The neonatal brain in critical congenital heart disease: Insights and future directions

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ABSTRACT

Neurodevelopmental outcomes are impaired in survivors of critical congenital heart disease (CHD) in several developmental domains including motor, cognitive and sensory outcomes. These deficits can extend into the adolescent and early adulthood years. The cause of these neurodevelopmental impairments is multi-factorial and includes patient specific risk factors, cardiac anatomy and physiology as well as brain changes seen on MRI. Advances in imaging techniques have identified delayed brain development in the neonate with critical CHD as well as acquired brain injury. These abnormalities are seen even before corrective neonatal cardiac surgery. This review focuses on describing brain changes seen on MRI in neonates with CHD, risk factors for these changes and the association with neurodevelopmental outcome. There is an emerging focus on the impact of cardiovascular physiology on brain health and the complex heart-brain interplay that influences ultimate neurodevelopmental outcome in these patients.

Introduction

Severe congenital heart disease (CHD) requiring corrective surgery occurs in 6–8 per 1000 live births with up to half of these cases requiring an operation in the neonatal period to survive (Hoffman and Kaplan, 2002). With improved surgical techniques, mortality has steadily declined with an increasing number of adults living with CHD (Marelli et al., 2007, 2016). Given the changing epidemiology of CHD, much effort has been devoted to describe and understand the neurodevelopmental outcomes and quality of life for survivors of CHD. Although children with CHD rarely exhibit overt neurologic dysfunction, many may face deficits in multiple developmental domains including overall intellectual functioning, memory, executive function, speech and language, gross and fine motor and visual-spatial skills (Newburger et al., 2012; Sananes et al., 2012; Rhein von et al., 2012; Naef et al., 2017). Long-term data suggests that these deficits continue into adolescence and young adulthood with potential significant impact on societal contribution and ultimately long-term neurocognitive function (Marelli et al., 2016; Bellinger et al., 2011; Schaefer et al., 2013).

A natural assumption was that the adverse outcomes in infants with CHD were directly related to brain injuries sustained during neonatal cardiac interventions. However, in the recent era with advances in neonatal brain imaging, it has become apparent that brain abnormalities are seen even before surgical repair and the relationship between the brain and the heart is complex, occurring at many levels through fetal and postnatal development. This review will focus on 1) neonatal brain development in the context of CHD; 2) timing, appearance and mechanism of acquired brain injuries and 3) current knowledge on the relationship between neonatal brain changes in CHD and neurodevelopmental outcomes.

Brain development is delayed in CHD

Neonatal brain MRI studies have demonstrated evidence that brain development is delayed in CHD prior to corrective surgery (Miller et al., 2007). In fact, fetal brain MRI studies suggest that delayed brain development begins in utero likely as a result of aberrations in fetal circulation leading to abnormal oxygen and nutrient delivery to the brain (Limperopoulos et al., 2010; Sun et al., 2015). In contrast to human cardiac development that is largely complete by gestational week seven (Srivastava, 2006), brain development extends over a much longer period of time that extends into the third trimester and postnatally. Brain...
maturation during the 3rd trimester of pregnancy is notable for a dramatic increase in connections and neuronal activity. Consequently, blood flow to the developing brain increases and is estimated to be a quarter of the combined ventricular output in the third trimester demonstrating the unique interplay between the heart, circulation and the brain that is critical for normal brain development (Rudolph, 2011, 2016). Fetal cerebral oxygen consumption is almost half of all fetal oxygen consumption (Reference Ranges of Blood, 2014). Not surprisingly then, chronic hypoxia alters neuronal and glial protein expression in the fetal brain (Pearce, 2006). In a preterm sheep model of the 3rd trimester of gestation, perinatal cerebral ischemia resulted in cortical maturation impairments evident on diffusion tensor imaging, with widespread disturbance of dendritic arbor development and synapse formation of cortical neurons (Dean et al., 2013). Analogous changes in development of the cerebral cortex are observed using DTI in preterm neonates (MRI obtained at a median of 32 weeks gestation and at 40 weeks gestation) with impaired postnatal growth (Vinnall et al., 2013).

