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Neurodevelopmental Outcomes in Children with Congenital Heart Disease – What can we impact?

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Abstract

Objectives—The objectives of this review are to discuss the scope of neurologic injuries in newborns with congenital heart disease, the mechanisms of injury, including pre-natal, pre- intra- and postoperative factors, neurodevelopmental outcomes and therapeutic strategies for the timely intervention and prevention of neurologic injury.

Data Source—MEDLINE, PubMed

Conclusion—At the current time, important research is underway to (1) better understand the developing brain in the fetus with complex congenital heart disease, (2) to identify modifiable risk factors in the operating room and intensive care unit in order to maximize long-term neurodevelopmental outcomes and (3) develop strategies to improve family psychosocial health, childhood development and health-related quality of life following hospital discharge. Crucial in this effort is the identification of an early post-operative surrogate variable with good predictive validity for long-term outcomes. If an appropriate surrogate variable for long term outcomes can be identified, and measured relatively early after surgical intervention for complex congenital heart disease, reliable clinical trials can be undertaken to improve upon current outcomes.

Keywords

neurologic injury; pediatrics; cardiac surgery; cardiopulmonary bypass; outcomes

Introduction

Prior to the early 1980s, it was uncommon for children with complex congenital heart disease (CHD) to survive into later childhood. The nearly simultaneous advances in congenital cardiac surgery, echocardiography, and intensive care medicine were coupled with the availability of prostaglandins and the developing discipline of interventional

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cardiology. Together, these factors resulted in a dramatic fall in surgical mortality, with complex repairs taking place at increasingly younger ages. At many large centers, palliative surgery followed by later repair was replaced by primary repair in infancy, while staged reconstructive surgery for various forms of functionally univentricular heart, including those with the hypoplastic left heart syndrome, was improving with steadily falling rates of surgical mortality. As a result, the early part of the 21st century has seen an increasing number of children entering primary and secondary schooling. Research into their academic and behavioral outcomes has revealed some sobering realizations about the outcomes in these children. For the purposes of this manuscript, complex CHD will refer to morphological abnormalities significant enough to require surgical or catheter intervention as neonates or young infants.

Scope of the Problem

An estimated 30,000 to 40,000 children are born in North America each year with CHD and approximately one third require surgical intervention during the first year of life. For the group of children with complex CHD, neurodevelopmental disabilities are common, affecting approximately half of the survivors as they mature (1–6). These disabilities are typically mild, but also commonly occur in combination, and occasionally are quite debilitating. Formal evaluations of preschool and school-aged children born with complex CHD demonstrate a pattern of neurodevelopmental sequelae which may appear alone or in combination. These include mild cognitive impairment; oral-motor dyscoordination, expressive speech and language abnormalities; impaired visual-spatial and visual-motor skills; attention-deficit/hyperactivity disorder (ADHD); motor delays; learning disabilities; and later problems with executive function and diminished health-related quality of life (Table 1). Indeed, neurodevelopmental challenges are more common in children and young adults with complex CHD than all cardiovascular problems combined. The need for early intervention, rehabilitative services, and special education reduces the quality of life for these children and their families, as well as resulting in significant costs to society (1). As children progress through school, low scores in terms of academic achievement, learning disabilities, behavioral problems, difficulties with social cognition and attention deficit/hyperactivity disorder may result in academic failure, development of poor skills in both the classroom and socially, low self-esteem, behavioral disinhibition, and ultimate delinquency. Given these findings, there is active interest in better understanding the mechanisms of brain injury in these children, in order to design treatment trials and improve long-term outcomes for future patients. In addition, there is active interest in adapting techniques used to treat these disabilities in children without complex CHD to this growing population (7–9).

Mechanisms of Injury

Central nervous system (CNS) injury in children with CHD is a result of a complex interaction of patient-specific factors and environmental influences, including, but not limited to, the effects of various interventions such as cardiac surgery and perioperative care (figure 1). The risk of a poor developmental outcome varies according to the specific cardiac defect. In addition, there is significant interindividual variation in developmental outcome, even among children with the same cardiac defect. Although cerebral ischemia before,

during, and after the surgical repair of complex CHD has been proposed to be the primary mechanism of CNS injury, additional in-hospital and later factors may contribute to neurologic dysfunction. These factors can broadly be divided into three main categories and time-frames: (1) prenatal, (2) perioperative, and (3) post-discharge. From a research perspective, it is difficult to separate out the relative contributions of these three mechanistic categories, as they co-exist in the majority of neonates.

Pre-natal Mechanisms of Brain Injury

There is growing recognition that the brain is abnormal at birth in many neonates with complex CHD. Particularly with the recent advances in fetal and post-natal Magnetic Resonance Imaging (MRI), imaging studies have identified a surprisingly high incidence of white matter injury, stroke and hemorrhage, as well as brain immaturity at birth (10–13). MRI and previously reported echocardiography-Doppler studies have confirmed abnormalities of fetal blood flow and reduced substrate delivery that lead to immaturity of the developing brain (14–17). In addition, there is an increased incidence of congenital structural CNS abnormalities in association with complex CHD (10, 12, 18). In combination, these functional and anatomic abnormalities seen in the newborn with complex CHD might best be considered coexisting “Congenital Brain Disease” (CBD), and appear to be present in nearly half of these neonates.

