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Optimizing Neurodevelopmental Outcomes in Neonates with Congenital Heart Disease

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Abstract

Neurodevelopmental impairment is a common and important long-term morbidity among infants with congenital heart disease (CHD). More than half of those with complex CHD will demonstrate some form of neurodevelopmental, neurocognitive, and/or psychosocial dysfunction requiring specialized care and impacting long-term quality of life. Preventing brain injury and treating long-term neurological sequelae in this high-risk clinical population is imperative for improving

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neurodevelopmental and psychosocial outcomes. Thus, cardiac neurodevelopmental care is now at the forefront of clinical and research efforts. Initial research primarily focused on neurocritical care and operative strategies to mitigate brain injury. As the field has evolved, investigations have shifted to understanding the prenatal, genetic, and environmental contributions to impaired neurodevelopment. This review summarizes the recent literature detailing the brain abnormalities affecting neurodevelopment in children with CHD, the impact of genetics on neurodevelopmental outcomes, and the best practices for neonatal neurocritical care, focusing on developmental care and parental support as new areas of importance. A framework is also provided for the infrastructure and resources needed to support CHD families across the continuum of care settings.

Table of Contents Summary:

This review summarizes brain abnormalities affecting neurodevelopment in children with congenital heart disease, impact of genetics, and best neonatal neurocritical care practices for optimizing outcomes.

INTRODUCTION

Advances in medical and surgical management of infants with congenital heart disease (CHD) have improved survival and contributed to a rapidly growing population of affected children, adolescents, and adults.[1] These successes have created an urgent need to address the long-term sequelae of CHD, with neurodevelopmental impairment now recognized as the most common morbidity experienced by infants who undergo cardiac surgery.[2] The seminal work of the Boston Circulatory Arrest Trial initially highlighted the importance of neurodevelopmental outcomes in this population.[3] Since then, it has become well-documented that nearly half of children with complex CHD experience neurodevelopmental and psychosocial impairments that impact their health-related quality of life.[2, 4-11] By adolescence, 65% receive educational and/or psychosocial services.[10] Critically, these deficits persist into adulthood, affecting educational achievement, quality of life, employment, and insurance status (Table 1).[12, 13]

While optimization of neurodevelopmental outcomes initially centered on neurocritical care and operative strategies, prenatal, genetic, and environmental contributions have become important areas of focus as the field has evolved (Figure 1). Concomitantly, there has been increasing recognition of the need for infrastructure and resources to support CHD families as they navigate the continuum of neurodevelopmental care settings, including the transition to adult providers. This review summarizes the literature across these critical aspects of cardiac neurodevelopmental care.

The research strategy used to inform this review involved searching Pubmed MeSH settings to identify peer reviewed articles on neurodevelopmental and psychiatric outcomes in CHD published since 2000. Additional studies were included based on the authors' personal knowledge (including publications before 2000). Non-full text and non-English publications were excluded. Authors independently reviewed studies and included/excluded based on the evidence strength. This manuscript is part of a larger series of articles simultaneously published as a Supplement in *Pediatrics* by the Neonatal Cardiac Care Collaborative

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BRAIN INJURY AND ALTERED BRAIN DEVELOPMENT

Prenatal Brain Abnormalities

Recent literature has characterized the timing and patterns of brain injury and altered brain development in CHD (Figure 2). Over the last decade, it has become clear that brain development is altered *in utero* in CHD fetuses.[14] These abnormalities persist through adulthood without evidence of "catch up" growth.[15-17] Prenatal aberrations in brain development are evident on ultrasound and magnetic resonance imaging (MRI) by the second and third trimesters of pregnancy.[18-23] A large, population-based study of ultrasound biometry identified CHD-related brain alterations by 20 weeks gestation.[18] Smaller fetal MRI cohorts have shown altered cortical development at 22-25 weeks[19, 20] preceding reductions in brain volumes that occur by 30 weeks.[14, 19]

This *in utero* vulnerability is not surprising given the negative impact of aberrant cardiac anatomy on fetal cerebral hemodynamics and substrate delivery (e.g., glucose, oxygen) during a period of rapid brain development. Aerobic glycolysis is a critical component of typical brain development throughout this window,[24] with increased oxygen delivery facilitating synapse formation, gyrification, sulcation, and increased brain weight from the second to third trimester.[25] Normal fetal-placental-cardiac hemodynamics are essential for supplying oxygen and nutrients to the fetus, and placental abnormalities, including decreased weight, vascular abnormalities, and altered perfusion, are prevalent in CHD.[26-29] Pro-angiogenic genetic variants are also common and associated with altered placental function and smaller birth head circumference.[30] Abnormal cardiac anatomy may also disrupt cerebral oxygen/nutrient delivery via hypoxia and/or altered cerebral blood flow.[31] In one cohort, CHD fetuses demonstrated 10% and 32% reductions in cerebral oxygen saturation and consumption, respectively, with both associated with smaller brain size.[23] Further, CHD fetuses have elevated lactate on MR spectroscopy, indicative of cerebral anaerobic metabolism.[14]

Preterm models indicate the oligodendroglial lineage plays an important role in this impact of CHD-related hypoxia on brain development.[32] Selective vulnerability of pre-myelinating oligodendrocytes to hypoxia/hypoperfusion causes arrested white matter maturation and hypomyelination. Cortical abnormalities follow, driven by impairments in thalamocortical and cortico-cortical connectivity. Intrauterine and perinatal chronic hypoxia models mimicking CHD physiology also demonstrate decreased neuronal progenitor cells in the subventricular zone, as well as hypomyelination and abnormal cortical development.[33, 34] Similar findings are evident in neuropathological specimens from CHD infants.[34]

Postnatal Brain Abnormalities

Up to 40% of CHD infants who undergo cardiothoracic surgery have preoperative brain injury, and another third display new injury postoperatively.[35-38] The most common

pattern is white matter injury (WMI), though stroke/infarct also occur.[35, 38] Infants with abnormal brain development on prenatal and/or preoperative MRI are at heighted risk of perioperative injury.[35, 36, 39] Further, moderate-severe injury on pre- and/or post-operative MRI is associated with slower brain growth over the 2-3 weeks surrounding cardiac surgery[40] suggesting a “two-hit” phenomenon. Data linking WMI with neurodevelopmental deficits have been mixed, but moderate-severe injury is clearly associated with worse neurodevelopmental outcomes.[38]

