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REVIEW

Complex Congenital Heart Disease: Neurological and Developmental Sequela through Early Childhood and Adolescence

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As more children with complex congenital heart disease (CHD) survive into childhood and beyond, there is a growing recognition of neurological and developmental abnormalities in some of the survivors. Over a decade ago, much emphasis was placed on the conduct of cardiopulmonary bypass and its role in neurodevelopmental disabilities. Much has been learned in the intervening years regarding the multi-factorial causes of abnormal development in school age, in particular, the role of prenatal, perioperative, socioeconomic and genetic influences. This review will highlight some of the recent advances in our understanding of the protean causes of neurological, behavioral and developmental abnormalities in children and young adults with complex forms of congenital heart disease, which in many ways is remarkably similar to that seen in survivors of prematurity.

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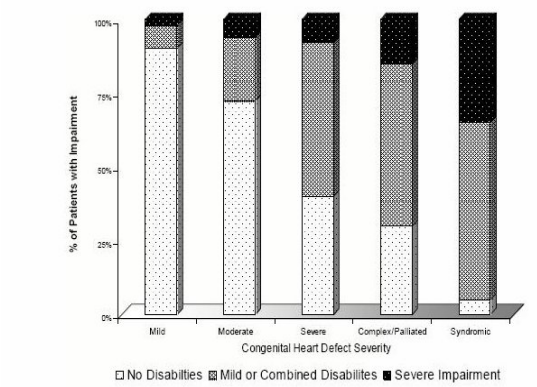
Scope of the Problem

Prior to the early 1980s, it was uncommon for children with complex congenital heart disease to survive into later childhood. The nearly simultaneous advances in congenital heart surgery, echocardiography and intensive care were coupled with the availability of prostaglandin and the developing discipline of interventional 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, and staged reconstructive surgery for various forms of univentricular heart – including hypoplastic left heart syndrome – was improving with steadily falling surgical mortality rates. As a result, the last decade has seen an increasing number of children entering primary and secondary schooling, and research into their academic and behavioral outcomes has revealed some sobering realizations about the outcomes in these surgical survivors.

As a group, patients with complex congenital heart disease – and for the remainder of this review this will include children who require cardiac surgery as neonates or young infants – have a significantly higher incidence of academic difficulties, behavioral abnormalities, fine and gross motor delays, problems with

visual motor integration and executive planning, speech delays, inattention and hyperactivity. Injury to the central nervous system in infants with congenital heart disease is characterized by abnormalities of tone, feeding difficulties, delays in major motor milestones and abnormalities in speech. As these children get older, the need for special services in school is significantly increased compared to the general population. As children progress through school, low academic achievement scores, learning disabilities, behavioral problems and Attention Deficit/Hyperactivity Disorder may result in academic failure, poor classroom and social skills, low self-esteem, behavioral disinhibition and ultimate delinquency. Depending upon a number of factors, including the underlying congenital lesion and the associated surgical management, genetic contributions, additional perinatal events such as profound hypoxia-ischemia from a delayed diagnosis, or postoperative events such as low cardiac output syndrome, the incidence of abnormalities may range from infrequent to ubiquitous. For example, in cohort studies of children with transposition of the great arteries, a small fraction may have severe developmental impairment, perhaps one-half are normal in all respects, and nearly one-half will have a combination of speech, motor, behavior or learning issues. The percentage of children with more 'significant' heart disease (for example, totally anomalous pulmonary venous return with obstruction, hypoplastic left heart syndrome, interruption of the aorticarch) who are developmentally 'normal' is significantly decreased, with perhaps only one-third of those tested having no dysfunction in any domain. While most of these abnormalities are relatively mild, and may only be determined by formal testing—they result in a so-called "high prevalence, low-severity" developmental "signature." A schematic representation is shown in [Table/Fig 1] .

Importantly, the combined outcomes of developmental delay, academic difficulties and behavioral abnormalities – in combination – represent the single most common morbidity affecting the quality of life in school age survivors with congenital heart disease; more common than late mortality, severe exercise impairment, unplanned reoperations, bacterial endocarditis or significant arrhythmias. The later implications of these findings through adulthood are uncertain, and must continue to be a robust area of research. Our current understanding of the etiology of these findings is discussed below.