Fetal Cerebrovascular Physiology and Oxygen Delivery

Ultrasound studies in the fetus have revealed that cerebral vascular resistance is altered in the presence of congenital cardiac disease. Fetuses with left-sided disease such as the hypoplastic left heart syndrome, have been found to have decreased cerebral vascular resistance compared to normal (14, 15). In patients with aortic atresia, the fetal cardiac output from the arterial duct must deliver flow cephalad to the brain as well as caudad to the low resistance placenta. It is speculated that cerebral vascular resistance must therefore be lower than normal to allow adequate blood flow to the developing brain. In contrast, fetuses with right-sided obstructive lesions such as tetralogy of Fallot have been shown to have increased fetal cerebral vascular resistance (15). In these children, it is speculated that the obstruction to flow into the pulmonary arteries changes the usual delivery from the patent arterial duct caudad to the placenta. In these cases, the left ventricle must contribute to placental blood flow antegrade from the ascending aorta, with a resultant increase in cerebral vascular resistance. The impact of these alterations in fetal cerebral vascular resistance is unclear, but almost certainly plays a role in subsequent neurological development and has significant implications for the transition from fetal to neonatal circulation.

In the normal fetus, the intracirculatory patterns created by the normal fetal connections result in preferential streaming of the most highly oxygenated fetal blood to the developing brain, and most desaturated blood to the placenta. When significant structural disease exists within the heart, these beneficial patterns are likely to be altered. Recently confirmed by fetal magnetic resonance T-2 relaxation measurements, fetuses with transposition of the great arteries have the blood with the lowest saturation of oxygen returning to the ascending aorta and brain, while blood with the highest saturation returns to the abdominal organs and

placenta (17, 19). Speculation on the consequences of the transposed fetal circulation (as an explanation for the high incidence of macrosomia in these infants) dates back nearly 50 years and has also been offered as an explanation for the increased incidence of relative microcephaly and long-term developmental challenges seen so often in transposition of the great arteries (20). Complete mixing, as seen in those with functionally univentricular hearts, and limitations on compensatory lowering of cerebrovascular resistance, produce reduced fetal cerebral oxygen delivery. The contribution of the placenta adds complexity to the issue as it has been noted that placenta weights are much lower than normal and placental vascularity is abnormal (21). Furthermore, MRI measurements of umbilical vein oxygen saturations have been shown to be much lower than expected, suggesting placental dysfunction (17).

It has long been recognized that the neurologic status of newborns with complex CHD is frequently abnormal prior to open heart surgery, including tone abnormalities, abnormal posturing, weak cry, and poor coordination of suck, swallow, and breathing (22, 23). Following birth, cerebral blood flow has been shown to be significantly lower than normal in some patients, due to low cardiac output, competition with pulmonary vascular resistance, or a low diastolic blood pressure (“steal”) secondary to a patent ductus arteriosus (24). In some lesions such as total anomalous pulmonary venous return with obstruction and transposition of the great arteries with an intact atrial and ventricular septum, profound hypoxemia and acidosis may result immediately after birth secondary to the uncorrected complex CHD. Certain procedures, such as balloon atrial septostomy, have been linked to an increased risk of stroke by some authors (25, 26) but not others (27–29). Genetic syndromes, present in a significant proportion of children with complex CHD, play a role in abnormalities of brain structure as well as developmental delays (30). Finally, all patients with a right to left shunt have the potential for air or particulate embolism to reach the brain from intravenous catheters. Hypoxemia, low cardiac output, and cardiac arrest in patients with uncorrected complex CHD may contribute to CNS ischemia, injury and developmental delay (31, 32), adding to the abnormalities that may be present at birth (10–13, 33).

Microcephaly

Head circumference at birth is a surrogate for growth of the brain, and in neonates without congenital cardiac disease, microcephaly is independently associated with later developmental delays and academic difficulties. The incidence of microcephaly at birth is increased in children with complex CHD, approaching 25% of children in some reports (10, 33–35), persists into later infancy, and is associated with later developmental abnormalities (36). While the causes are speculative, and most certainly multifactorial, Shillingford et al reported on a series of children with the hypoplastic left heart syndrome where the median head circumference was only at the 18th percentile. In this study, patients with microcephaly had significantly smaller ascending aortas than those without, suggesting that reduced blood flow to the brain from the left ventricle secondary to anatomical hypoplasia of the ascending aorta may result in diminished brain growth (34).

Decreased CNS Maturity

Microcephaly, structural and biochemical immaturity of the white matter (33) and delay in cortical folding and white matter myelination (11) have led researchers to delve into investigations of fetal brain development. In her landmark paper, Dr. Limperopoulos performed fetal brain MRIs on 50 fetuses with CHD and 55 fetuses without (16). Cross-sectional data from this study reveals striking differences in brain growth, with CHD fetus' diverging from normal at the beginning or the 3rd trimester of development. Fetuses with aortic arch anomalies fared the worst, with the most stagnant brain growth. Further work from this dataset showed measures of fetal cortical complexity similarly diverged from normal starting at the same time (37).

Periventricular Leukomalacia/White Matter Injury (PVL/WMI)