Longer-term brain abnormalities in CHD include reductions in white and gray matter volumes and abnormal gyrification, sulcation, microstructure, metabolism, and cerebral connectivity, many of which are already present preoperatively (Figure 2).[15-17, 35, 41-51] Due in part to these abnormalities, children with complex CHD have high rates of deficits across academic and neurodevelopmental performance domains, altered language and motor skills, and lower health-related quality of life.[2, 10, 13, 15-17, 35, 41-43, 51-57] These data highlight the complexity of brain development in CHD, where fetal brain abnormalities predispose the infant to perioperative injury and ongoing aberrations in brain development that impact neurodevelopmental and psychiatric outcomes long after cardiac surgery.[2, 13]

CLINICAL UTILITY OF IMAGING

Initial data suggest abnormal brain development on fetal MRI is associated with increased perioperative brain injury risk.[39, 58] However, the expertise and resources required for fetal MRI currently prevent its routine clinical application to obtain detailed brain measures. Postnatal imaging is more accessible and commonly used. Many centers routinely perform cranial ultrasound screening pre-operatively in all CHD infants. Cranial ultrasound is 82% sensitive and 93% specific for intraventricular hemorrhage when compared to clinically acquired computed tomography or MRI.[60] This same study showed the odds of developing intraventricular hemorrhage increased 1.3-fold for each week decrease in gestational age, resulting in an incidence >50% for very preterm CHD infants, although the majority was low-grade hemorrhage. However, ultrasound may miss many abnormalities seen on MRI, particularly WMI.[59] There are currently no conclusive data supporting routine MRI to guide critical care approaches or surgical timing, with only one cohort reporting that clinically-silent preoperative lesions do not worsen postoperatively.[61] Neuroimaging studies are key components of ongoing research efforts that may inform future clinical practice. In the interim, detailed neurological examinations and consultation with neurology and/or dedicated neurocritical care services may facilitate decision-making regarding neuroimaging.

Recommendations:

1. The utility of routine clinical fetal or postnatal MRI in CHD is unclear. However, regular, detailed neurological examinations before and after cardiac surgery can be useful to identify infants who would benefit from neuroimaging (Class IIa/LOE C-EO).

2. Cranial ultrasound may be considered to screen for intraventricular hemorrhage or major structural abnormalities in all CHD infants but may not be useful for WMI (Class IIb, LOE C-LD).

3. When available, consultation with pediatric neurology and/or neurocritical care services can be beneficial for facilitating optimal neuroimaging use (Class IIa/LOE C-EO).

GENETIC INFLUENCES ON NEURODEVELOPMENTAL OUTCOME

CHD occurs in common and rare genetic disorders and syndromes (Table 2), some of which are known to be associated with neurodevelopmental dysfunction, while other genetic abnormalities have less clear neurodevelopmental implications.[62] Genetic factors have been previously recognized as major neurodevelopmental determinants in CHD, independent of cardiac defect or surgical repair.[52, 63] These include greater risk of motor and cognitive delays in early childhood and school-age[64-67] and greater intellectual impairments, poorer academic achievement, worse executive functioning, increased autism symptoms, and lower health-related quality of life in adolescence.[56, 68, 69] These relationships likely begin in the prenatal period and may be independent of or additive to the effects of hemodynamic alterations. Recently, impaired head growth in CHD fetuses showed better correlation with the presence of a genetic syndrome and/or extracardiac anomaly than abnormal fetal hemodynamics.[70]

An increasing focus on the genetic underpinnings of CHD have established that genetic variants outside of known syndromes are also important. For example, genotyping apolipoprotein E, a cholesterol metabolism regulator involved in neuronal and white matter repair, may be valuable because of associations between the ε2 allele and motor and behavioral deficits in CHD.[71, 72] New sequencing technologies and strategies for analyzing genetic data also provide key insights. Studies utilizing rare variant burden analyses implicate neurotransmitter, axon guidance, and RASopathy gene pathways in neurodevelopmental disability associated with CHD.[73] Further, novel and known pathogenic copy-number variants have been associated with motor delay,[74] and damaging *de novo* variants in high-heart, high-brain expressing genes are upregulated in CHD patients with neurodevelopmental disability.[75] Importantly, adolescents with these variants demonstrate atypical left hemisphere sulcal development on MRI, [76] with similar abnormalities in CHD fetuses.[20] These data suggest genetic pathways for abnormal brain development in CHD.

Early diagnosis of genetic disorders is a key component of assessing neurodevelopmental risk and optimizing outcomes.[2, 62] Genetic evaluation begins prenatally for CHD as reviewed by Haxel and colleagues elsewhere in this issue. A Scientific Statement from the American Heart Association (AHA) provides recommendations for clinical genetic testing, including karyotype, chromosomal microarray, and targeted testing, as well as ethical considerations and use of genetic counselors.[62] Testing results and limitations of the testing should be discussed amongst clinicians and genetic specialists, communicated to parents, and documented in the medical record. Genetic specialists can also address cost effectiveness and financial burden.

Recommendations:

1. Prenatal and/or postnatal genetic testing, including karyotype and chromosomal microarray, can be effective for informing neurodevelopmental risk in CHD infants (Class IIa/LOE B-NR).
2. Additional targeted genetic testing may be considered based upon individual phenotypes; the role of routine expanded genetic sequencing remains unclear (Class IIb/LOE C-LD).
3. Vigilant neurodevelopmental surveillance should be incorporated into routine care for CHD infants with genetic syndromes (Class I/LOE B-NR).