(Table/Fig 1) Schematic representation of developmental abnormalities in children with congenital heart disease. Children with milder forms of congenital heart disease (for example, ventricular septal defect without an associated genetic syndrome), as a group, have a low incidence of developmental abnormalities, and more than mild abnormalities are rare. Increasingly complex forms of congenital heart disease (for example transposition of the great arteries or totally anomalous pulmonary venous return) are associated with increasing numbers of children with developmental deficits, and only the minority of children with extremely complex heart disease (for example, functionally univentricular heart, hypoplastic left heart syndrome) are completely normal in all respects. Finally, congenital heart disease associated with chromosomal abnormalities (for example Down and DiGeorge Syndromes) or multiple congenital anomalies are nearly always associated with developmental abnormalities, in many cases, severe. Modified from Wernovsky G. Cardiol Young. 2006;suppl I:92-104.

Congenital Brain Disease

Given that the central nervous and cardiovascular systems form nearly simultaneously in early gestation, it is not surprising that there is an increased incidence of structural brain abnormalities in children with structural heart abnormalities. Many children with multiple congenital anomalies or chromosomal abnormalities – many of whom have coexisting congenital heart disease – will have developmental delay as a significant component of late morbidity. In addition to genetic factors which may affect both systems from a macroscopic perspective, congenital heart disease may alter cerebral blood flow, oxygen delivery or both, and result in secondary effects of the vulnerable fetal central nervous system.

In some respects, the brain of the full term neonate with congenital heart disease structurally resembles that of a preterm neonate, and interestingly, school age survivors of complex heart surgery have developmental findings which are very similar to survivors of premature birth, suggesting a similar pathological response to injury. Serial studies of the fetal brain – utilizing ultrasound and magnetic resonance imaging – are currently underway and are increasing our understanding of the interactions between the abnormal fetal cardiovascular system and cerebral development.

Microcephaly

Head circumference at birth is a marker for brain development, and in neonates without congenital heart disease, microcephaly is independently associated with later developmental delays and academic difficulties. Multiple cohort studies have shown the incidence of microcephaly at birth is increased in children with congenital heart disease, approaching one-fourth of children in some reports, and persists into later infancy. While the causes are speculative, and most certainly multifactorial, recent work from our institution in children with Hypoplastic Left Heart Syndrome – where the median head circumference at birth is only at the 18th percentile – revealed that patients with microcephaly had significantly smaller ascending aortas than those without, suggesting that reduced flow to the brain secondary to anatomic hypoplasia of the ascending aorta may result in diminished brain growth (Shillingford AJ, in press).

The "Open Operculum"

The term operculum insulae denotes the region that covers the insulae Relie and is made up of frontal, temporal and parietal cortical convolutions. In magnetic resonance and computer tomographic imaging studies of neonates with complex congenital heart disease, underdevelopment of the operculum may be seen in nearly one-quarter of the patients, and is a marker for functional immaturity of the brain. This may be a unilateral or bilateral finding, and has been termed "underoperculinization" or an "open" operculum. The operculum is thought to be related to oral motor coordination, taste and speech-particularly expressive language. In adult patients who develop a stroke in this area of the brain (Foix-Chavany-Marie syndrome), deficits include impairment of voluntary movements such as chewing and deglutition, dysarthria and taste abnormalities. Given the high prevalence of feeding problems, expressive language delay and oral-motor apraxia in children with complex heart disease, as well as the increasing recognition of a high prevalence of an open operculum, one can speculate that some patients with these developmental disabilities may have a structural underdevelopment of the operculum as the etiology. Further research into this hypothesis is ongoing.

Periventricular Leukomalacia

White matter injury – a common finding in premature infants – has been increasingly recognized in full term neonates with congenital heart disease. Mahle and colleagues studied 24 neonates preoperatively with magnetic resonance imaging of the brain, and found periventricular leukomalacia in [4]; a number which nearly tripled after cardiac surgery. Spectroscopy in this cohort revealed elevated brain lactate in slightly over half of the patients. Licht and associates have recently suggested that decreased cerebral blood flow preoperatively was significantly associated with lesions in the white matter, affecting slightly over one-quarter of the neonates. Finally, in a larger study reviewing 105 magnetic resonance imaging studies of the brain in children with congenital heart disease in the early postoperative period, periventricular leukomalacia was found in slightly over half of the neonates in the study, but rarely in older children.