Injury to the white matter, a common finding in premature infants, has been increasingly recognised in full-term neonates with complex CHD. In premature infants, severe degrees of periventricular leukomalacia have been associated with cerebral palsy, while mild degrees of injury have been associated with developmental delay, motor difficulties, and behavioral disorders, a developmental 'phenotype' remarkably similar to school-age children with complex CHD. Investigations into the causes of PVL/WMI in neonates with complex CHD have led to the recognition that preoperative factors and patient-specific factors (heart diagnosis, age at surgery, prenatal diagnosis, genetics) rather than surgical or postoperative factors are the major risks. The etiology regarding the alterations in fetal circulation effecting brain growth and maturation was first suggested by Miller and McQuillen in 2007 (33). In that report, the authors used diffusion tensor imaging and MR spectroscopy to demonstrate significant differences in white matter microstructure and biochemistry between newborn infants with complex CHD and infants without CHD. Soon afterward, we reported an MRI-based observational metric called the Total Maturation Scale that demonstrated brain maturation in full-term presurgical infants with CHD was equivalent to the expected brain maturation of a 35-week premature infant (11). Others have since shown that the Total Maturation Scale predicted not only the risk for pre- and postoperative WMI but also abnormalities on neurodevelopmental testing in childhood and adolescents (38–39). While delayed brain maturation results in populations of vulnerable premyelinating oligodendrocytes (40) to PVL/WMI, the actual injury likely results from deficient cerebral blood flow, low oxygen saturations or a combination of the two. Lynch et al showed that daily falls in cerebral oxygen saturations between birth and surgery increased the risk for postoperative PVL/WMI in babies with the hypoplastic left heart syndrome (41). Here, cerebral blood flow, measured at the same time, failed to compensate for the falling saturations. Thus PVL/WMI results from a combination of cellular vulnerability and limitations in oxygen delivery. Petit et al found similar findings in neonates with transposition of the great arteries (27) that a longer wait to surgery with unrepaired complex CHD resulted in increased injury to the CNS.

Genetic Susceptibility to Neurologic Injury and Developmental Dysfunction

All of the above risk factors do not fully explain either the high frequency or the pattern of neurodevelopmental dysfunction described in children with complex CHD, suggesting that other patient-specific factors may be important determinants of neurologic injury.

Intellectual development and cognitive function are highly heritable and probably are dependent on multiple genes, as well as on environmental factors. Numerous inherited defects or syndromes that are associated with compromised mental development and intellectual capacity (e.g., Down syndrome, Williams syndrome, DiGeorge syndrome) may have complex CHD as one of the phenotypic outcomes. Although the genetic basis for most cardiac defects has not been delineated, specific genetic anomalies have been implicated in the pathogenesis of some defects. For example, microdeletions of chromosome 22 are associated with DiGeorge syndrome and a variety of heart defects, including tetralogy of Fallot, truncus arteriosus, and interruption of the aortic arch. Developmental abnormalities are present in all children with 22q11 microdeletions, even those with no cardiac abnormalities (42). Thus, children with cardiac defects and 22q11 microdeletions may be developmentally impaired independent of the cardiac defect and cardiac surgery, however, recent studies suggest that the effects may be additive (43–45).

Risk of disease or injury in response to an environmental stimulus is a complex interaction between genetic susceptibility and environmental exposures. Interindividual variation in “disease risk” and in the response to environmental factors is significant. The “risk” may be modified by age, gender, ethnicity, and the extent of exposure to environmental factors. Multiple genes are involved in determining an individual’s response to a specific environmental factor. Interindividual variation in response to environmental exposures, such as cardiac surgery, probably is due in part to genetic polymorphisms. Common genetic variants, often due to single nucleotide substitutions, occur with a frequency of greater than 1%. For a child with complex CHD, environmental factors include cardiac surgery, use and/or duration of deep hypothermic circulatory arrest (DHCA), the inflammatory response to the synthetic surface of the cardiopulmonary bypass circuit, need for repeated operations, response to pressor or sedating medications, and socioeconomic status. The role of genetic polymorphisms in determining susceptibility to CNS injury in children with CHD is not known. Recent studies suggest that polymorphisms of apolipoprotein E ($\epsilon 2$ polymorphism) may be predictors of adverse neurodevelopmental sequelae following infant cardiac surgery (46–49), and similar finding have been reported in adults with the $\epsilon 4$ polymorphism (49–51). Antagonistic pleiotropy is the term to describe how a polymorphism may be beneficial early, but harmful later in life (52). It is likely that multiple genes modulate the CNS response to cardiopulmonary bypass, DHCA, and other environmental factors modifying the risk and pattern of injury (53).

The underlying cardiac diagnosis may have a significant and independent impact on neurodevelopmental outcome and may modulate the effects of neuroprotective strategies. Presence of a ventricular septal defect in patients with transposition of the great arteries is a significant risk factor for poor developmental outcome (54–56). In a study of the effect of intraoperative pH management, developmental and neurologic outcomes were evaluated in infants undergoing repair of a variety of cardiac defects at less than 9 months of age who

were randomized to either alpha-stat or pH-stat blood gas management strategy during deep hypothermic cardiopulmonary bypass (57). Children with transposition of the great arteries with or without ventricular septal defect, tetralogy of Fallot, isolated ventricular septal defect, atrioventricular canal defect, truncus arteriosus, and total anomalous pulmonary venous return were enrolled. There was no effect of treatment on the Psychomotor Developmental Index (PDI) score of the Bayley Scores of Infant Development. The Mental Developmental Index (MDI) score, however, varied significantly depending on treatment group and diagnosis. For patients with transposition of the great arteries and tetralogy of Fallot, use of pH-stat resulted in a slightly higher MDI, although the difference was not statistically significant. Of interest, in the ventricular septal defect subgroup, the treatment effect was opposite with use of alpha-stat management, resulting in significantly improved scores. Cardiac diagnosis had a significant effect on outcomes: PDI and MDI scores were significantly higher in the transposition of the great arteries group compared with those noted for the other cardiac defects.

