Hypoplastic Left Heart Syndrome
Long-term Survival and Neurodevelopmental Outcomes

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The prognosis for neonates born with hypoplastic left heart syndrome (HLHS), considered a uniformly fatal condition as recently as the early 1980s, has dramatically improved. The increase in the out of hospital survival for the neonatal intervention (contemporary range - 77%-93%) accounts for the majority of the improvement (1-5). Reduction in mortality is accounted for by the continued innovation and refinement in surgical and interventional techniques, including an alternative source of pulmonary blood flow (RV to PA shunt), hybrid palliation, and heart transplantation, earlier diagnosis and referral to tertiary care centers, and advancements in the intensive care of peri-operative patients. Risk factors for mortality include: low birth weight, genetic syndromes, pre-operative shock, obstruction to pulmonary venous return, and severe ventricular dysfunction. Both the superior cavo-pulmonary anastomoses and the Fontan procedures are associated with both low operative (< 3%) and long-term mortality. In spite of progressively lower Stage I mortality, death following hospital discharge after Stage I and prior to 2nd stage reconstruction remains unchanged at between 7-15% (6-8). Given the heterogeneous nature of the events resulting in death, there is a need to identify patients at risk, to increase and standardize inter-stage surveillance and to promptly investigate subtle abnormalities (9).

At the same time survival was continuing to improve, clinicians began to examine the quality of life of this growing cohort of patients. The most significant consistent morbidity found was abnormal neurodevelopmental outcomes. Cross-sectional studies of school age survivors of staged reconstruction reveal a high frequency of neurodevelopmental disabilities manifest as a common pattern of dysfunction consisting of cognitive impairment, abnormalities in speech and language, gross and fine motor delay, ADHD, and learning disabilities (10). Investigators initially examined the intra-operative course as it was presumed by most that the etiology of the adverse neurodevelopmental outcomes was hypoxic-ischemic injury sustained during the procedure. It was postulated that this injury occurred either as a result of the strategies necessary to conduct the procedure itself including institution of bypass with either low flow or hypothermic circulatory arrest, cooling, hemodilution and pH management or secondary to abnormal flow patterns, suboptimal hemodynamics or arterial desaturation. Not only were investigators not able to prove cause and effect, but there was data to suggest that factors other than the intra-operative experience may play a role in neurodevelopmental outcomes. This prompted looking at a broader time frame, beginning during gestation, and examining other mechanisms of injury. Given

that only a percentage of patients that were exposed to a nearly identical clinical course experienced abnormal outcomes, clinicians began to attempt to identify patients at risk.

Some cardiac malformations including HLHS, IAA, obstructed total veins, genetic syndromes including DiGeorge and certain polymorphisms of the Apolipoprotein E genotyte are risk factors for neurodevelopmental sequelae after infant heart surgery (11). Neonates with HLHS have a significant incidence of structural and/or functional brain abnormalities that exist prior to any post-natal intervention including: microcephaly (25-50%), open operculum (25%), periventricular leukomalacia (PVL) (20%), an increase in white matter lactate (50%) and low cerebral oxygenation measured by near-infrared spectroscopy (12-13). These findings raise the concern for chronic cerebral hypoperfusion that might adversely affect the brain long before the conduct of a surgical intervention. Licht et al. performed pre-procedure structural brain magnetic resonance imaging (MRI) and used pulse arterial spin-label perfusion MRI to measure cerebral blood flow (CBF) (14). In a cohort of 25 anesthetized neonates with congenital heart disease, 10 of which had HLHS, the average CBF (20 $\pm$ 10 ml/100 grams/min) was considerably lower than in otherwise normal neonates under conscious sedation (50 ml/100 grams/min). Patients with PVL had a lower CBF compared to those without. Recently, Tabbutt et al. reported the results of neurodevelopmental testing using Bayley Scales of Infant Development II at one year of age in a cohort of 89 infants who underwent staged palliation. For the group, the median motor (PDI) scores were more affected than the mental (MDI) scores, with 47% and 11% of the scores 2 standard deviations below the mean for the general population for PDI and MDI respectively. Multivariate analysis identified suspected or confirmed genetic syndromes, younger gestational age and earlier surgical era (1998-2001) as risk factors negatively impacting outcome.

In 2007, we need to continue to whittle away at mortality. We are just beginning to scratch the surface in our understanding of why some patients have abnormal neurodevelopmental outcomes when others go through what we consider to be the same process unscathed. The focus of the care of neonates with HLHS needs to be on striving to insure that the quality of life of the survivors closely approximates that of children without congenital heart disease. This will require elucidating the mechanisms that are responsible for the abnormal findings and identifying modifiable risk factors. Only when this is accomplished will we be able to develop strategies to minimize or prevent these abnormal outcomes. Until then, it is imperative that these children are screened as early as possible for evidence of any neurologic abnormality and to intervene in an attempt to minimize the impact of this abnormality on their quality of life and that of others around them.

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