Periventricular Leukomalacia is believed to arise from several factors, including the

high susceptibility of the immature oligodendrocyte to hypoxic ischemic injury, as well as the watershed distribution of cerebral blood flow to this area between the small arteries that penetrate from the cortex and those that arise centrally and run radially outward. This watershed area is particularly prone to ischemia during decreases in cerebral perfusion pressure. 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 behavior disorders - a developmental signature remarkably similar to school-age children with congenital heart disease.

Additional Anatomical Findings At Birth

Congenital central nervous system (CNS) anomalies are known to be coincident with CHD. In a prospective study by Miller et al, head ultrasound examinations were performed on full term infants with CHD before and after surgical interventions. Brain abnormalities were noted in 27% of the infants, and nearly half of the anomalies were present before surgery (such as holoprosencephaly and agenesis of the corpus callosum)

Fetal Cerebrovascular Physiology And Oxygen Delivery

Recent ultrasound studies have revealed that cerebral vascular resistance is altered in the presence of congenital heart disease. Using Doppler interrogation of middle cerebral artery flow, both Donofrio and colleagues and Kaltman and associates have shown that fetuses with left-sided heart disease (for example, Hypoplastic Left Heart Syndrome) had decreased cerebral vascular resistance compared to normal. In patients with aortic atresia, for example, the fetal cardiac output from the ductus arteriosus must deliver blood 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 central nervous system. Kaltman also showed that fetuses with right sided lesions (for example, Tetralogy of Fallot) had increased fetal 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.

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 heart disease exists, these beneficial flow patterns are likely to be altered. Although not yet confirmed by fetal magnetic resonance spectroscopy (studies are underway), fetuses with transposition of the great arteries are likely to have the blood with the lowest oxygen saturation returning to the ascending aorta and brain, while blood with the highest oxygen saturation will return to the abdominal viscera and placenta – a “transposed” fetal circulation previously speculated by Naeye nearly 40 years ago as an explanation for the high incidence of macrosomia in these infants. Complete mixing lesions such as seen in univentricular hearts will have intermediate values of fetal cerebral oxygen saturation, but lower than that seen in the normal fetus.

Perioperative Contributors

Preoperative Factors

Neonates with complex congenital heart disease frequently require hospitalization immediately after birth, many to receive intravenous prostaglandin infusion, some requiring intubation, mechanical ventilation, or invasive interventions such as balloon atrial septostomy. All of these interventions carry risks to the central nervous system, especially the potential for paradoxical embolus to the brain of air or particulate matter in children with intracardiac right to left shunts. These patients also have oxygen

saturations that are below normal, potentially compromising cerebral oxygen delivery. Licht and colleagues recently reported that – in addition to diminished oxygen content – neonates with critical congenital heart disease had diminished cerebral blood flow as well. Under conditions of general anesthesia and mechanical ventilation with normocapnia, cerebral blood flow was, on average, less than half that seen in normal term newborns. The cerebral vascular response to increased inspired carbon dioxide was preserved, suggesting normal autoregulation of cerebral blood flow, at least over the short term.

Intraoperative Factors

The conduct of cardiopulmonary bypass and other support techniques during open heart surgery has received considerable attention, and has been the subject of active and gratifying research. As opposed to all of the risk factors for abnormal neurological development discussed thus far, variation in intraoperative support, such as the conduct of cardiopulmonary bypass, is one of the few modifiable risk factors which may be altered to improve long term neurological outcomes. Potential modifiable technical features of cardiopulmonary bypass are shown in [Table/Fig 2] .