The Effect of Cardiac Surgery on the Brain

Even though there is increasing evidence that congenital and acquired CNS injury occurs in a significant fraction of children with CHD before surgery, many still focus on intraoperative management as the primary mechanism of CNS injury. This is due to the fact that, as opposed to all of the risk factors for abnormal neurological development discussed thus far, variation in intra-operative support, such as the conduct of bypass, is one of the few more easily modifiable risk factors which may be altered to improve long-term neurological outcomes. A partial list of factors which may contribute to CNS injury during surgical repair include hypoxemia, cerebral hypoperfusion, and cerebral embolism (particulate and/or air), as well as many of the details of mechanical support during surgery (DHCA or continuous cardiopulmonary bypass), use of hemodilution, the degree and rate of cooling, use of steroids, glucose management and type of blood gas management. Use of bypass exposes the blood to the foreign surfaces of the bypass circuit, initiating a systemic inflammatory response characterized by neutrophil activation, complement activation, and increased circulating levels of inflammatory cytokines. This inflammatory response may result in increased capillary permeability, tissue edema, and organ dysfunction. When continuous cardiopulmonary bypass is utilized, perfusion to the body and brain is maintained. When DHCA is utilized, there is a period of obligate global cerebral ischemia followed by reperfusion. Use of DHCA provides a bloodless surgical field, facilitating meticulous completion of the repair, and decreases the duration of blood exposure to the bypass circuit, but at the cost of a period of global cerebral ischemia. Continuous cardiopulmonary bypass - either in a typical manner or via regional techniques maintains perfusion to the brain and body but increases the duration of blood exposure to the bypass circuit, which may increase the severity of the inflammatory response. Use of continuous bypass avoids the period of cerebral ischemia but results in a greater increase in total body water and potentially more severe dysfunction of other organs, such as the heart and lungs (58, 59). These multiple facets of bypass have received considerable attention, and have been the subject of active research. Of the many potential modifiable technical features of intraoperative support

mentioned above, there are three that been most extensively studied, particularly with randomized clinical trials.

pH Management

At Children's Hospital, Boston, developmental and neurological outcomes were evaluated in infants undergoing biventricular repair of a variety of cardiac defects at less than nine months of age who were randomized to either alpha-stat or pH-stat management during deep hypothermic cardiopulmonary bypass (60). Although there were some benefits reported with the use of pH-stat management for outcomes in the immediate peri-operative period, the use of either strategy was not consistently related to either improved or impaired neurodevelopmental outcomes in childhood (61). On the Bayley Scales of Infant Development, there was no effect of treatment on the PDI. The MDI, in contrast, varied significantly depending on the underlying anatomical diagnosis. For patients with transposition of the great arteries and tetralogy of Fallot, use of pH-stat resulted in a slightly higher mental developmental index, although the difference was not statistically significant. In patients with a ventricular septal defect, the effect was opposite, with use of alpha-stat management resulting in significantly improved scores. There was a significant effect of cardiac diagnosis on outcomes. Both scores of the Bayley examinations were significantly higher in those with transposition of the great arteries compared to the other cardiac defects. Despite the equivocal data in this early report, with no longer-term follow-up yet available nor confirmatory data from other randomised trials, many centers are currently utilizing pH-stat management – particularly during cooling on bypass - in all operations on neonates and infants. Further research in this area, based upon additional potential modifiers, for example, cardiac diagnosis, age, genetics and severity of pre-operative hypoxemia should continue.

Hematocrit During Bypass

During cardiopulmonary bypass, hemodilution has been widely applied based upon the notion that increased viscosity is detrimental during periods of profound or even moderate hypothermia. Work in animals suggesting that higher hematocrit levels conferred better cerebral protection has also been more extensively investigated in two human randomized clinical trials (62, 63). The results of these trials indicated that hematocrit levels during bypass below 24% were associated with lower scores in the psychomotor development index of the Bayley Scales of Infant Development, although no further improvement was seen comparing hematocrit levels of 25% to 35%. In addition, lower hematocrit levels were associated with a more positive fluid balance after surgery and higher serum lactate levels. Pooled data from these two studies was analyzed and an inflection point was determined to be at around 28% (64). These findings have been confirmed by multiple authors, and higher hematocrits during bypass are being utilized by most centers (65).

Deep Hypothermic Circulatory Arrest

Much has been written on the potentially deleterious effects of prolonged circulatory arrest with profound hypothermia in cardiac surgery for neonates and infants. It is generally agreed that more prolonged periods of uninterrupted circulatory arrest will result in an increased

risk of adverse neurological outcomes (66, 67). Close inspection of the data, however, shows that the effects of short durations of circulatory arrest are inconsistently related to adverse outcomes, and that the effect of circulatory arrest is not a linear phenomenon. As mentioned previously, the effects are most likely modified by other pre- and postoperative factors related to the patient. Some reports, most in an earlier era of cardiac surgery demonstrate a detrimental effect of circulatory arrest on a variety of outcomes relating to the CNS, while some demonstrate either an inconsistent effect or no effect. Some have taken the stance that, since the majority of studies suggest a negative effect of circulatory arrest, it should be avoided at all costs. Innovative and challenging strategies have been designed to provide continuous cerebral perfusion during reconstruction of the aortic arch or intracardiac repair. The avoidance of circulatory arrest, however, by necessity requires an increased duration of cardiopulmonary bypass (68). This has consistently been shown to have an adverse effect on outcomes in both the short and longer term. A randomized trial comparing circulatory arrest to continuous cerebral perfusion completed at the University of Michigan demonstrated no improvement in developmental scores at one year of age (69). Similar findings were reported in a contemporaneous but non-randomized study at Children's Hospital of Boston (70). It seems imprudent to change practice based upon studies with only short-term developmental assessment. Developmental studies in infants have very limited predictive validity for long-term outcomes, either for patients with or without CHD.