NEONATAL NEURODEVELOPMENTAL CARE

Prenatal Diagnosis and Delivery Planning

Infants with a prenatal diagnosis of CHD demonstrate less frequent and less severe brain injury and better brain development compared to those with a postnatal diagnosis.[77] Prenatal diagnosis also correlates with improved cognition in children with transposition of the great arteries.[78] This neuroprotective effect is presumably related to the expectant care provided for the known diagnosis postnatally, leading to more favorable postnatal hemodynamics.[38] Gestational age at birth is also important for CHD infants. Elective delivery at<39 weeks gestation is associated with increased mortality, morbidity, and worse outcomes.[79] Lower gestational age also increases the likelihood and severity of brain injury and abnormal brain development[80-82] and is a key predictor of adverse motor, cognitive, language, and psychiatric outcomes.[79, 83, 84] The AHA Scientific Statement on fetal cardiac medicine supports multidisciplinary approaches to avoid elective delivery at <39 weeks, to create specialized care plans that optimize postnatal hemodynamics, and to consider maternal complications and fetal well-being in delivery decision-making.[85] Additional data and recommendations regarding delivery timing are discussed by Haxel and colleagues elsewhere in this issue.

Intensive Care, Perioperative Management, and Neuromonitoring

Cardiac intensive care strategies and operative management are modifiable variables that contribute to optimizing neurodevelopmental outcomes. Risk factors for perioperative brain injury and worse neurodevelopmental outcomes include hypoxemia; impaired cerebral oxygenation and hemodynamics; longer time from birth to surgery; prolonged cardiopulmonary bypass and circulatory arrest; larger base deficit during cardiopulmonary bypass; inadequate levels of hypothermia while on cardiopulmonary bypass and/or hyperthermia during the early postoperative period; greater hemodilution on cardiopulmonary bypass; pre- and postoperative cardiac arrest and the need for cardiopulmonary resuscitation; utilization of pre- or postoperative extracorporeal membrane oxygenation (ECMO) support; and single ventricle physiology and aortic arch obstruction.[35, 86-97] Cardiac surgery-related brain injury appears to occur via hypoxic/ischemic effects on oligodendrocyte precursor cells, which is exacerbated by prior hypoxic exposures and alters white matter development.[98-100] Intensive care unit events and postoperative complications that increase length of stay and/or result in repetitive

anesthetic exposure contribute to worse neurodevelopmental outcomes. These include higher inotropic score, extubation failure, infection (e.g., bacteremia/sepsis, mediastinitis), arrhythmias, postoperative seizures, electroencephalogram (EEG) abnormalities, ECMO, and additional cardiac and non-cardiac operations (e.g., residual lesions requiring re-intervention, gastrostomy tube).[10, 52, 101-110]

In an attempt to minimize perioperative neurological injury risk, many centers have adopted the use of continuous, non-invasive monitors that provide surrogate markers of oxygen delivery, such as near-infrared spectroscopy (NIRS). This technology provides information on regional tissue oxygenation, expressed as an oxygen saturation (rSO_2). In the days after birth, cerebral oxygenation declines and reaches a threshold where WMI risk likely increases.[89] In one cohort, lower cerebral rSO_2 intraoperatively predicted acute neurologic injury postoperatively.[111] Reduced rSO_2 variability in the immediate postoperative period may reflect impaired cerebral autoregulation leading to poor outcomes.[112] Further, utilizing NIRS in combination with blood lactate postoperatively enhances prediction of mortality and poor neurodevelopmental outcomes.[113] Perioperative neurological management may also include monitoring for seizure activity. Approximately 10-30% of CHD infants have electrographic seizures perioperatively, and up to 60% have abnormal background patterns.[114-119] Brain injury and altered brain development are associated with abnormal EEG, and new postoperative seizures may suggest new brain injury.[116, 119, 120] While amplitude-integrated EEG (aEEG) can detect seizures and provide trends in background activity, conventional video EEG remains the standard of care. Adverse neurodevelopmental outcomes are seen in children who have seizures on conventional EEG,[102, 121] whereas background patterns, but not seizures, relate to outcome for aEEG.[114] Similar to neuroimaging, there are currently no standardized recommendations for use of NIRS or EEG in all CHD infants, although the American Clinical Neurophysiology Society recommends EEG monitoring in neonates undergoing early cardiopulmonary bypass.[122] Despite data showing an association of reduced rSO2 and seizures with poorer neurodevelopmental outcomes, there is not yet evidence that incorporation of these monitoring strategies improves neurodevelopmental outcomes.

While perioperative management is critical for mitigating neurologic risk, operative and postoperative factors explain ≤5% of neurodevelopmental outcome variance, whereas pre-operative and patient-specific factors account for ~25%.[97] Non-modifiable factors associated with adverse neurodevelopmental outcomes include lower maternal education (e.g., less than high school compared to graduate school), lower socioeconomic status, genetic disorders/variants, prematurity, and cardiac diagnosis.[97] These data highlight the need to optimize current practices while exploring new neuroprotective strategies.

Developmental Care in the Intensive Care Unit

CHD infants require surgical interventions during periods of developmental immaturity. Therefore, in addition to providing optimal medical care, the critical care environment must foster autonomic and behavioral subsystem development.[123] Implementation of developmental and kangaroo care improves outcomes in premature infants.[124-126] Recently, individualized, family-centered developmental care has been identified as a promising

neuroprotective model for the cardiac intensive care environment.[127] Straightforward modifications include cycled-lighting to maintain circadian rhythms; music exposure to minimize noxious stimulation; physiologic positioning with flexion, spinal alignment, swaddling; and non-pharmacologic comfort measures.[128-133] Early engagement with therapy services is often essential for instituting these modifications.[132] Kangaroo care has not only been shown to be safe for CHD infants, but actually improves cardiopulmonary status following extubation and optimizes feeding tolerance.[134-137]

Oromotor development and coordination of sucking and feeding are among the earliest manifestations of motor control.[138] Feeding dysfunction in CHD can lead to impaired somatic growth, which remains critical to motor and cognitive outcomes.[135] Furthermore, CHD infants who breastfeed have higher weight-for-age scores,[139] likely secondary to fewer episodes of desaturation and temperature decreases.[140] Breastfeeding allows mothers to actively participate in their child's care, leading to improved maternal-child bonding.[141, 142] Orally fed CHD infants demonstrate more rapid white and gray matter brain maturation compared to their tube-fed counterparts,[135] emphasizing the importance of practices facilitating feeding via bottle or breast.