In the context of complex CHD, such as hypoplastic left heart syndrome (HLHS), left-sided cardiac structures are underdeveloped, leading to decreased oxygenation and perfusion of the brain due to intracardiac mixing and retrograde flow in the aortic arch. Similarly, in d-Transposition of the great arteries (TGA), although perfusion to the brain may be normal, the aorta and pulmonary artery are transposed, thus the higher oxygenated blood reaches the pulmonary vasculature as opposed to the cerebral vasculature. These physiologic aberrations continue into the transitional and postnatal time period. With a precipitous drop in pulmonary vascular resistance after birth, maintaining adequate cerebral blood flow can be challenging in the context of critical CHD with an open ductus arteriosus, thus perpetuating lack of adequate nutrient and oxygen delivery to the brain. Newborns with unrepaird cyanotic CHD have decreased cerebral oxygen delivery due to arterial desaturation as demonstrated using phase-contrast magnetic resonance imaging and T2 mapping with MRI brain volumetry (Lim et al., 2016). Although some of these critical cardiac lesions (i.e. TGA) are anatomically and physiologically corrected after the neonatal operation the effect of abnormal fetal and neonatal cardiac physiology may have lasting effects on the vulnerable developing brain. Furthermore, glucose and nutrient delivery to the fetal brain may also be impaired in utero and undergoes rapid transitions with postnatal physiologies (Rudolph, 2016). The impact of pre- and post-natal nutrition on the developing brain in the context of the cardiovascular arrangements of CHD merits ongoing study.

Although physiologically different, different types of critical cardiac lesions (e.g. HLHS and TGA) have demonstrated substantial delays in brain development in the fetal and pre-operative time period measured utilizing various MRI techniques including macroscopic, microscopic and metabolic measures of brain development.

Macroscopic brain development

Measurements of simple metrics of brain growth on MRI have identified smaller total and regional brain size at birth and in infancy in CHD as compared to controls (Ortinau et al., 2012, 2013). Cerebral MRI volumetry is a quantitative measure of total and regional brain volume providing an accurate means to assess brain volume and growth trajectory (Gholipour et al., 2011; Matsuzawa et al., 2001; Weisenfeld and Warfield, 2009). Sophisticated automated and manual volumetry techniques can model brain tissue characteristics during neonatal development and have identified decreased total and regional brain volumes in neonates with complex CHD prior to any corrective operation as compared to controls (Rhein von et al., 2015). All brain areas were affected including cortical and deep grey matter, white matter and cerebellar volumes. In addition, this has been noted in the third trimester fetus (Limperopoulos et al., 2010). In particular, fetuses with HLHS and lack of anterograde flow across the ascending aorta (aortic atresia) have the smallest global brain volumes noted on MRI, providing more evidence of the interplay between cardiac anatomy and physiology with brain development. Emerging studies are focusing on growth trajectories into childhood and adolescence utilizing these techniques, addressing differences by cardiac lesion and the impact of somatic growth on brain development.

The Total Maturation Score (TMS) is a semi-quantitative scoring system developed and validated in healthy preterm infants and has been used to assess macroscopic brain development in the neonate with CHD (Childs et al., 2001). Using this score, which combines elements of myelination, cortical folding, germinal matrix distribution and glial cell migration, researchers found that neonates with d-TGA and HLHS have evidence of lower TMS scores as compared to controls prior to any corrective operation (Licht et al., 2009).

Microscopic and metabolic brain development

Other quantitative techniques such as Diffusion tensor imaging (DTI) and spectroscopy have been applied to the newborn with CHD. DTI, which is a sensitive measure of regional brain microstructural development, has demonstrated evidence of higher apparent diffusion coefficient (ADC) and lower fractional anisotropy (FA) in pre-operative CHD neonates as compared to controls. Importantly, FA, increases in white matter with maturation of the oligodendrocyte lineage and early myelination (Drohobyshvsky et al., 2005).