(Table/Fig 2) Potential modifiable technical features of cardiopulmonary bypass

Table 1. Potentially Modifiable Intraoperative Risk Factors of Cerebral Injury
Air or Particulate Embolus
Rate and Depth of Core Cooling (if utilized)
Deep Hypothermic Circulatory Arrest (if utilized)
Reperfusion Injury and Inflammation
Rate of Core Rewarming/Hyperthermia
Hyperglycemia
Hypoxia
pH Management During Cardiopulmonary Bypass
Hematocrit Management During Cardiopulmonary Bypass

Deep Hypothermic Circulatory Arrest

Much has been written on the potentially deleterious effects of prolonged circulatory arrest with profound hypothermia in neonatal and infant heart surgery. It is generally agreed that prolonged periods of uninterrupted circulatory arrest may have adverse neurological outcomes. However, upon close inspection of the data, it is increasingly clear that the effects of short durations of circulatory arrest are inconsistently related to adverse outcomes, that the effect of circulatory arrest is not a linear phenomenon, and the effects are most likely modified by other patient-related, preoperative and postoperative factors. Some reports, most in an earlier era of cardiac surgery demonstrate a detrimental effect of circulatory arrest on a variety of central nervous system outcomes, while some demonstrate either an inconsistent effect or no effect. Some practitioners 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 bypass strategies have been designed to provide continuous cerebral perfusion during complex arch reconstruction or intracardiac repair. It must be emphasized that the avoidance of circulatory arrest by necessity requires an increased duration of cardiopulmonary bypass, which has consistently been shown to have an adverse effect on both short term and longer-term outcomes. A randomized trial of circulatory arrest and continuous cerebral perfusion has recently been completed at the University of Michigan, with short term studies soon to be reported in the literature (Ohye R, personal communication) and long term studies in the planning stages.

It seems imprudent to change practice based upon studies with only short term developmental assessment, as it is clear that developmental studies in infants have very limited predictive validity for long term outcomes, both in patients with and without congenital heart disease. Perhaps the best conducted study in this regard-which emphasizes this point-is the Boston Circulatory Arrest Study, with multiple reports from Bellinger, Newburger, Jonas and colleagues. In this cohort, 171 children with transposition of the great arteries were randomly assigned an intraoperative support strategy of predominantly deep hypothermic

circulatory arrest or predominantly low flow cardiopulmonary bypass during the arterial switch operation. Earlier reports suggested that the group as a whole was performing below expectations in many aspects of evaluation, with worse outcomes for the circulatory arrest group in the areas of postoperative seizures, motor skills at one year of age, as well as behavior, speech and language at age 4 years. Mean Intelligence Quotient at age 4 was lower than expected at 93, with no difference across treatment assignment. Many centers began avoiding even short periods of circulatory arrest based upon these and other reports. However, in 2003, quality of life assessments and detailed standardized testing were reported in this group. Neurodevelopmental analyses of this cohort at 8 years of age revealed that the Intelligence Quotient scores for the cohort as a whole are now closer to normal (98 versus the population mean of 100).

However, the group demonstrated 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. The circulatory arrest group scored worse on motor and speech functioning, while the low-flow bypass group 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, learning problems, and speech problems. More than a third of the population received remedial school services, and one in ten had repeated a grade. Thus, in this population of patients who underwent the arterial switch operation between 1988 and 1992, there appears to be a correlation between congenital heart disease and its surgical repair with later speech and language difficulty, behavioral difficulties and execution planning in childhood. Whether current modifications of support techniques will improve the long term outcomes remains the subject of ongoing study.

This well-designed trial with superb follow-up compliance enrolled neonates with transposition of the great arteries, with or without a ventricular septal defect, who were planned to undergo an arterial switch operation between 1988 and 1992. The results, thus, reflect the perioperative care delivered in that era, and thus may not be generalizable to the current era, or other congenital heart lesions. In addition, those patients randomized to predominantly continuous bypass did undergo a brief period of circulatory arrest; thus, the study does not compare use of circulatory arrest to no circulatory arrest. Nonetheless, the results serve to show the multiple factors which influence developmental outcome at school age, and that factors related to poorer outcome such as deep hypothermic circulatory arrest, 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.

