Genetic and Extracardiac Anomalies Are Associated With Inferior Single Ventricle Palliation Outcomes

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Background. We examined the effect of genetic syndromes and extracardiac (GS/EC) anomalies on single-ventricle (SV) palliation with focus on hospital and interstage death and progression toward subsequent palliation stages.

Methods. First-stage palliation was performed in 530 neonates with SV: Norwood in 284 (53%), shunt in 173 (33%), and band in 73 (14%). Outcomes were compared between those with GS/EC anomalies (121 [23%]) and without GS/EC anomalies (409 [77%]). Regression analyses were adjusted for other risk factors (age, sex, prematurity, weight, SV anomaly, and first-stage palliation operation).

Results. GS/EC anomalies varied among SV defects (range, 3% for double-inlet left ventricle to 100% for atrial isomerism). Patients with GS/EC anomalies required significantly longer durations of mechanical ventilation and intensive care unit and hospital stay. Although patients had comparable rates of extracorporeal membrane oxygenation (13% vs 11%, $p = 0.552$) and unplanned reoperation (16% vs 11%, $p = 0.189$), hospital mortality was higher in patients with GS/EC anomalies (24% vs 12%, $p = 0.0008$). After discharge, patients with GS/EC anomalies had higher interstage death, with lower progression to Glenn (60% vs 77%, $p = 0.002$) and lower 10-year survival (56% vs 76%, $p < 0.001$). After adjustment for other risk factors, GS/EC anomalies significantly affected survival in almost all subgroups of patients.

Conclusions. The presence of GS/EC anomalies varies among SV anomalies and is associated with additional risk factors such as prematurity and low weight. After adjusting for other risk factors, GS/EC anomalies are associated with prolonged recovery after first-stage palliation and increased hospital and interstage death, with subsequently fewer patients progressing toward Glenn shunt. The increased death risk in those patients is highest in the first 6 months and persists for 2 to 3 years after first-stage palliation, suggesting the need for more vigilant monitoring and outpatient care in these high-risk patients.

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The reported incidence of genetic syndromes and major extracardiac (GS/EC) anomalies in neonates with congenital heart disease is 20% to 30% [1–5]. GS/EC anomalies are associated with prolonged recovery and worse outcomes after neonatal cardiac operations [3, 4, 6–8]. In addition, neonates with GS/EC anomalies often have associated risk factors such as prematurity, low birth weight, and poor clinical condition [4]. GS/EC anomalies might subsequently affect timing of a surgical intervention and complicate perioperative care and home management. [3, 4, 6–8]. Although GS/EC anomalies have been identified to be associated with poor hospital survival in patients with various single-ventricle (SV) anomalies, the effect of GS/EC anomalies on progression toward subsequent palliative stages has not been well studied [4, 9–14].

We aimed to examine the prevalence of GS/EC anomalies in neonates with SV anomalies undergoing first-stage palliation, to report associated risk factors, and to assess the effect of GS/EC anomalies on hospital outcomes, resource utilization, progression toward Glenn and later Fontan operations, and midterm survival.

Patients and Methods

Inclusion Criteria

From 2002 to 2012, 530 neonates born with SV anomalies underwent first-stage palliation at Children's Healthcare of Atlanta, Emory University. Patients were identified using our institutional surgical database. Demographic, anatomic, clinical, operative, and hospital details were abstracted from medical records for analysis. The hospital's Institutional Review Board approved this study and

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waived the requirement for individual consent for this observational study.

Screening for GS/EC Anomalies

Neonates who are admitted to the cardiac intensive care unit at our institution undergo chromosomal analysis if they have cardiac defects commonly associated with genetic anomalies (eg, conotruncal lesions, complete atrioventricular septal defect), hypoplastic left heart syndrome, extracardiac malformations (eg, imperforate anus, tracheal-esophageal fistula), or any dysmorphic features. During the course of this current study, the type of chromosomal analysis changed. In the earlier phase, those neonates underwent standard metaphase karyotype chromosomal analysis (450 to 550 bands), high-resolution banding (600 to 850 bands), and fluorescent in situ hybridization studies; in the later phase starting in 2010, chromosomal microarray testing became the standard study for chromosomal analysis in our unit.