Parental Well-being in the Intensive Care Unit

Growing evidence suggests the long-term behavioral, social, and emotional difficulties of children with CHD may be partially attributable to parental mental health beginning prenatally.[143-145] A systematic review found 80% of CHD parents report trauma symptoms, 25-50% report elevated depression and/or anxiety symptoms, and 30-80% report severe psychological distress.[146] Prenatal exposure to maternal psychological distress has recently been associated with altered fetal brain metabolism, hippocampal growth, and cortical development in healthy pregnancies.[147] Further, abnormal hippocampal and cerebellar development are seen in CHD fetuses exposed to maternal stress and anxiety.[148] In the hospital setting, parental stressors include feelings of inadequate preparation and knowledge, concerns about outcomes, infant appearance, the intensive care environment, altered parental roles, financial burdens, and inadequate support.[149, 150] Importantly, stress is experienced differently by parents. While mothers tend to focus on the baby, fathers tend to focus on supporting mother and child.[150]

Parental mental health interventions are necessary to support CHD families and optimize neurodevelopment. A recent review of parental mental health during intensive care identified only five trials of infants with congenital anomalies (four included CHD; two included fathers).[151] Although available evidence is minimal, these data suggest interventions are efficacious for reducing parental anxiety and improving maternal coping, mother-infant attachment, parenting confidence, clinical care satisfaction, and infant development.[151]

Transition to Home

To date, no data have been published linking neurodevelopmental outcomes to the discharge process and transition to home. However, this is a period of unanticipated physical and emotional transitions where greater parental education and support are needed.[152, 153] Use of discharge specialists increases parents' perceived discharge readiness.[154] Parental education

on referral for early intervention services and outpatient therapies should be a priority at discharge to facilitate this transition. Support of parental well-being during this period is also critical.

Recommendations:

1. Intensive care management should minimize clinical complications and exposure to clinical factors that increase neurodevelopmental risk (Class I/LOE B-NR).
2. Incorporation of NIRS and EEG into intensive care management may be considered to identify CHD infants at higher neurological risk (Class IIb/LOE C-LD).
3. Incorporation of developmental care approaches, including appropriate positioning, cycled lighting, noxious stimuli minimization, non-pharmacologic comfort measure use, kangaroo care, and oral/breastfeeding, may be considered in the intensive care unit to optimize neurodevelopmental outcomes (Class IIb/LOE C-LD).
4. Screening for parental psychological distress may be reasonable in the intensive care environment as a component of neurodevelopmental care (Class IIb/LOE C-LD).

CONTINUUM OF NEURODEVELOPMENTAL CARE THORUGHOUT CHILDHOOD

Childhood Outcomes

Children with CHD have a distinct neurodevelopmental profile of early motor deficits, cognitive delays, language impairments, executive dysfunction, inattention, emotional and behavioral disorders, and issues with social cognition.[2, 13] Up to 50% display impairments across one or more domains.[7] Increasing neurodevelopmental risk occurs with increasing CHD severity.[7] However, significant variation in neurodevelopmental outcomes is present among those with the same cardiac diagnosis,[155] likely due to patient-specific risk factors outlined in the AHA and American Academy of Pediatrics (AAP) Scientific Statement on CHD outcomes (Table 3).[2]

It is important to recognize the dynamic nature of neurodevelopment in children with CHD.[156] Motor delay tends to be prevalent in the first year of life and may improve during early childhood.[157, 158] However, even at age 10 years, deficits are still common, particularly within adaptive motor function, static balance, and movement quality.[159] Infant surgery and exposure to the intensive care environment are key factors affecting motor development.[160] Lower socioeconomic status and maternal education are associated with worsening fine motor skills.[161] Cognitive and language impairments are also present early, but generally do not demonstrate improvement, and may worsen, particularly in children with genetic syndromes and lower socioeconomic status.[157, 158, 161, 162] Of interest, a cognitively stimulating home environment is associated with better cognitive development,[163] whereas parental stress is associated with worse cognition.[164] At school-age, cognitive ability

typically falls in the low-normal range.[165] Lower scores in language, attention, and executive function measures are common.[8] In a recent cohort, parent-reported executive dysfunction was present in >60% of school-aged children[166] and strongly correlated with health-related quality of life.[57, 167] Working memory and flexibility appear to be notably problematic, though behavioral dysregulation is prominent in children born preterm, of male sex, or with arch obstruction.[166] Behavioral and emotional deficits become more evident throughout childhood and are associated with impairments in other domains, including motor and language development.[159, 168, 169]

Screening and Evaluation of Childhood Neurodevelopment

While neurodevelopmental disabilities are common, deficits are mild for many CHD children and may not be detected without formal testing.[64] The dynamic nature of neurodevelopmental outcomes and evolution of children's risk category highlight the need for continual surveillance and use of early intervention services.[170] The AHA/AAP 2012 Scientific Statement provides guidelines for neurodevelopmental evaluation in CHD, using a medical home model that includes the family, primary care providers, and specialty services.[2] Consistent with general AAP recommendations, primary care providers are the foundation for the medical home, providing neurodevelopmental surveillance at every visit, standardized developmental screening at 9, 18, and 30 months of age, and autism screening at 18 and 24 months.[2, 171, 172] CHD-specific guidelines expand these recommendations by incorporating a risk assessment for all children with CHD.[2] Those identified as high-risk should be referred for formal developmental and medical evaluations (Table 3). Developmental evaluation includes referral to early intervention/special education services and multidisciplinary cardiac neurodevelopmental follow-up programs. The medical evaluation includes a developmental history, growth and feeding assessment, motor and audiologic examinations, evaluation by a developmental pediatrician or pediatric neurologist and, if indicated, a geneticist. Medical and developmental re-evaluation is recommended between ages 12-24 months, 3-5 years, and 11-12 years.[2] A variety of neurodevelopmental assessment tools are available across ages and have been summarized in two recent publications from the Cardiac Neurodevelopmental Outcome Collaborative.[173, 174] An important component of formal neurodevelopmental evaluation across all ages is the communication of results, and any limitations of the testing (e.g., related to cooperation of the child), between clinicians and the family, as well as documentation of these discussions in the medical record.