Postoperative Factors

It has long been recognized that systemic blood flow is reduced in the first 24-48 hours following cardiac surgery, typically reaching a nadir in the first night after cardiac surgery. At this time, the central nervous system may be especially vulnerable to secondary insults of decreased oxygen delivery, particularly after circulatory arrest. Currently, close attention to cardiac output, oxygen delivery and oxygen consumption seems warranted from a central nervous system perspective, however, bedside techniques for quantitative assessment of these parameters is limited, particularly if there are residual intracardiac shunts.

Following cardiopulmonary bypass, with or without circulatory arrest, autoregulation of cerebral blood flow may be impaired, making the neonate and infant particularly

vulnerable to periods of low cardiac output and/or hypoxemia. Although many studies in laboratory animals demonstrated various factors that adversely affect cerebral blood flow following cardiopulmonary bypass, it has been previously difficult to reproduce these studies in postoperative neonates and infants. However, recently, Bassan and colleagues utilized transcranial Doppler and cerebral near-infrared spectroscopy to study cerebral blood flow in the cardiac intensive care unit in 43 neonates and infants following biventricular repair. In this study cohort, approximately one in six patients demonstrated bnormalities of cerebrovascular pressure autoregulation, with risk factors including hypercapnia higher mean arterial pressure during the time of the measurements. To date, the potentially deleterious effects of significant hypocapnia—which decreases total cerebral blood flow – and hypotension (for ethical reasons) have not been reported in postoperative neonates. Further research is mandatory to determine the combined effects of cardiac output, mechanical entilation, and cerebral blood flow, especially in the immediate postoperative period.

Seizures occur in the immediate postoperative period in up to 20% of neonates, depending upon the detection method; clinical seizures are significantly less prevalent than those detected on continuous electroencephalographic monitoring. The etiology is most-likely multifactorial, but is likely to be more prevalent in younger patients, those with prolonged periods of circulatory arrest, or those with coexisting central nervous system abnormalities.

In addition to the identified factors above, the immediate post operative period typically requires invasive monitoring, mechanical ventilation and significant medical support, especially in the neonate and young infant. While these therapies have resulted in significant improvements in mortality, they increase the risk of factors which may adversely affect the central nervous system, including paradoxical embolus of air or particulate matter from peripheral or central intravenous access, fever, hyperglycemia and swings in cerebral blood flow brought on by acute changes in mechanical ventilation. Newburger and colleagues have recently demonstrated in the Boston Circulatory Arrest cohort that longer hospital and intensive care unit length of stay in the newborn period was associated with worse developmental outcomes at age 8 years. These effects were significant, even when controlling for other factors known to adversely affect long-term outcome, such as seizures, intraoperative support duration, reoperations and other postoperative events. Children with transposition whose length of stay was in the fourth quartile had mean intelligence quotients 7.6 points lower than those in the first quartile. Further investigation into the multiple potential mechanisms of central nervous system injury in the intensive care environment must continue.

Following hospital discharge, some neonates remain at risk for ongoing central nervous system injury. Chronic hypoxemia, as a result of ongoing palliation and/or intentional intracardiac right to left shunting, may result in neurodevelopmental impairment. In children with transposition, older age at repair, as a surrogate for duration of hypoxemia, has been associated with worse outcomes during follow-up. Cohort studies -many from a much earlier era of cardiac surgery when delayed repair was common – consistently show lower scores in children with “cyanotic” lesions compared to “acyanotic” lesions. However, simple comparisons of heart disease with and without associated hypoxemia are confounded by the multiple factors present in children with “cyanotic” heart disease, including earlier age at repair and exposure to bypass, more complex surgical procedures, abnormal fetal flow patterns, and many of the factors mentioned in this review. In children with structurally normal hearts and hypoxemia from other causes (for

example, chronic lung disease, sleep disordered breathing, high altitude), chronic or intermittent hypoxemia has been associated with adverse effects on development, behavior and academic achievement. The presence of hypoxemia undoubtedly plays some role in patients with congenital heart disease, but is most likely modified by other factors and is difficult to measure the effect of hypoxemia in isolation.