Follow-Up

Time-related outcomes were determined from recent office visits documented in our electronic record system or from direct correspondence with other pediatric cardiologists outside the system. Mean follow-up duration was 5.9 ± 4.1 years and was 91% complete.

Statistical Analysis

Statistical significance was evaluated at the 0.05 level, and data analyses were performed using SAS 9.4 software (SAS Institute, Inc, Cary, NC). Patient demographic and clinical characteristics were evaluated using means and SDs or medians and ranges for continuous variables, or counts and percentages for categoric variables. Differences between the study groups (GS/EC anomalies present vs absent) were assessed using *t* tests for continuous variables and χ^2 tests for categoric variables. In situations of nonnormality, the *t* test was replaced by a nonparametric equivalent (Mann-Whitney *U* or Kolmogorov-Smirnov test); likewise, an exact form of the Pearson χ^2 test was implemented when expected frequency counts were low (<5). Continuous outcomes of interest included durations of ventilation and intensive care unit and postoperative hospital stay; concurrently, hospital death, need for extracorporeal membrane oxygenation (ECMO), and unplanned reoperation were evaluated. Continuous outcomes were log-transformed before statistical modeling.

General linear regression and binary logistic regression models were used to evaluate the effect of GS/EC anomalies on continuous and binary outcomes, respectively. Unadjusted and adjusted estimates are reported with associated 95% confidence intervals (CIs). In the adjusted analyses, estimates were controlled for weight, age, sex, prematurity, underlying SV anomaly, and type of first-stage palliative operation (Norwood, shunt, band).

Time until death after the initial operation was modeled using a parametric survival model. Parametric probability estimates for time-dependent outcomes (ie, death) were based on models using multiple, overlapping phases of risk from PROC HAZARD. The HAZARD procedure uses maximum likelihood estimates to resolve risk distribution of time-to-event data in up to three phases of risk (early, constant, and late hazard). Nonlinear optimization-based algorithms were used to iteratively calculate maximum likelihood estimates. Smoothed survival curves were generated using the HAZPRED procedure.

Competing risk analysis was performed to model the probability over time of each of the following two mutually exclusive end points after first-stage palliation: death or transplantation and survival to Glenn, with the remaining patients being alive without Glenn. After Glenn, mutually exclusive end points were death or transplantation and survival to Fontan, with the remaining patients being alive awaiting Fontan.

The overall risk for death, our primary outcome, was strongest in the first 6 months after the initial operation. Given this trend, an early-phase model was most appropriate for these data. The effect of study group (GS/EC present vs absent) on early-phase death was examined parametrically among subsets of patients. Effects of study group on the probability of death are given as hazard ratios with 95% CIs.

Results

Patients' Characteristics

Between 2002 and 2012, 530 neonates with SV underwent first-stage palliation. Of those, 121 (23%) had GS/EC anomalies and 409 (77%) did not.

Chromosomal abnormalities were identified in 107 neonates and included Down syndrome (n = 6), 22q11.2 deletion syndrome (n = 4), laterality sequences (ie, heterotaxy syndrome; n = 58), sex chromosome–related syndromes (ie, Turner, Klinefelter, XYY; n = 6), chromosomal abnormalities involving various mutations (ie, CHARGE [coloboma, heart defect, atresia choanae, retarded growth and development, genital abnormality, and ear abnormality], Dandy-Walker, cat eye, Pfeiffer; n = 8), chromosomal abnormalities involving various monosomies, trisomies, deletions, or duplications (ie, cri du chat, Jacobsen; n = 10), single gene abnormalities (ie, sickle cell, CHILD [congenital hemidysplasia with ichthyosiform erythroderma and limb defects], Mowat-Wilson; n = 4), multifactorial syndromes associated with genetic origins (ie, VACTREL [vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities]; n = 2), and severe dysmorphia without an identified chromosomal abnormality (n = 9). In addition, the GS/EC anomalies group included 14 neonates who had major extracardiac anomalies without genetic syndromes (ie, tracheoesophageal fistula, intestinal atresia, imperforate anus, Hirschsprung disease, and omphalocele).

Median age was 6 days (interquartile range [IQR], 4 to 10 days), and median weight was 3.1 kg (IQR, 2.8 to 3.5 kg) with 77 (15%) weighing 2.5 kg or less. Overall, 78 (14%)