Navigating the School System

Navigating school systems and providing school-based interventions are essential components of neurodevelopmental care (Table 4).[175, 176] Neuropsychological or educational evaluations are undertaken to facilitate individualized education plans (IEPs) and 504 plans.[177] Testing is repeated every 2-3 years, with IEPs and 504 plans updated annually to provide home-school communication. Homebound instruction can be established for medically-indicated absences. It is beneficial to have an education specialist, or school liaison, facilitate the interaction between the parents/guardians and the school system to provide support and implement recommendations.[178] The education specialist facilitates school-based therapies and curriculum modifications, which include extra time for tests/

homework, note taking, recording classes, reading or scribing during tests, and quiet testing environments.[179] Education of school staff regarding the child's medical condition, disability risk, and learning needs is another important component. Recently, children with CHD with executive dysfunction were found to receive similar school services as those without difficulties.[166] This highlights the critical need for continued education amongst schools and the benefit of school liaisons, who can encourage parents to become empowered advocates. As cardiac neurodevelopmental programs evolve, education specialists/school liaisons will be an important component of care that can be supported through a number of mechanisms including local health and school systems.

Optimizing Family Support

Caring for a child with CHD can place significant strain on the family dynamic as parents navigate the complexity of their child's care. Implementation of targeted support strategies for mothers, fathers, and siblings are essential and span medical, classroom, and home arenas (Table 5). Navigating early intervention referrals and routine neurodevelopmental screening can be challenging. A recent cohort from the Single Ventricle Reconstruction Extension Study identified that less than half of children were receiving early intervention services at age one year, and over one-third never received services despite high rates of neurodevelopmental delay.[170] These findings highlight referral patterns and the need to support parents. Multidisciplinary cardiac neurodevelopmental follow-up programs can provide a collaborative platform for primary care providers to utilize as a "home base" for accessing early interventions, rehabilitative services, behavioral management, counseling, school-based support, and care transitions. Family-specific support typically focuses on parental wellbeing and support networks and can be provided by primary care providers and/or cardiac neurodevelopmental follow-up programs,[151, 180, 181] with referral to mental health specialists as indicated. Recent data have identified that parents of children with medical complexity are often unsure of where to find community help or resources for mental health needs, suggesting that policy makers and health care organizations consider family mental health as a component of improving health systems.[182]

Recommendations:

1. Developmental surveillance by primary care providers at every well child visit can be beneficial for all children with CHD. Standardized developmental screening can also be beneficial at 9, 18, and 30 months, with autism screening at 18 and 24 months. Primary care providers and/or subspecialists can perform this screening (Class IIa/LOE C-LD).
2. A risk assessment should be performed in children with CHD and those who meet the below criteria should be considered high-risk for neurodevelopmental disabilities (Class I/LOE A):
    a. Neonates/infants requiring open heart surgery
    b. Children with cyanotic heart conditions not requiring open heart surgery during neonatal period/infancy
    c. CHD with comorbidities (Table 3)

d. Other conditions at discretion of medical home providers

3. Children with CHD who meet high-risk criteria can be referred to multidisciplinary cardiac neurodevelopmental follow-up and early intervention programs for developmental evaluation and to relevant providers for medical evaluation of growth, feeding, and audiologic assessment (Class IIa/LOE B-NR).

4. Medical and developmental re-evaluation by the primary care provider and/or a subspecialist can be beneficial between ages 12-24 months, 3-5 years, and 11-12 years (Class IIa/LOE C-LD).

5. Education specialists can be beneficial for facilitating the interaction between parents/guardians and the school system and school-based interventions (Class IIa/LOE C-EO).

6. Screening for parental stress and mental health problems, and referral for psychosocial intervention, during neurodevelopmental assessments may be reasonable to promote better family functioning and outcomes (Class IIb/LOE C-LD).

ADOLESCENTS AND ADULTS WITH CHD

Improving survival for patients with even severe cardiac lesions has led to a larger population of adults than children with CHD,[1] resulting in a rapid evolution of adolescent and adult CHD neurodevelopmental care. Neurodevelopmental disability occurs twice as commonly in adolescents with CHD than typically-developing children.[183] These deficits span working memory, perceptual reasoning, cognitive flexibility, and executive and motor function domains[183, 184] (Table 1) and correlate with CHD complexity.[185] The persistence of neurodevelopmental disability into adulthood, particularly in those with severe CHD, has been associated with higher unemployment, reliance on disability, and lower education levels.[186] Evaluation of these deficits encompasses use of formal assessment tools.[187] Efforts to improve outcomes include targeted childhood interventions, medical management of inattention/hyperactivity, and career counseling.[188]

In addition to neurodevelopmental disabilities, adolescents and adults with CHD have an increased incidence of comorbid psychiatric disorders including anxiety, depression, post-traumatic stress disorder, attention difficulties, adjustment disorder, and early onset dementia.[189, 190] Up to 69% of CHD patients with mood or anxiety disorders do not receive psychotherapy or psychotropic drugs,[191] highlighting the need for lowering thresholds for referral to and/or adoption of psychologists into comprehensive programs.[192] Given this high prevalence and limitations in access to therapies, it is essential that routine care include screening for these disorders coupled with standardized treatment referral pathways. Approaches for mental health care in pediatric practices[193] and psychosocial screening tools for adolescents and young adults,[194] are available from the AAP. Additional tools may be useful for adults with CHD.[195, 196]

The complex co-morbidities found in the adult CHD population make it imperative that care is transitioned from pediatric- to adult-centered providers. Currently there are many barriers

to this transition (Table 6). It is estimated that only 48% of CHD adolescents successfully transfer to adult centers.[197] The most recent AHA recommendations include a three-step process spanning many years.[198] The pre-transition period occurs throughout childhood and is dedicated to creating a foundation for lifelong care. Ideally, at age 12-14, patients advance to a transition curriculum with inclusion of residual hemodynamic concerns, insurance planning, future education, and employment goals. The third phase is transfer, when responsibility shifts from the pediatric to adult provider, ideally by age 21. A well-planned and coordinated effort is paramount to success. Each individual should have a detailed plan including their specific cardiac physiology, medical history, previous interventions, medication list, diagnostic studies, functional status, and comorbidities. Successful models include a dedicated staff member who assumes primary responsibility[199] and use of resources including mobile applications and webpages, such as gottransition.org.[200]

Recommendations:

1. Screening for neurodevelopmental and psychological disorders should continue in adults with CHD and be coupled with standardized treatment pathways (Class I/LOE C-LD).
2. Transition of care from the pediatric to adult clinical care arena through the medical home model should use a structured plan including parental partnership (Class I/LOE C-LD).