Similarly, metabolic compounds in the brain such as N-acetyl aspartate (NAA), choline (Cho), creatine (Cr) and lactate, are known to be abnormal in the newborn with CHD (10% lower NAA/Cho ratio as compared to controls). Comparing these findings to those obtained in premature newborns without CHD, full-term newborns with CHD appear approximately one month delayed compared to term born healthy children (Miller et al., 2007). These metabolites are also known to be abnormal beginning in the third trimester fetus with CHD. By placing a volume of interest within the cerebral hemisphere at the level of the centrum ovale, metabolic information was obtained on the developing white matter with evidence of lower NAA/Cho ratio as compared to controls. Similar to the volumetric analysis, fetuses with HLHS and aortic atresia had the lowest NAA/Cho ratios (Limperopoulos et al., 2010). In line with these differences by cardiac anatomy, those with aortic atresia have also been found to have a greater degree of impairment in microstructural brain development as compared to HLHS patients with antegrade flow across the aorta (Sethi et al., 2013). In particular, those with aortic atresia had lower white matter FA and higher ADC. Thus, single ventricle anatomy and physiology appears to directly impact brain development beginning in the third trimester of fetal life (Limperopoulos et al., 2010). In addition to anatomy playing a role, physiology and hemodynamic stability appear to impact neonatal brain development. Prenatally diagnosed neonates with single ventricle physiology and d-TGA had higher FA and lower ADC on pre-operative MRIs as compared to those that were postnatally diagnosed (Peyvandi et al., 2016). This likely reflects the relatively stable hemodynamic state of the prenatally diagnosed patient as opposed to the instability during the immediate neonatal period often seen in the postnatally diagnosed patients.

Fetuses with HLHS are now recognized to have a progressive fall-off in cortical and subcortical gray matter, as well as white matter volumes, through the third trimester (Clouchoux et al., 2012). These volumetric changes were preceded by delays in cortical folding. In this context of abnormal cortical development, the subventricular zone (SVZ) represents the largest late gestation and postnatal niche of neural stem/progenitor cells (NSPCs). Recent studies in humans have identified streams of migrating neural progenitors that integrate into the frontal lobes after birth (Paredes et al., 2016). Analyses of a piglet CHD model demonstrates that postnatal hypoxia impairs the generation and migration of neural progenitors destined to become forebrain interneurons and reduces overall cortical growth (Morton et al., 2017). Consistent with earlier neuropathology descriptions (Paredes et al., 2016), these data emphasize the brain vulnerability in CHD is not limited to the white matter and...
highlight the need to better define the mechanisms of delayed brain development in the setting of CHD so that new therapeutic targets can be identified.

These fetal and neonatal studies reflect developmental disturbances of fetal origin. Although in some sub-types of CHD, the neonatal operation can be considered “corrective” (i.e. restoring normal cardiac physiology), the long-term effects of fetal and neonatal physiologic aberrations on brain development and neurodevelopmental outcomes are unclear. However, given the evidence of continued brain MRI abnormalities and neurodevelopmental impairments in adolescents with CHD, abnormal fetal and pre-operative physiology likely have lasting effects. How these changes in brain maturation are mitigated through improvements in pre- or post-natal cerebral oxygen delivery or nutrient supply are questions in pressing need of investigation with advanced brain and cardiovascular imaging.

Acquired brain injury with CHD

Neonates with CHD are at increased risk of newly acquired brain injury. Focal brain injury in the term newborn can be clearly and reliably detected with conventional MRI, and with greater resolution than with either ultrasound or computed tomography. The most common brain injuries encountered in this patient population including focal white matter injury (WMI) and small focal strokes (<1/3-2/3 of the arterial distribution) (Fig. 1). These injuries are largely clinically silent and can be overlooked with routine clinical screening ultrasounds.

Similar to the premature newborn, WMI has specific imaging characteristics defined by punctate periventricular lesions associated with T1 hyperintensity with or without restriction of water diffusion. The mechanism of WMI is thought to be secondary to hypoxic-ischemic and inflammatory injury to susceptible immature premyelinating...
oligodendrocytes similar to the mechanism seen in preterm infants (Miller et al., 2005). In the preterm neonate, WMI occurs in a characteristic distribution in the periventricular white matter, predominantly centrally (Guo et al., 2017). Several large prospective studies have been performed using pre- and post-operative brain MRI to determine the frequency of acquired brain injury and associated risk factors in newborns with CHD. Risk factors for brain injury have been identified in the pre, intra- and post-operative time periods. These are summarized in Table 1.

Approximately 40% of newborns with critical CHD are found to have evidence of brain injury pre-operatively in the form of WMI or small focal strokes (Mahle et al., 2002; Licht et al., 2004; Miller et al., 2004; McQuillen et al., 2007). Risk factors for pre-operative brain injury include hypoxemia and time to surgery (Petit et al., 2009), preoperative base deficit, cardiac arrest and the need for balloon atrial septostomy (McQuillen et al., 2006). Cardiac anatomy and physiology also play a role in acquired brain injury. Neonates with HLHS and aortic atresia are at increased risk of pre-operative WMI (Goff et al., 2013).