Genetic and Environmental Factors

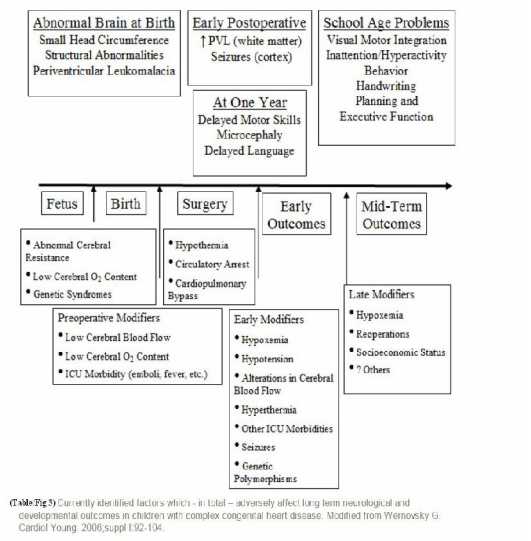
Socioeconomic status is perhaps the strongest predictor of eventual neurodevelopmental outcome, and is a reflection of both the child's environment and the genetic factors for development inherited from his or her parents. Multiple studies have shown the relationship between socioeconomic status and/or parental intelligence and outcome in children with congenital heart disease. Children with identified genetic syndromes with known chromosomal abnormalities (e.g., Down, Williams and DiGeorge syndromes, Trisomy 13 and 18, etc.) as well as multiple ongenital anomaly associations (e.g., CHARGE and VACTERL associations) frequently have coexisting CHD; in total perhaps 1/3 of all children with CHD have additional abnormalities besides their heart disease. Sub-chromosomal gene abnormalities are being discovered with increasing frequency in this patient population, and most studies report worse outcome in children with associated congenital anomalies compared to children with the same lesion without additional anomalies.

Future Directions

While advances in the medical and surgical fields have allowed the ability to 'mend' children born with congenital heart disease, the increasing number of survivors has created a growing cohort of children with potential academic difficulties. The causes are clearly multifactorial, additive and incompletely understood. Much has been learned about cardiopulmonary bypass and the short period of time these children spend in surgery; much more work needs to be done to understand the modifiable risk factors in the perioperative period, the influences of the timing of surgery and whether or not improved monitoring of the central nervous system in the intensive care unit setting will improve neurological and developmental outcomes.

Summary

[Table/Fig 3] represents some of the current understanding regarding the multiple factors which may adversely affect the central nervous system in children with complex congenital heart disease – a remarkably similar "phenotype" as that seen in school-age children who were born prematurely. There is a growing body of literature showing suboptimal outcomes in school age children, particularly with respect to attention, behavior, higher-order executive function, handwriting and school performance. Many of the risk factors for adverse outcomes are co-linear, such as abnormalities of the fetal circulation, the need for prolonged intensive care, complex operations with cardiopulmonary bypass with or without deep hypothermia and circulatory arrest, prolonged hypoxemia and multiple reoperations. Thus, it is difficult to conclude which, if any, are most explanatory. Many of the reports on the effects of cerebral consequences of cardiopulmonary bypass, in particular, are conflicting, and there is a need for ongoing laboratory experiments and controlled clinical trials before sweeping changes to intraoperative management are undertaken, with particular attention to long-term outcomes in school-age children. Neurodevelopmental abnormalities are widely prevalent and are major contributors to adverse health-related quality of life outcomes. Further research must continue, in the laboratory, inpatient, and outpatient settings.



(Table/Fig 5) Currently identified factors which - in total – adversely affect long term neurological and developmental outcomes in children with complex congenital heart disease. Modified from Wernovsky G. Cardiol Young. 2006;suppl I:92-104.

Selected References

[1]. Bassan H, Gauvreau K, Newburger JW, Tsuji M,Limperopoulos C, Soul JS, Walter G, Laussen PC, Jonas RA, duPlessis AJ. Identification of pressure passive cerebral perfusion and its mediators after infant cardiac surgery. Pediatr Res. 2005;57:35-41.

[2]. Bellinger DC, Jonas RA, Rappaport LA, Wypij D, Wernovsky G, Kuban KC, Barnes PD, Holmes GL, Hickey PR, Strand RD.Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. N Engl J Med. 1995;332:549-55.