CONCLUSIONS

Neurodevelopmental care has become a critical component of treating children with CHD. Brain injury and abnormal brain development occur through multifactorial pathways that begin prenatally and underlie longstanding neurodevelopmental deficits. A multifaceted, longitudinal family-based approach to screening, evaluation, and treatment of neurodevelopmental disabilities is essential for optimizing neurodevelopmental outcomes. Recognition of high-risk clinical factors, incorporation of parental and family support, and implementation of developmental care strategies in the intensive care environment are important aspects of clinical practice. Genetic testing, neuroimaging, NIRS, EEG, and parental mental health screening may be useful in evaluating neurodevelopmental risk and are areas of ongoing investigation. Beyond the inpatient setting, routinely screening and evaluating neurodevelopment throughout childhood and adolescence, incorporating school liaisons in neurodevelopmental programs, and providing support and resources as children transition to adult care providers all facilitate a comprehensive longitudinal neurodevelopmental approach.

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Abbreviations:

CHD	congenital heart disease
ECMO	extracorporeal membrane oxygenation
EEG	electroencephalogram
IEP	individualized education plans
MRI	magnetic resonance imaging
WMI	white matter injury

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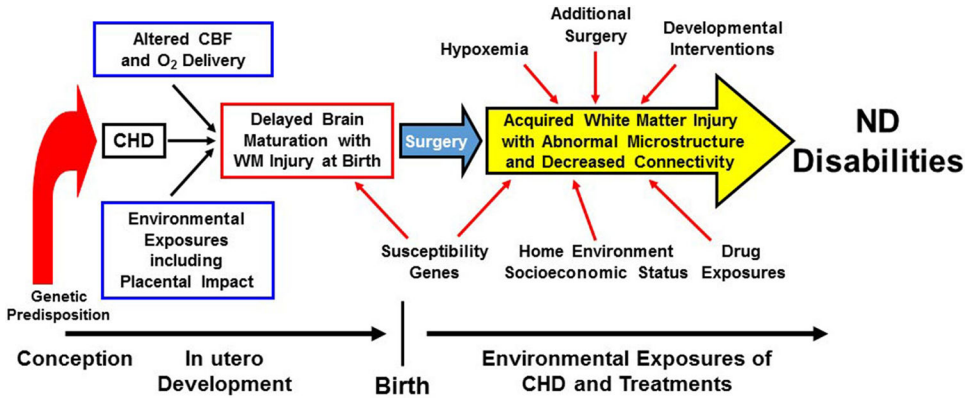

Figure 1.

Risk Factors for Neurological and Neurodevelopmental Abnormalities. Schematic representation of prenatal, perioperative, and social/environmental factors that contribute to neurodevelopmental disabilities in CHD. Prenatally, abnormal cardiac anatomy can alter blood flow and oxygenation to the developing brain, leading to impaired brain development. Concurrently, other pregnancy exposures including abnormal placental development and function and parental well-being can also have a negative impact on the brain. Genetic disruption of brain development may also occur via underlying genetics syndromes or pathogenic variants. Susceptibility genes (i.e., apolipoprotein E ε2) can further contribute to postoperative neurodevelopmental deficits. A variety of physiologic/intensive care exposures, such as hypoxemia, additional surgery, and drug exposure are important predictors in the neurocritical care arena. Finally, home environment and socioeconomic status can have a positive or negative influence, depending on the infant's environment, whereas developmental care interventions that begin in the intensive care unit and continue after discharge may have neurodevelopmental benefit. CBF, cerebral blood flow; ND, neurodevelopment; WM, white matter. Adapted with permission from J. William Gaynor.

