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Neurodevelopment and quality of life for children with hypoplastic left heart syndrome: current knowns and unknowns

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Abstract

The aim of this review is to describe the current state of knowledge related to neurodevelopmental outcomes and quality of life for children with hypoplastic left heart syndrome and to explore future questions to be answered for this group of children.

Keywords

Hypoplastic left heart syndrome; Neurodevelopment; Norwood; Quality of Life

Neurodevelopment and quality of life rank among the most important outcomes to be measured for children with congenital cardiac disease. The operative and peri-operative successes of the 1980s and 1990s for children with hypoplastic left heart syndrome, and the resulting improved survival, have led to the ability to focus on neurodevelopment and quality of life outcomes when evaluating treatment for this high-risk diagnosis. It is commonly understood that myriad factors affect neurodevelopmental outcomes for children with hypoplastic left heart syndrome, as seen in other complex cardiac anomalies. This review will summarise what is known about the degree of neurodevelopmental impairment and quality of life for children with hypoplastic left heart syndrome, describe the factors recognised to influence these outcomes, and explore some of the many questions remaining for developmental and quality of life outcomes for these children.

Cross-sectional measurements of intelligent quotient and other developmental and behavioural functioning

It is now well described that children with complex congenital cardiac disease are at increased risk for developmental delays and disabilities, as well as behavioural abnormalities. The diagnosis of hypoplastic left heart syndrome is associated with increased

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incidence and severity of impairment when compared with other congenital cardiac malformations.[1,2]

In a recent series, development has been demonstrated to be delayed in older infants and toddlers. Tabbutt et al[3] evaluated development in 83 1-yearolds with hypoplastic left heart syndrome using the Bayley Scales of Infant Development II, which includes the Mental Development Index and the Psychomotor Development Index, each with standardised means for the general population of 100 and a standard deviation of 15 points. The mean score on the Mental Development Index for these study participants was 90 and the mean score on the Psychomotor Development Index was measured at 73. Goldberg et al[4] similarly found the mean Mental Development Index to be 92 and the Psychomotor Development Index to be 77 among a group of 1-year-olds with hypoplastic left heart syndrome participating in a randomised trial. As with developmental outcomes for other congenital cardiac diseases, Psychomotor Development Index scores are consistently lower than the Mental Development Index for children with hypoplastic left heart syndrome.

Multiple investigators have measured neurological outcomes for pre-school and school-aged survivors of hypoplastic left heart syndrome. The earliest reports were quite dismal.[5] Subsequently, multiple groups reviewed their single-centre experience and developmental outcomes for children with single ventricle anomalies following the Fontan operation.[2,6–8] Among Fontan survivors in these series, mean intelligence quotient levels were within the normal range, yet there was a consistent ‘‘left shift’’ in each and every report, with an increased rate of lower intelligence quotients and developmental disabilities for Fontan patients compared with the general population. Visual motor integration was detected as an area of particular delay.[6] In a historical cohort including some of the first survivors of staged reconstruction, Mahle et al[8] evaluated school-aged children with Fontan physiology and found that on neurological examination 69.5% had evidence of attention deficit disorder and approximately one-third were reported to receive special education services. In summary, these studies[2,6–8] clearly demonstrated that children with hypoplastic left heart syndrome who have survived staged Fontan palliation can have normal developmental outcomes, but nonetheless are at significant risk for learning disorders, lowered academic achievement, and behavioural abnormalities.

Factors that may influence developmental outcomes

Multiple factors likely influence neurodevelopment in children with hypoplastic left heart syndrome, including associated neurological malformations, genetic conditions, anatomic factors, surgical techniques, and intra-operative perfusion methods.

Abnormalities of the central nervous system were identified by Glauser et al[9,10] through autopsy series to include acquired malformations in 45% and congenital malformations in 29% of infants with hypoplastic left heart syndrome. These findings have been reinforced using magnetic resonance imaging. Consistent with the hypothesis that foetal brain growth may be impaired in the foetus with hypoplastic left heart syndrome due to reduced blood flow through a diminutive aorta, Shillingford et al[11] found that microcephaly among newborns with hypoplastic left heart syndrome was associated with a smaller ascending aorta. Recently, using magnetic resonance measures of myelination, cortical folding, involution of glial cell migration bands, and the presence of germinal matrix tissue, Licht et al[12] found the brain structures of term infants with hypoplastic left heart syndrome to be 1 month less mature than those of healthy newborns. Magnetic resonance spectroscopy has also been used to gauge maturation of brain metabolism in patients with congenital cardiac disease,[13,14] with consistent findings that term newborns[13] and third trimester foetuses[14] have delayed brain maturation for gestational age compared with healthy, gestational age-

matched controls. The immature brain may be more susceptible to injury, and indeed younger gestational age among infants with hypoplastic left heart syndrome has been associated with developmental delay as measured by Bayley Scales of Infant Development at 1 year of age.[3] These data suggest that elective delivery before 39–40 weeks of gestation should be avoided if possible.