[3]. Bellinger DC, Rappaport LA, Wypij D, Wernovsky G,Newburger JW. Patterns of developmental dysfunction after surgery during infancy to correct transposition of the great arteries. JDev Behav Pediatr. 1997;18:75-83.

[4]. Bellinger DC, Wypij D, Kuban KC, Rappaport LA, Hickey PR,Wernovsky G, Jonas RA, Newburger JW. Developmental and neurological status of children at 4 years of age after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. Circulation. 1999;100:526-32.

[5]. Bellinger DC, Wypij D, duDuplessis AJ, Rappaport LA, Jonas RA, Wernovsky G, Newburger JW. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries:the Boston Circulatory Arrest Trial. J Thorac Cardiovasc Surg. 2003;126:1385-1396.

[6]. Clancy RR, McGaurn SA, Goin JE, Hirtz DG, Norwood WI,Gaynor JW, Jacobs ML, Wernovsky G, Mahle WT, Murphy JD,Nicolson SC, Steven JM, Spray TL. Allopurinol neurocardiac protection trial in infants undergoing heart surgery using deep hypothermic circulatory arrest. Pediatrics. 2001;108:61-70.

[7]. Clancy RR, McGaurn SA, Wernovsky G, Gaynor JW, Spray TL, Norwood WI, Jacobs ML, Goin JE. Risk of seizures in survivors of newborn heart surgery using deep hypothermic circulatory arrest. Pediatrics. 2003;111:592-601.

[8]. Clancy RR, Sharif U, Ichord R, Spray TL, Nicolson S, Tabbutt S, Wernovsky G, Gaynor JW. Electrographic neonatal seizures after infant heart surgery. Epilepsia. 2005;46:84-90.

[9]. du Plessis AJ, Chang AC, Wessel DL, Lock JE, Wernovsky G,Newburger JW, Mayer JE, Jr. Cerebrovascular accidents following the Fontan operation. Pediatr Neurol. 1995;12:230-36.

[10]. Gaynor JW, Gerdes M, Zackai EH, Bernbaum J, Wernovsky G, Clancy RR, Newman MF, Saunders AM, Heagerty PJ, D'Agostino JA, McDonald-McGinn D, Nicolson SC, Spray TL, Jarvik GP. Apolipoprotein E genotype and neurodevelopmental sequelae of infant cardiac surgery. J Thorac Cardiovasc Surg.2003;126:1736-45.

[11]. Gaynor JW, Nicolson SC, Jarvik GP, Wernovsky G,Montenegro LM, Burnham NB, Hartman DM, Louie A, Spray TL,Clancy RR. Increasing duration of deep hypothermic circulatory arrest is associated with an increased incidence of postoperative electroencephalographic seizures.J horac Cardiovasc Surg.2005;130:1278-86.

[12]. Gaynor JW, Jarvik GP, Bernbaum J, Gerdes M, Wernovsky G, Burnham NB, D'Agostino JA, Zackai E, McDonald-McGinn DM, Nicolson SC, Spray TL, Clancy RR. The relationship of postoperative electrographic seizures to neurodevelopmental outcome at 1 year of age after neonatal and infant cardiac surgery. JThorac Cardiovasc Surg. 2006;131:181-89.

[13]. Goldberg CS, Schwartz EM, Brunberg JA, Mosca RS, Bove EL, Schork MA, Stetz SP, Cheatham JP, Kulik TJ. Neurodevelopmental outcome of patients after the fontan operation: A comparison between children with hypoplastic left heart syndrome and other functional single ventricle lesions. J Pediatr. 2000;137:646-52.

[14]. Hoehn KS, Wernovsky G, Rychik J, Tian ZY, Donaghue D,Alderfer MA, Gaynor JW, Kazak AE, Spray TL, Nelson RM. Parental decision-making in congenital heart disease. Cardiol Young. 2004;14:309-14.