Perhaps the best conducted study in this regard, which emphasizes this point, is the Boston Circulatory Arrest Study (58, 71–82). In this study, a cohort of children with transposition of the great arteries undergoing the arterial switch operation were randomly assigned to intraoperative support with predominantly DHCA or to predominantly cardiopulmonary bypass at low flow. Earlier reports suggested that the group as a whole was performing below expectations in many aspects of evaluation, with worse outcomes for those undergoing circulatory arrest in the areas of post-operative seizures (71), motor skills at 1 year of age (72), as well as behavior, speech, and language by the age of 4 years (73–75). Mean intelligence quotient at the age of 4 was lower than expected at 93, with no difference according to treatment assignment (75). Many centers began avoiding even short periods of circulatory arrest based upon these and other reports. Neurodevelopmental analyses when the patients were aged 8 years revealed that the intelligence quotients for the cohort as a whole are now closer to normal, at 98 versus the population mean of 100 (76). The patients did demonstrate significant deficits in visual-spatial and visual-memory skills, as well as in components of executive functioning such as working memory, hypothesis generation, sustained attention, and higher-order language skills. In other words, the children had difficulty coordinating skills in order to perform complex operations. Those repaired using circulatory arrest scored worse on motor and speech functioning, while those undergoing bypass at low flow demonstrated worse scores for impulsivity and behavior. When compared to a normative sample, parents of the entire cohort reported significantly higher frequencies of attention problems, developmental delay, and problems with learning and speech. More than one-third of the population required remedial services at school, and one in ten had repeated a grade. At age 16, no significant impact was seen based upon intraoperative management; the early negative effects of hypothermic arrest were no longer seen, and in fact, some outcomes were worse in the arm randomized to low-flow cardiopulmonary

bypass (80). However, additional concerns became apparent: executive dysfunction and “theory of mind” abnormalities were prevalent (79), patients were 4 times more likely to be taking psychotropic medications compared to cardiovascular medications, and the number who received behavioral therapies and/or additional help at school increased to 65% (79). One-third had brain abnormalities detected on MRI (80, 81). Additional recent investigations confirm these abnormalities in multiple centers throughout the world (29, 39, 83, 84).

Whether current modifications of bypass techniques will improve the outcomes in the long term remains the subject of ongoing study. This well-designed trial, with superb follow-up, enrolled neonates who were planned to undergo an arterial switch operation between 1988 and 1992. Hence, the results reflect the peri-operative and surgical care delivered in that era, and thus may not be generalizable to the current era, or to other congenital cardiac lesions. For example, some features of routine post-operative care in that era, including extension of the anaesthetic period for at least 48 hours, active rewarming in the intensive care unit after surgery, and hyperventilation to reduce the risk of pulmonary hypertension, may each independently adversely affect neurodevelopmental outcomes. In addition, those patients randomized to predominantly continuous bypass also underwent a relatively brief period of circulatory arrest. Thus, the study does not compare use of circulatory arrest to no circulatory arrest. The results, nonetheless, serve to show the multiple factors which influence developmental outcome at school age, and show that factors related to poorer outcome, such as DHCA, which seem apparent and significant on early testing, may be attenuated or even abolished during longer-term follow-up, as other factors assume a more important role. More recently pooled 2-year neurodevelopmental testing data from over 1700 patients from 22 international centers collected from 1996 to 2009 were analyzed. PDI and MDI scores (77.6 ± 18.8 and 88.2 ± 16.7 , respectively) were lower than normative means, and after controlling for a variety of risks, MDI improved only 0.38 points/year, hardly a drastic effect from over a decade of modifying surgical and medical care strategies (2).

Postoperative Factors

CNS injury may occur or be exacerbated in the postoperative period. As described, many studies have focused on the operating room as the site of CNS injury; however, events in the cardiac intensive care unit may be equally important. Cerebral ischemia can result from low oxygen delivery from decreased cardiac output, severe hypoxemia and/or severe anemia. Postoperative agitation, pain and/or hyperthermia may increase the metabolic needs of the brain, resulting in worsening CNS injury (85). In addition, postoperative cardiac arrest – with or without the need for mechanical circulatory support – may occur in as many as 20% of certain subgroups of newborns with complex CHD (86), and may result in significant CNS injury (86–90). Following cardiac surgery with bypass with or without DHCA, cerebral autoregulation may be impaired (91). Following surgery, especially in newborns and infants, there is a predictable and reproducible fall in cardiac output (58, 92–94). This period of decreased oxygen delivery, usually within the first 24 hours after surgery, represents a particularly vulnerable time for the CNS, especially if associated with increased oxygen consumption (95–97). At present, studies linking postoperative hemodynamic lability to long-term CNS outcomes are lacking. However, postoperative hypotension has been shown

to be related to new or worsened white matter injury (98), especially if combined with hyperventilation, which may further reduce cerebral blood flow (99, 100). Despite theoretical concerns of adverse neurodevelopmental effects, postoperative hyperglycemia has not been shown to correlate with adverse longer-term neurodevelopmental outcomes (101, 102). Finally, work is currently underway to investigate the correlation of noise, aminoglycoside usage and subsequent hearing loss in school age children with complex CHD (Burnham N, personal communication).