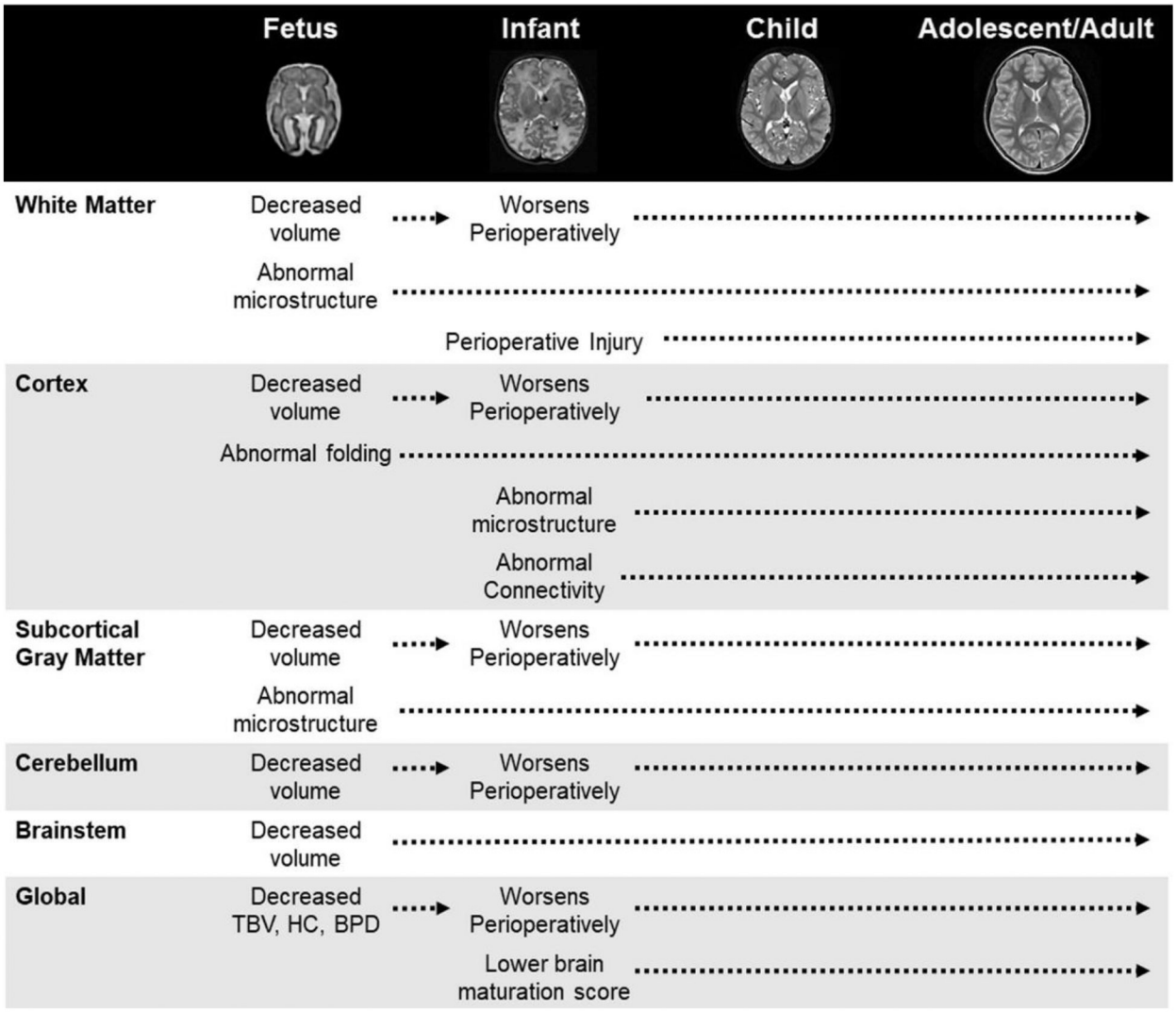

Figure 2.

Timing and Pattern of Neuroimaging Abnormalities. This timeline depicts abnormalities identified across key brain regions in neuroimaging studies of brain development in patients with CHD, beginning during the fetal period and extending into adolescence/adulthood. Representative T2-weighted images are provided for each developmental epoch depicting the significant change in brain size and structure that occurs during this period. As demonstrated, brain abnormalities in CHD are global in nature, involving white and gray matter regions at the micro- and macro-structural level. BPD, biparietal diameter; HC, head circumference; TBV, total brain volume.

Table 1.

Summary of Neurodevelopmental Outcomes by Age and Domain

Age Group	Domains Assessed	Outcome	Missing Domain(s)
Infants (birth to 12 months)	General Cognition Motor Skills Language Memory	Scores in normal range Deficits observed Scores in low-normal range Deficits observed	Executive Function Audiology
Toddlers (1-3.5 years)	General Cognition Motor Skills Language Behavioral-emotional Audiology	Deficits observed Deficits observed Deficits observed Deficits observed Scores in normal range	Executive Function Memory
Preschoolers (3.5-5 years)	General Cognition Academic Achievement Motor Language Processing Speed ADHD Symptoms Behavioral-Emotional Audiology	Scores in low-normal range Scores in normal range Deficits observed Deficits observed for more complex measures Deficits observed Deficits observed Deficits observed Slight deficits observed	Executive Function Memory
School-age children (5-12 years)	General Cognition Academic Achievement Language Speech Motor Skills Memory Executive Function Attention (sustained) ADHD Symptoms Visuospatial Skills Behavioral-Emotional Audiology	Scores in low-normal range Deficits observed Scores in low-normal range Deficits observed Deficits observed Deficits observed Deficits observed Deficits observed Deficits observed Deficits observed Deficits observed Scores in normal range	Some domains in single studies only, difficult to generalize Quality of life
Adolescents (13-18 years)	Academic Achievement Executive Function Memory Visuospatial Skills Attention (ADHD Symptoms) Behavioral-Emotional	Deficits observed Deficits observed Deficits observed Deficits observed Deficits observed Deficits observed	Motor skills Audiology Quality of life

Reprinted from *Congenital Heart Disease and Neurodevelopment, 1st Edition*, Kharitonova, M. and Marino B.S., An Emergent Phenotype: A Critical Review of Neurodevelopmental Outcomes for Complex Congenital Heart Disease Survivors During Infancy, Childhood, and Adolescence, pages 55-87, 2016 with permission from Elsevier.

Table 2.

Genetic Syndromes Associated with CHD

Common Syndromes	Rare Syndromes
Trisomy 21	LEOPARD syndrome
Trisomy 18	Kabuki syndrome
Trisomy 13	Costello syndrome
22q11 deletion syndrome	PHACES syndrome
Turner syndrome	Rubenstein – Taybi syndrome
Williams syndrome	Ellis- can Crevald syndrome
Jacobsen syndrome	Townes- Brocks syndrome
Alagille syndrome	Smith- Lemli -Opitz syndrome
Holt Oram syndrome	Goldenhar syndrome
Heterotaxy	Keutel syndrome
CHARGE syndrome	Cat eye syndrome
Cornelia de Lange syndrome	Char syndrome
Noonan syndrome	Simpson- Golabi- Behmel syndrome
VACTERL	Fryns syndrome
	Adams- Oliver syndrome
	Ritscher-Schinzel syndrome

Table 3.