Risk factors for intraoperative brain injury relate primarily to the methods of cardiopulmonary bypass and/or hypothermic total circulatory arrest. The Boston Circulatory Arrest Trial was a landmark trial that compared two methods of vital organ support in infants undergoing surgery to repair d-TGA with an arterial switch operation (Newburger et al., 1993). Although deep hypothermic circulatory arrest, which provides the surgeon with an empty and relaxed heart, clearly allows intricate surgeries to be performed, there was concern at the time regarding later adverse neurologic outcomes. An alternative method (low-flow bypass) was felt to maintain some amount of brain oxygen delivery, while still allowing the surgeon a relatively bloodless field. This particular study was a randomized clinical trial that compared these two methods (Newburger et al., 1993). Although earlier outcomes suggested a benefit to low-flow bypass (less post-operative seizures), longer-term studies found no significant difference in cognitive outcomes between the two groups. In particular, MRI studies at one year of age were no different between the two groups. However, other studies have shown that circulatory arrest is a risk factor for developing new post-operative WMI in the subgroup of neonates with arch obstruction (Beca et al., 2013). Other risk factors that have been examined include hypothermic blood pH management, hemodilution/hematocrit and maintaining regional cerebral perfusion during arch reconstruction with variable results (Wypij et al., 2008; Jonas et al., 2003). In an observational study, post-operative stroke was most common in neonates undergoing surgical repair with cardiopulmonary bypass with regional cerebral perfusion, a technique introduced as theoretically brain-protective (McQuillen et al., 2007). The variability in the literature for these intra-operative risk factors suggests that the major burden of risk for acquired brain injury occurs outside of the operative period. This has been demonstrated in a large sample of pooled patient data with 1770 patients. The authors showed that the relative contribution of surgical factors on neurodevelopmental outcome in CHD patients was much smaller than innate patient and preoperative factors (International Cardiac Col, 2016).

Risk factors for postoperative brain injury include hypotension and hypoxemia related to low cardiac output syndrome. Multiple studies have identified hypotension as a risk for new post-operative WMI (McQuillen et al., 2007; Galli et al., 2004). In general, patients with single ventricle anatomy carry a higher risk of new post-operative brain injury, which correlates with the higher postoperative hemodynamic instability, morbidity and mortality seen in these patients. More recently, timing of surgery is thought to influence the risk of post-operative brain injury in HLHS with a lower risk in those that undergo surgery earlier after birth (Lynch et al., 2014).

The relationship between brain immaturity and brain injury has been explored in the literature with variable results depending on the technique used to measure brain development. Semi-quantitative methods (TMS) have demonstrated an association between brain immaturity and the risk of pre- and post-operative brain injury (Andropoulos et al., 2010). However, quantitative methods (DTI and MRS), have shown an association between immaturity and the risk of pre-operative brain injury but not post-operative brain injury (Dimitropoulos et al., 2013). Both studies suggest that, in general, brain immaturity is a risk factor for peri-operative brain injury. As noted above, newborns with prenatal diagnosis of SVP and TGA demonstrate less preoperative brain injury and more robust microstructural brain development than those with postnatal diagnosis (Peyvandi et al., 2016). These findings complement those relating cardiovascular physiology and early brain development and suggest the potential of improved cardiovascular stability to promote optimal brain development.

### Neonatal brain imaging in CHD and outcomes

Although much is known about the brain in the context of CHD, there is limited data on the relationship between neonatal brain changes and neurodevelopmental outcome. In contrast, literature has clearly identified an association between brain injury/development in the premature neonate and neurodevelopmental outcome in infancy and childhood (Chau et al., 2013). Cross-sectional studies performed in infancy (12 months of age) and in adolescent years demonstrate a clear association between measures of brain maturity, volume and connectivity and neurodevelopment (Rollins et al., 2014; Rollins et al., 2017; Panigrathy et al., 2015; Rhein von et al., 2014) in the patient with CHD; however, there are a paucity of longitudinal studies assessing the predictive abilities of neonatal brain imaging in CHD (Table 2). Among the few studies in the literature, the relationship between acquired neonatal brain injury and neurodevelopmental outcome is mixed. A prospective cohort study with a modest sample size of subjects with d-TGA demonstrated that pre-operative WMI, but not new post-operative WMI, was associated with lower scores on motor and language development (Bayley Scales of Infant and Toddler Development-III (Andropoulos et al., 2012)). In a follow-up study the same group assessed a larger number of subjects with a mixed group of CHD lesions and found that new post-operative WMI, but not pre-operative WMI, was associated with lower cognitive scores at 12 months of age (Andropoulos et al., 2014). In contrast, Beca et al. failed to find any associations