Length of Stay

Compared to cardiac surgery at older ages, neonates with complex CHD may have protracted stays in the intensive care unit - averaging nearly a month in most reports - with a significant number of outliers with even considerably longer lengths of stay (103). Increased length of stay has been associated with increased risks of medical error, costs, parental stress, reoperation and other cardiac and non-cardiac morbidity (103–107). In the Boston Circulatory Arrest Study, length of stay was independently associated with worse cognitive function at 8 years of age, even after adjustment for factors related to the length of stay (e.g., sepsis, low cardiac output) or cognitive outcomes (e.g., maternal education, socioeconomic status) (76). Virtually all studies reporting short and longer term neurodevelopmental outcomes have two consistent factors independently related to worse outcomes: increased length of stay and lower socioeconomic status (77, 80, 108–110). While some aspects of length of stay may not be modifiable, many units are now actively investigating strategies to reduce length of stay (e.g., timing of surgery, early extubation, minimizing delayed sternal closure, etc.) in hopes of improving longer term outcomes. (While socioeconomic status is not modifiable per se, children from disadvantaged families may be at highest risk, and particular attention must be given to neurodevelopmental care during the hospitalization and after discharge.) One aspect of increased length of stay in particular is the use of prolonged sedation, including narcotics and benzodiazepines, along with the use of volatile anesthetic agents during cardiac surgery, which may adversely affect neurodevelopment. Increasingly it is being recognized that the *cummulative* exposure to these agents in infancy is related to worse outcomes (111–114).

Longer-term Effects of the ICU Stay

Finally, it is clear that multiple factors for adverse outcomes co-exist in neonates who experience a long initial hospital length of stay; all of these have been shown to increase parental stress, anxiety, and feelings of helplessness and inadequacy (figure 2a). This is superimposed on the early traumatic events of receiving the diagnosis of complex CHD, the uncertainty of survival, separation from the infant, possible setbacks, postpartum depression, witnessing medical procedures and paraphernalia, and vicarious trauma (witnessing events in other patients). Following discharge, home care of the neonate following surgery for complex CHD is exceptionally complex, with feeding issues common, multiple medications, feelings of inadequacy, disruption of the family routine, and many other issues (115–119). These factors incurred early on lead to an abnormal maternal-child dyad and ultimately to behavioral challenges (figure 2b), which almost certainly have long term effects on parenting styles, psychosocial health and the development of the “fragile child” (figure 3). Indeed,

maternal worry and mental health (along with a small component of the child's visual-perceptual skills) accounted for 27.9% of the variability in child behavior adjustment at the end of the first year of school, 5–10 times more explanatory than any surgical or intraoperative factor described to date (120). In his seminal work, McCusker and colleagues have shown in a randomized trial that perioperative efforts to reduce maternal worry utilizing advanced practice nursing have significant benefits to both the mother and child (121). Acute stress disorder in parents during the neonatal hospitalization is common (122), and has been shown to be related to symptoms of post-traumatic stress disorder later in life (122, 123), which may independently effect family functioning, child self-image and child-rearing schema. Attention to this important, modifiable risk factor for later neurodevelopment both in the inpatient and outpatient settings holds promise for improvement in our patients with complex CHD.

Summary and Future Directions

Although children with mild types of CHD appear to have normal CNS and neurodevelopmental outcomes (124–125), children with complex CHD constitute an at-risk population with a significant incidence of adverse developmental outcomes. Current techniques for developmental evaluation in neonates and infants are imprecise predictors of late outcomes. Evaluation of preschool- and school-aged children reveals a pattern of neurodevelopmental dysfunction characterized by mild cognitive impairment, motor dysfunction, impaired visual-spatial and visual-motor skills, and attention and academic difficulties. There are significant problems with expressive speech and language and a high incidence of learning disabilities. The factors resulting in CNS injury and developmental dysfunction in these children are multiple, and incompletely understood. Developmental dysfunction results from a complex interaction between patient-specific factors (genetic susceptibility, cardiac diagnosis, fetal development) and environmental factors (preoperative events, techniques of support during surgical repair, postoperative events, socioeconomic status). Currently, reported risk factors do not adequately explain the pattern or incidence of CNS injury following cardiac surgery in infants, suggesting that other patient-specific factors may modulate the response to CHD and cardiac surgery, increasing the risk of adverse neurodevelopmental sequelae. Children with complex CHD are at risk for cerebral ischemia before, during, and after cardiac surgery; therefore, factors, that impair CNS recovery following ischemia may be important determinants of long-term neurologic outcome.

At the current time, important investigations are underway to (1) understand the developing brain in the fetus with complex CHD, (2) to identify modifiable risk factors in the operating room and intensive care unit in order to maximize long-term neurodevelopmental outcomes and (3) develop strategies to improve family psychosocial health, childhood development and health-related quality of life following hospital discharge. Crucial in this effort is the identification of an early post-operative surrogate variable with good predictive validity for long-term outcomes. MRI is showing great promise in this area, with correlations now being seen with early structural changes, particularly in the white matter, with intermediate neurodevelopmental outcomes (81–83). If an appropriate surrogate variable for long term

outcomes can be identified, and measured relatively early after surgical intervention for complex CHD, reliable clinical trials can be undertaken to improve upon current outcome.

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Potential Etiologies for Central Nervous System Abnormalities

Pre-Natal	Preoperative	Intraoperative	Postoperative	Childhood
Genetic Abnormalities	Abnormal Cerebral Vascular Resistance	Embolism	Embolism	Repeat Surgeries
Abnormal Placenta	Abnormal Cerebral Vascular Resistance	Inadequate Perfusion	Low Cardiac Output	Cardiac Arrest
Abnormal Cerebral Vascular Resistance	Decreased Oxygen Delivery	Decreased Oxygen Delivery	Hypoxemia	Total Anesthesia Exposure
Decreased Oxygen Delivery	Decreased Substrate Delivery	Decreased Substrate Delivery	Seizures	Total Narcotic Dose
Decreased Substrate Delivery	Increased CMRO ₂	Anesthetic Exposure	Hyperventilation/Alkalosis	Total Benzodiazepine Dose
Environmental Exposures	Birth Asphyxia	Abnormal Oxygen Consumption	Abnormal Oxygen Consumption	Low Socioeconomic Status
Transitional Circulation		Reperfusion Injury	Dopamine, Narcotics and Benzodiazepines Exposures	Maternal Depression
		Circulatory Arrest	ICU Exposures (Infections, Thrombosis)	Parental Stress
		Regional Cerebral Perfusion		Patient Anxiety/Stress
				Patient Self/Body Image