Genetic factors are likely important contributors to neurodevelopmental outcomes for children with hypoplastic left heart syndrome. Among the 88 patients with hypoplastic left heart syndrome enrolled in the apolipoprotein E trial conducted at the Children's Hospital of Philadelphia, 35% were found to have a genetic syndrome or chromosomal abnormality and this sub-group, compared with those without genetic abnormalities, was found to have lower scores on the Bayley Scales of Infant Development II at 1 year.[3]

Over time, prenatal diagnosis has become more common with a large percentage of children with hypoplastic left heart syndrome identified as having the cardiac malformation during foetal life. Although foetal diagnosis has not been demonstrated to improve survival, there are some data that point to a positive influence on neurological outcomes associated with a prenatal diagnosis. Mahle et al[15] showed that neurological events, including coma or seizure, were less likely to occur after prenatal diagnosis. Potentially, the prenatal diagnosis enabled stabilisation and initiation of prostaglandin therapy before closure of the arterial duct and therefore reduced the risk of decompensation compared with neonates with a postnatal diagnosis. Although it is likely that this early avoidance of neurological events is associated with improvement of long-term neurodevelopmental outcomes, the long-term implications of these early findings remain uncertain.

Cardiac surgery, a necessity for survival for infants diagnosed with hypoplastic left heart syndrome, may carry some significant risk for neurological injury. Periventricular leukomalacia, necrosis of the cerebral white matter in the region of the lateral ventricles, has been demonstrated by magnetic resonance imaging in 50% of newborns following cardiac surgery with cardiopulmonary bypass and is more likely in newborns with prolonged cardiopulmonary bypass time.[16]

The standard Norwood operation has incorporated the use of deep hypothermic circulatory arrest during the aortic arch reconstruction. Owing to the fact that deep hypothermic circulatory arrest includes cooling the patient to 18 degrees centigrade, exsanguination of the blood volume to the bypass machine, and cessation of perfusion while the aortic arch reconstruction is performed, many have surmised that this technique exacerbates the risk of brain injury. The development of regional cerebral perfusion, a method used to supply oxygenated blood to the brain even during aortic arch reconstruction,[17,18] has grown out of this concern. Despite the intuitive impression that some cerebral blood flow is better than no cerebral blood flow, periventricular leukomalacia has been demonstrated at the same rate for newborns undergoing the Norwood operation with a strategy of regional cerebral perfusion as with the standard use of deep hypothermic circulatory arrest.[19] Furthermore, a single-centre trial of regional cerebral perfusion compared with deep hypothermic circulatory arrest was unable to demonstrate a beneficial impact on development with measurement of the Bayley Scale of Infant Development II at pre-stage 2 operation, or at 1 year of age.[4] Consensus on this issue is challenging, as regional cerebral perfusion can be delivered at a variety of rates and temperatures and through multiple cannulation techniques. Further study, likely with a multi-centre trial, will be required to address this question satisfactorily.

Other operative techniques may influence developmental outcomes as well. Haemodilution while on cardiopulmonary bypass has been instituted to avoid risks associated with increased viscosity related to cooling. However, haemodilution is recognised to reduce the

oxygen-carrying capacity of blood and thus could reduce oxygen delivery to the brain. For children undergoing cardiac surgery for two ventricle repairs, a strategy of haemodilution to haematocrit levels on cardiopulmonary bypass of 20%, compared with a strategy of haemodilution to 30%, was associated with lower scores on the psychomotor development index at 1 year of age.[20] Owing to the fact that this trial did not include any patients with single ventricle physiology, further study of haemodilution in this group who will remain hypoxaemic, even after the Norwood operation, may be warranted.

Instability in the intra-operative and peri-operative periods is thought to exacerbate risks to the central nervous system, and thus increased monitoring techniques both in the operating room and in the intensive care unit have become more common.[21–23] Continuous electroencephalogram monitoring, near-infrared spectroscopy, and/or transcranial Doppler ultrasound have all been described[21–23] and are being adopted by many centres despite limited evidence of any utility in improving neurological outcomes. Kussman et al[24] have described lower scores on the psychomotor development index and increased evidence of structural brain abnormalities associated with decreased cerebral oxygen delivery as measured by near-infrared spectroscopy during the peri-operative period in patients undergoing biventricular repairs. Whether employment of near-infrared spectroscopy and additional monitoring techniques will enhance longer-term developmental outcomes for children undergoing cardiac surgery and whether these findings should influence techniques for children with hypoplastic left heart syndrome remains unknown.

The Single Ventricle Reconstruction Trial, conducted by the Pediatric Heart Network, was the first multi-centre randomised surgical trial in congenital cardiac disease. Participants with hypoplastic left heart syndrome and other related single ventricle malformations were randomised to undergo the Norwood operation with one of the two shunt types, a modified Blalock–Taussig shunt or a right ventricle to pulmonary artery conduit.[25] The primary outcome for this trial was transplant-free survival at 1 year. Participants randomised to the right ventricle to pulmonary artery shunt were found to have better survival to this time point.[26] Among the secondary endpoints was neurodevelopmental outcome at 14 months of age.[25] Although results of this portion of the study are currently being analysed, inclusion of neurodevelopment as an important outcome reflects the understanding that these health-related quality of life outcomes should be considered routinely when evaluating any intervention for children with hypoplastic left heart syndrome.