[15]. Hoehn KS, Wernovsky G, Rychik J, Gaynor JW, Spray TL,Feudtner C, Nelson RM. What factors are important to parents

making decisions about neonatal research? Arch Dis Child Fetal Neonatal Ed. 2005;90:F267-F69.
[16]. Kirshbom PM, Flynn TB, Clancy RR, Ittenbach RF, Hartman DM, Paridon SM, Wernovsky G, Spray TL, Gaynor JW. Late neurodevelopmental outcome after repair of total anomalous pulmonary venous connection. J Thorac Cardiovasc Surg. 2005;129:1091-97.
[17]. Licht DJ, Wang J, Silvestre DW, Nicolson SC, Montenegro LM, Wernovsky G, Tabbutt S, Durning SM, Shera DM, Gaynor JW, Spray TL, Clancy RR, Zimmerman RA, Detre JA. Preoperative cerebral blood flow is diminished in neonates with severe congenital heart defects. J Thorac Cardiovasc Surg.2004;128:841-49.
[18]. Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, Tchervenkov C. Neurologic status of newborns with congenital heart defects before open heart surgery. Pediatrics. 1999;103:402-8.
[19]. Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B,Rohlicek C, Tchervenkov C. Neurodevelopmental status of newborns and infants with congenital heart defects before and after open heart surgery. J Pediatr. 2000;137:638-45.
[20]. Limperopoulos C, Majnemer A, Rosenblatt B, Shevell MI, Rohlicek C, Tchervenkov C, Gottesman R. Association between electroencephalographic findings and neurologic status in infants with congenital heart defects. J Child Neurol. 2001;16:471-76.
[21]. Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, Tchervenkov C, Darwish HZ. Functional limitations in young children with congenital heart defects after cardiac surgery.Pediatrics. 2001;108:1325-31.
[22]. Limperopoulos C, Majnemer A, Shevell MI, Rohlicek C,Rosenblatt B, Tchervenkov C, Darwish HZ. Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects. J Pediatr. 2002;141:51-58.
[23]. Mahle WT, Clancy RR, Moss EM, Gerdes M, Jobes DR, Wernovsky G. Neurodevelopmental outcome and lifestyle assessment in school-aged and adolescent children with hypoplastic left heart syndrome. Pediatrics. 2000;105:1082-89.
[24]. Majnemer A, Limperopoulos C. Developmental progress of children with congenital heart defects requiring open heart surgery. Semin Pediatr Neurol. 1999;6:12-19.
[25]. Newburger JW, Jonas RA, Wernovsky G, Wypij D, Hickey PR, Kuban KC, Farrell DM, Holmes GL, Helmers SL, Constantinou J, . A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. N Engl J Med.1993;329:1057-64.
[26]. Newburger JW, Wypij D, Bellinger DC, du Plessis AJ, Kuban KC, Rappaport LA, Almirall D, Wessel DL, Jonas RA, Wernovsky G. Length of stay after infant heart surgery is related to cognitive outcome at age 8 years. J Pediatr. 2003;143:67-73.
[27]. Schultz AH, Jarvik GP, Wernovsky G, Bernbaum J, Clancy RR, D'Agostino JA, Gerdes M, McDonald-McGinn D, Nicolson SC, Spray TL, Zackai E, Gaynor JW. Effect of congenital heart disease on neurodevelopmental outcomes within multiplegestation births. J Thorac Cardiovasc Surg. 2005;130:1511-16.
[28]. Uzark K. Counseling adolescents with congenital heart disease.J Cardiovasc Nurs. 1992;6:65-73.
[29]. Uzark K, Lincoln A, Lamberti JJ, Mainwaring RD, Spicer RL, Moore JW. Neurodevelopmental outcomes in children with Fontan repair of functional single ventricle.Pediatrics. 1998;101:630-33.
[30]. Uzark K, Jones K. Parenting stress and children with heart disease. J Pediatr Health Care. 2003;17:163-68.
[31]. Wernovsky G, Stiles KM, Gauvreau K, Gentles TL, duPlessis AJ, Bellinger DC, Walsh AZ, Burnett J, Jonas RA, Mayer JE, Jr., Newburger JW. Cognitive development after the Fontan operation. Circulation.2000;102:883-89.
[32]. Wernovsky G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. Cardiol Young. 2006;16 Suppl 1:92-104.