Categories of Pediatric CHD Patients at High Risk for Developmental Disorders or Disabilities

1. Neonates/infants requiring open heart surgery (cyanotic and acyanotic types), for example, HLHS, IAA, PA/IVS, TAPVC, TGA, TOF, tricuspid atresia.
2. Children with other cyanotic heart lesions not requiring open heart surgery during the neonatal or infant period, for example, TOF with PA and MAPCA(s), TOF with shunt without use of CPB, Ebstein anomaly.
3. Any combination of CHD and the following comorbidities:
3.1. Prematurity (<37 wk)
3.2. Developmental delay recognized in infancy
3.3. Suspected genetic abnormality or syndrome associated with DD
3.4. History of mechanical support (ECMO or VAD use)
3.5. Heart transplantation
3.6. Cardiopulmonary resuscitation at any point
3.7. Prolonged hospitalization (postoperative LOS >2-wk in the hospital)
3.8. Perioperative seizures related to CHD surgery
3.9. Significant abnormalities on neuroimaging or microcephaly *
4. Other conditions determined at the discretion of the medical home providers

CHD indicates congenital heart disease; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; PA/IVS, pulmonary atresia with intact ventricular septum; TA, truncus arteriosus; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; PA, pulmonary atresia; MAPCA, major aortopulmonary collateral arteries; CPB, cardiopulmonary bypass; DD, developmental disorder or disability; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device; and LOS, length of stay.

* Normative data by sex, including percentiles and *z* scores, are available from the World Health Organization (www.who.int/childgrowth; accessed February 2010).

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Table 4.

School Based Interventions to Support Learning Needs

Type of Intervention	Examples
Regular evaluations including psychological, education, and speech and language	• Evaluations within neurodevelopmental clinic or school setting
Collaboration between education liaison in the neurodevelopmental clinic and school setting to share diagnostic information and recommendations	• Meeting to share medical and developmental history and explanation of possible neurodevelopmental impact of CHD • Annual meetings with school staff and at all transitions to new school buildings
Development of formal educational plans	• IEP's • 504 Plans
Homebound Instruction	• Full-time or partial to maintain schoolwork while missing school for medical reasons
Development of formal medical plan	• Activity restrictions • Administration of medication • Emergency plan
Development of accommodation and modification plans	• Extended time • Quiet testing environment • Scribe • Reader • Access to teacher notes/outlines
School based interventions	• Occupational therapy • Physical therapy • Speech/language therapy
Vocational skill training or programming	
Advocacy assistance	• Family education from school liaison regarding special education rights and supports available • Assistance navigating the special education process

* Created with assistance from Vicki Baker, MS, LPC, St. Louis Children's Hospital

Table 5.

Toolkit for Supporting Parents

Neurodevelopmental Assessment
• Summary of neurodevelopmental sequelae (Table 1) • AHA Scientific Statement on evaluation and management of neurodevelopmental outcomes[2] • School based interventions to support learning (Table 4)
Psychosocial Assessment
• Early psychosocial intervention to evaluate caregiving needs and enhance parenting • Use of standardized instruments and interviews to explore parental mental health - anxiety, depression, post-traumatic stress disorder, guilt, parent-child interaction • Counseling services through psychologist, social worker, pastoral care, comfort care/palliative care team • Promoting effective parent-infant transactions • Inquiring about parental mental health, stress, and family functioning during medical check-ups and hospitalizations • Development of coping strategies – exercise, sleep, narrative therapy, cognitive behavioral therapy, stress management • Mental health care for parents of babies with CHD[151] • Best practice guidelines: Supporting parents in the NICU[201]
Care Coordination
• Identification of care team for child, utilization of “medical home” model • AAP Policy Statement for Patient and Family-Centered Care Coordination[202] • National Resource Center for Patient/Family-Centered Medical Home[203] • Understand role of each team member • Clear and open communication between patient, family, and providers • Ask questions • Inpatient care conferences between medical team and family • Sign up for MyChart for access to healthcare records • Discharge coordinator to facilitate transition home • Family resource center – therapeutic recreation, summer programs, parent networks, school resources
Care Transition
• AHA Scientific Statement on transition to adulthood in adolescents with congenital heart disease[198] • Maintenance of a schedule • Home videoconferencing for families of children with complex CHD after discharge • Treatment adherence • Home based services – skilled nursing, respite care, early intervention, family support program • Identification of resource needs – transportation, interpretive services • Transition care facility
Social Support Networks
• Identification of existing social support systems - extended family and friends, parent and sibling support groups • Focus on self and family preservation (spousal and sibling relationships) • Support groups – Sisters By Heart[204]

- Pediatric Congenital Heart Association[205]
- Mended Hearts[206]

- Education regarding CHD
  - National Heart, Lung, and Blood Institute, Health Topics, CHD[207]
  - Center for Disease Control and Prevention, CHD[208]
  - AAP Congenital Heart Public Health Consortium[209]
  - AHA Health Topics, CHD[210]

Financial Assistance

- Contact family financial advocate
- Learn about health plan
- Short and long term financial assistance
  - Private assistance – charities, disease specific organizations, churches
  - Government assistance – Medicaid and Supplemental Security Income (SSI)
- Debt management program
- Family and Medical Leave Act (FMLA)

Table 6.

Barriers to Transition from Pediatric to Adult Centers

Domain	Barriers to Transition	Recommendation
Health Care System	• Limited/no insurance coverage • Lack of ACHD provider availability/training • Institutional deficits due to lack of staff/training in transition	• Create structured transition plan using dedicated coordinator • Offer resources to establish/maintain adequate insurance coverage
Neurocognitive	• Neurodevelopmental delay • Knowledge barriers concerning diagnosis or transition process • Maturity of patient to adhere to plan • Ability to assume decision-making responsibilities	• Use technology to target disease knowledge and self-management behaviors • Formal evaluation for signs of transition readiness
Psychosocial	• Deficit in self-management skills • Impaired psychosocial functional including anxiety/depression • Unstable life circumstances	• Evaluate/refer for management of comorbid diagnoses • Access to social worker
Relationships	• Parent/patient attachment to provider • Different beliefs regarding quality between pediatric/adult providers • Lack of expectation to transition • Legal issues regarding healthcare power of attorney	• Allow patient to meet/interact with provider before transition • Create joint clinic visits attended by pediatric and adult providers • Begin transition preparation early in adolescence