It is noteworthy that although investigation continues to evaluate the influence of modifiable factors, such as perfusion techniques and surgical strategies, it appears that the variability of developmental outcomes explained by these factors is likely small. Evidence for this comes from Fuller et al[27] who found that patient-specific factors explain a larger portion of the variability. The similar developmental outcomes demonstrated in children with hypoplastic left heart syndrome who were treated primarily with cardiac transplantation, and had average full-scale intelligence quotients one standard deviation below that of the general population, reinforces this observation.[28] It is likely that treatment options interact with each patient’s genetic milieu to determine the influence of any particular intervention. The tools to evaluate such interactions are sure to be a part of the future.

Given the possibility of only minimal influence of surgical strategy on neurodevelopment and the reality that many intrinsic risk factors are not modifiable, attention must now focus on modifiable factors in the peri-operative period, such as ventilator strategies and nutrition, as well as family- and patient-centred strategies including physical, occupational, and speech and language therapies that may be used to improve outcomes. Importantly, support and education of the family has been shown to improve both maternal and child outcomes in other forms of complex cardiac disease, and is likely to have a similar impact in infants with

hypoplastic left heart syndrome.[29,30] In recent years, some congenital cardiac centres have developed programmes for surveillance of development in children with complex congenital cardiac diseases. Early identification of delays and earlier prescribed interventions may play a role in optimising functional outcomes. Further exploration of this approach is required to determine the best timing and combination of interventions to improve long-term developmental functioning for this high-risk group.

Quality of life outcomes

It is likely that neurodevelopmental function, as well as other associated morbidities and functional outcomes, influences quality of life. Whereas Uzark et al[31] did demonstrate that children with more complex congenital cardiac disease rated their quality of life lower than those with less serious congenital cardiac disease, others have shown that among a group with a particular diagnosis, health-related quality of life does not directly correlate with severity of disease.[32,33] Quality of life is a subjective measure that incorporates personal perceptions, expectations, and satisfaction, in addition to the influence of disease.[32,33] Data do support that relative perceptions are involved in measures of functional status, which are tied to quality of life. Studying a large multicentre cross-section of Fontan patients, Lambert et al[34] found that parents rated their child's functional status lower than the patient himself. In addition, in a smaller cohort, Fontan patients with a sibling were found to rate their functional status lower than Fontan patients without siblings.[35] Mellander et al[36] did evaluate quality of life among a group of 18 children with hypoplastic left heart syndrome who survived to 2 years of age, and were 2.7–10.5 years of age at the time of the study. Compared with healthy controls, the patients with hypoplastic left heart syndrome had lower self-esteem, more psychosomatic symptoms, and lower acceptance among peers. Compared with controls, however, their parents reported less time for their child and a higher rate of separations/divorces. Brosig et al[37] measured quality of life-related outcomes for children 3–6 years of age with hypoplastic left heart syndrome and transposition of the great arteries. Although at this age, quality of life, as measured by the Pediatric Quality of Life Inventory, was not different between these patients and healthy controls, the parents of children with hypoplastic left heart syndrome did report higher levels of parenting stress and that their child's illness had a negative impact on the family more often than parents of children with transposition of the great arteries.

As the community that cares for children with complex congenital cardiac disease and hypoplastic left heart syndrome strives to optimise outcomes for the individual, it is also valuable to consider the societal implications. Owing to the fact that more people with complex congenital cardiac disease survive to adulthood, improving behavioural and developmental outcomes will not only help to improve quality of life for the individuals but will also improve prospects that people born with hypoplastic left heart syndrome will be able to maintain jobs, engage in healthy relationships, and contribute positively to their communities and the larger society. Resource investment in determining the treatments that will optimise these important outcomes will have great worth.

Summary

In conclusion, as a group, children with hypoplastic left heart syndrome are at increased risk for adverse neurodevelopmental and behavioural outcomes, decreased functional status, and quality of life outcomes. These important outcomes must be considered when evaluating any new treatment approach. Efforts to modify surgical techniques may be somewhat helpful, although more investigation is required to understand the benefits of each approach before adoption as standard care. Patient-specific factors such as underlying genetic condition and gestational age do appear associated with developmental outcomes, encouraging avoidance

of elective pre-term delivery, consideration of interactions between genetics and treatment strategies, and investment in understanding the role of early intervention for developmental delays. There is extreme variability across institutions in the peri-operative management strategies,[38] but little investigation has been conducted on the impact of these variable strategies on central nervous system outcomes. Survival for large cohorts of patients with hypoplastic left heart syndrome is a relatively recent achievement. Further research to optimise psychosocial outcomes for these survivors has important implications for both the individual and society.

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