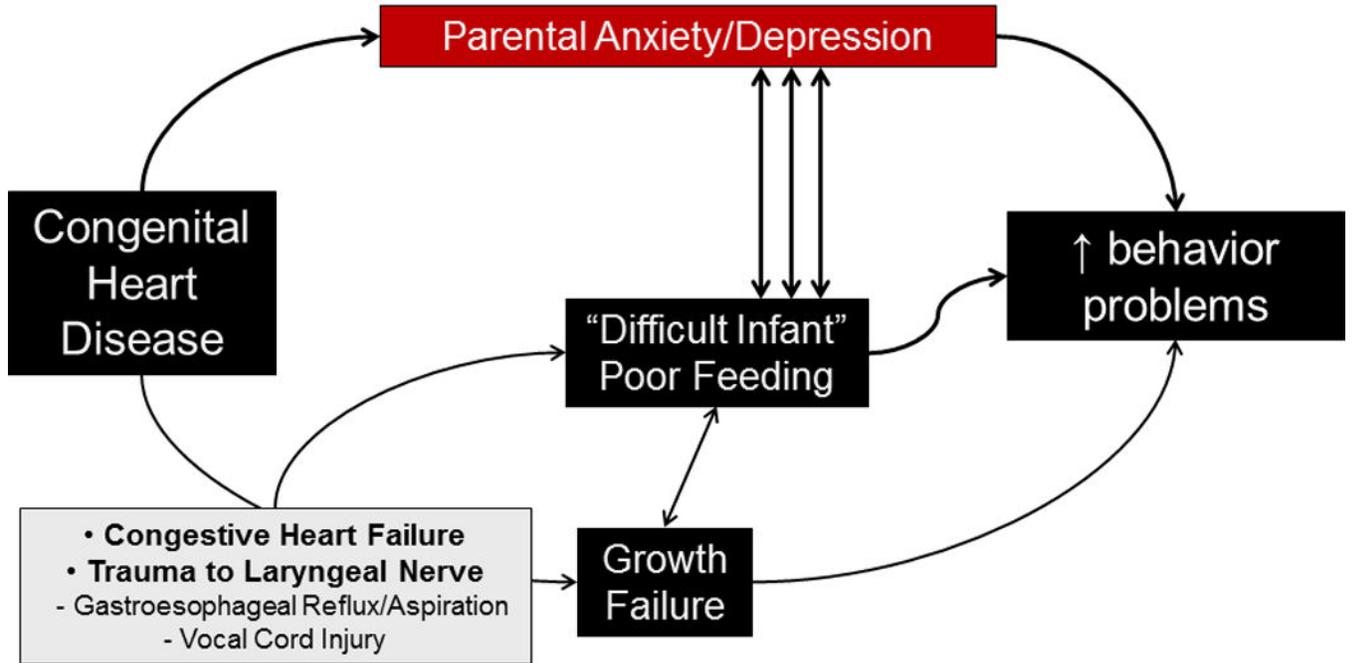
Potential Neurological and/or Developmental Findings

Pre-Natal/Birth	Perioperative/ICU	Childhood
Immature Cortical Folding	Increased or New White Matter Injury	Delayed Motor Milestones
White Matter Injury	Seizures	Delay and Apraxia of Speech
Delayed Myelination	Coma	Visual-Motor Difficulties
Hemorrhage	Stroke and thrombosis	Visual-Spatial Difficulties
Open Operculum	Hemorrhage	Clumsiness
Microcephaly	Poor Brain Growth	Autism Spectrum Disorders
Structural brain abnormalities	Abnormal Mental Status	Attention Deficit/Hyperactivity Disorder
	Poor Oral-Motor Coordination	Impaired Memory
		Executive Function Abnormalities
		Anxiety
		Depression
		Diminished Social Cognition

Figure 1.

Current model relating measured neurodevelopmental outcomes at various timepoints with potential etiologic factors in children with complex congenital heart disease. ICU=Intensive Care Unit

