been shown to be consistently curative except heart transplantation (HTx).[5–8]

The 2006 Pediatric Heart Transplant Study (PHTS) evaluation of Fontan patients undergoing HTx found no difference in survival between PLE and non-PLE patients but only included 25 PLE patients in the cohort.[8] This study was limited by a small sample size and limited duration of follow-up. More recently, reports from larger centers, including PLE patients in the current era, found worsened survival in Fontan patients with preserved ventricular systolic function, most of whom had PLE.[5,9] This creates a more concerning picture for PLE patients after HTx.

Compared with the 2006 PHTS Fontan study, which examined patients who received transplants from 1993 to 2001, the growth of the PHTS database over recent years allows a significantly larger cohort of modern-era patients with at least 1 year of follow-up to be analyzed and allows PLE patients to be analyzed as a separate group entirely. This analysis can now include evaluation of risk factors within the PLE patient group that were not performed in the previous PHTS Fontan study. Thus, to better understand the influence of PLE on waiting list and HTx outcomes, this study used the PHTS database to (1) compare the characteristics and pre-HTx and post-HTx outcomes of Fontan patients with and without PLE, and (2) determine unique pre-HTx risk factors for pre-HTx and post-HTx outcomes in PLE patients. We hypothesized that Fontan patients with PLE possess disease-specific characteristics that increase their risk of poor outcome after HTx.

Methods

Patient population and data collection

This retrospective cohort study analyzed data from 3,668 patients undergoing HTx between January 1, 1999, and December 31, 2012, at 35 participating PHTS institutions. Demographic, clinical, and event data were collected for all HTx recipients from each participating center. As has been previously described, the data were collected using coded event forms and sent to the data analysis center at the University of Alabama in Birmingham, where the information was entered into a secure database, verified, and corrected as needed.[10] Institutional Review Boards from participating centers approved all studies. The study excluded patients who received multiple solid-organ transplants. Follow-up on all patients was complete through December 31, 2012.

Outcome measures

The a priori primary outcome measure was death after HTx. The secondary outcomes studied were time to the first infection and time to the first rejection episode. The PHTS manual defines the outcome "rejection" as a clinical circumstance (biopsy or otherwise driven) leading to an increase in immunotherapy and the outcome "infection" as evidence of an infectious process requiring intravenous therapy or a life-threatening infection requiring oral therapy.[11]

Statistical analysis

We examined data using standard descriptive statistics, including mean and standard deviation, median and interquartile range (IQR), or number and percentage of the total, as appropriate, based on the data's distribution. Continuous variable distributions were evaluated for equality of variance, and *t*-tests were used for continuous variable comparisons because they are robust in symmetric distributions.

From 3,686 pediatric patients entered into the PHTS undergoing HTx between 1999 and 2012, 356 Fontan patients were stratified into cohorts by the presence or absence of PLE as reported at the time of HTx listing. PLE is reported as a "yes" or "no" check box on the PHTS data-collection forms. The PHTS form manual of operations for form completion does not provide any guidance regarding what constitutes a diagnosis of PLE; centers respond to this item at their own discretion. Similarly, the patient factor "failure to thrive" is also a "yes" or "no" check box without specific criteria set by the PHTS.

Two-group comparisons for individual patient factors were performed using appropriate parametric or non-parametric tests as dictated by the statistical characteristics of the data, with *t*-tests being used for most comparisons of continuous variables. Competing-outcomes analyses examined the temporal influence of PLE on simultaneous risks of death or HTx in patients on the HTx waiting list. Cox proportional hazard analysis examined risk factors for waiting list death censored for HTx in the overall Fontan cohort. Kaplan-Meier time-to-event analyses with log-rank test comparisons evaluated the temporal influence of PLE on post-HTx outcomes.

All study patient status was available up to the 10-year study period or until death. No minimum time to follow-up was required to be included in the post-HTx analyses, although every surviving patient had at least 1 year of post-HTx follow-up. Cox proportional hazard analysis assessed PLE as a risk factor for death within the entire study cohort. The PLE cohort was further analyzed using Cox proportional hazard analysis (the variables analyzed are listed in Tables 1 and 2) to determine independent risk factors for post-HTx death and Kaplan-Meier time-to-event analyses with right censoring to evaluate the temporal influence of specific factors that could indicated more severe PLE, including intensive care unit hospitalization at HTx, inotrope dependence at HTx, or having a low (<17 kg/m^2) or high (>21 kg/m^2) body mass index (BMI) at HTx, on death within the PLE cohort.