cCHD: Infant – Parental Interactions



cCHD: Child – Parental Interactions

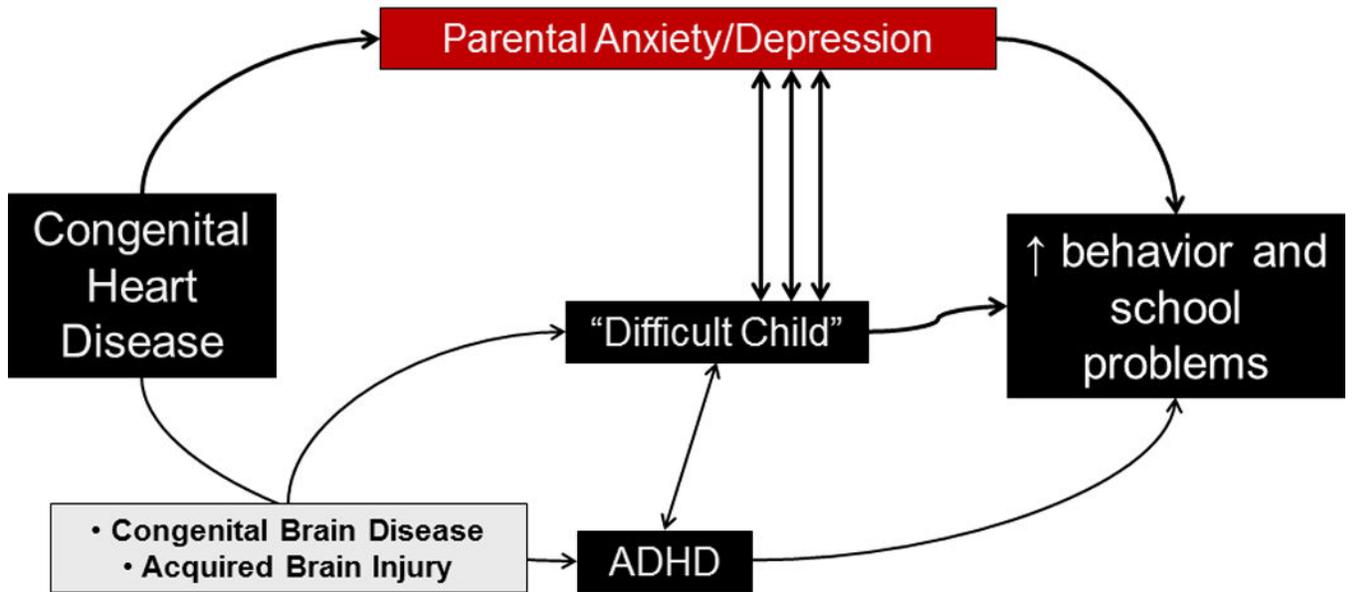


Figure 2.

- a.** The potential interactions between complex congenital heart and brain disease, its treatment, and parental and patient outcomes in (a) the infant. ADHD=attention deficit hyperactivity disorder
- b.** The potential interactions between complex congenital heart and brain disease, its treatment, and parental and patient outcomes in (b) the child. ADHD=attention deficit hyperactivity disorder

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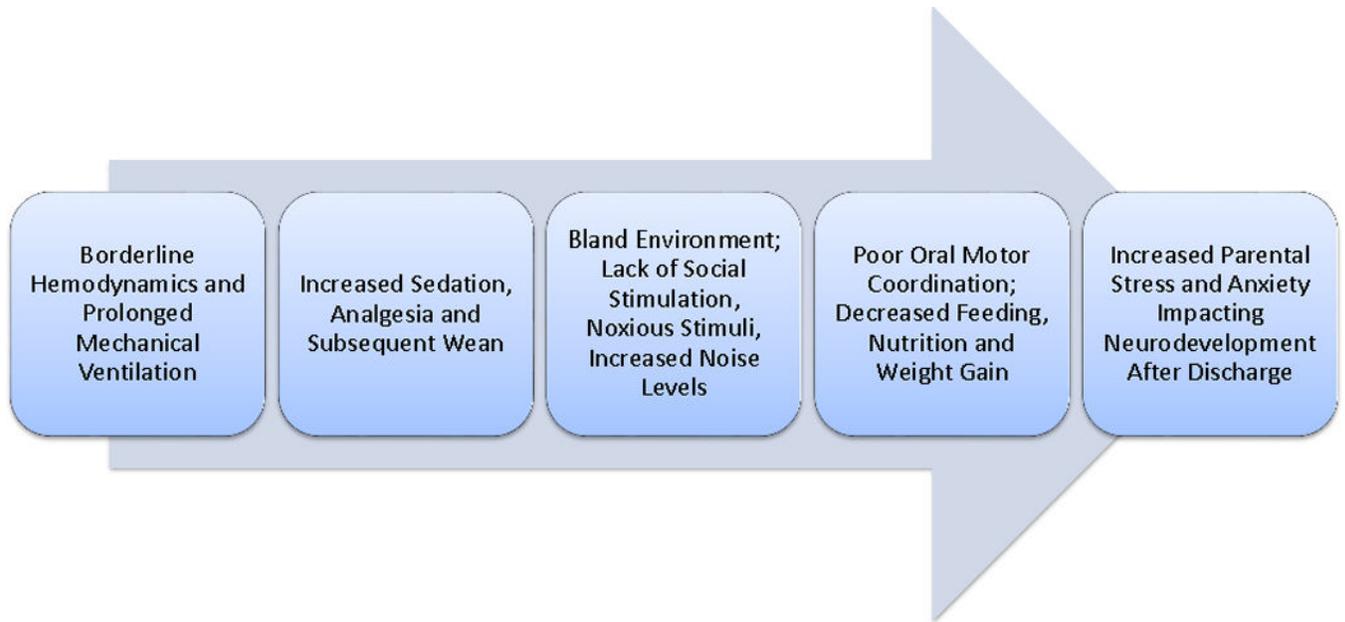


Figure 3.
The progression of multiple factors related to adverse neurodevelopment and ‘the fragile child’ following a prolonged intensive care unit stay

Table 1

Neurological, Developmental and Psychosocial Challenges Which Occur With Increased Frequency in Children, Adolescents and Young Adults Born With Critical Congenital Heart Disease

-
- Stroke
 - Seizures
 - Abnormal brain morphology and functional connectivity (MRI)
 - Abnormal brain growth, cerebral atrophy (CT, MRI)
 - CNS hemosiderin deposition (MRI)
 - Oral-motor dysfunction
 - Poor head control
 - Delayed gross and fine motor milestones
 - Apraxia of speech
 - Clumsiness
 - Problems with visual-spatial-motor integration
 - Inattention and hyperactivity
 - Cognitive impairment
 - Impaired memory
 - Autism spectrum disorders
 - Social awkwardness/Impaired social cognition
 - Anxiety
 - Depression
-

Legend: CNS= Central Nervous System; CT=Computerized Tomography; MRI=Magnetic Resonance Imaging