### Table 1

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<th>Risk factor</th>
<th>Preoperative</th>
<th>Intraoperative</th>
<th>Postoperative</th>
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<tr>
<td>Low arterial hemoglobin saturation</td>
<td>(Petit et al., 2009)</td>
<td>Prolonged total circulatory arrest</td>
<td>Low blood pressure</td>
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<td>(Wypij et al., 2003)</td>
<td>(McQuillen et al., 2007)</td>
<td>Galli et al., 2004)</td>
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<td>Length of time to surgery</td>
<td>(Petit et al., 2009; Lynch et al., 2014)</td>
<td>Decreased cerebral oxygen saturation (NIRS)</td>
<td>Low arterial PaO2</td>
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<td>(McQuillen et al., 2007; Andropoulos et al., 2013)</td>
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<td>Catheter based procedure (e.g. balloon atrial septostomy)</td>
<td>(McQuillen et al., 2006)</td>
<td>Cardiopulmonary bypass strategy (regional cerebral perfusion)</td>
<td>Prolonged cerebral regional oxygen saturation (NIRS &lt; 45% for &gt;3h) (McQuillen et al., 2007)</td>
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<td>(McQuillen et al., 2006)</td>
<td>(McQuillen et al., 2007)</td>
<td>Goldberg et al., 2007)</td>
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<td>Cardiac Arrest</td>
<td>(Dimitropoulos et al., 2013), (Block et al., 2010)</td>
<td>Hematocrit &lt; 24% (Wypij et al., 2008)</td>
<td>Morphologically immature brain (Total Maturation Score) (Beca et al., 2013; Andropoulos et al., 2010; Dimitropoulos et al., 2013)</td>
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<tr>
<td>Morphologically immature brain</td>
<td>(Total Maturation Score)</td>
<td>Single ventricle physiology</td>
<td>(McQuillen et al., 2007), (Beca et al., 2013) (Forbess et al., 2002)</td>
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<td>(Goff et al., 2013; Andropoulos et al., 2016; Dimitropoulos et al., 2013)</td>
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<td>Male sex</td>
<td>(Goff et al., 2013)</td>
<td>Aortic Atresia</td>
<td>(Goff et al., 2013)</td>
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<tr>
<td>Postnatal diagnosis of CHD</td>
<td>(Peyvandi et al., 2016)</td>
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between brain injury (pre- or post-op) and neurodevelopmental outcome at 2 years of age. However, they did find that relative brain immaturity (as measured by the TMS) on brain MRI at 3 months of age was associated with reduced performance in cognition, language and motor skills at 2 years of age (Beca et al., 2013). Although these studies were prospective with relatively large sample sizes, brain injury was largely treated as a dichotomous predictor, which may mask associations between different subtypes of injury and outcome. In addition, the majority of subjects had mild forms of injury that may not influence outcome.

Although the relationship between brain injury and outcome is unclear, emerging literature with newer imaging techniques may provide clarity on this relationship. In particular, a recent study found that fetal network connectivity and brain microstructural development (Andropoulos et al., 2012) demonstrated significantly stronger high-frequency (beta and gamma frequency band) connectivity and significantly weaker low-frequency (delta, theta, alpha frequency band) connectivity. These data suggest that delayed microstructural brain development has immediate functional consequences manifested by altered neuronal network connectivity. How these perturbations of developing neuronal networks impacts longer-term brain maturation and neurocognitive function is a key area for future study.

Conclusions

Neonates with complex CHD exhibit abnormalities in brain maturity and are at risk for acquired brain injuries. While these changes impact the white matter prominently, there is an increasing appreciation of abnormalities of cortical and subcortical gray matter development. These changes can be apparent even before undergoing neonatal cardiac surgery, suggesting that patient specific risk factors, cardiac physiology and the interplay between cardiac and brain development plays a critical role in overall brain health in CHD. The predictive ability of neonatal brain imaging is a work in progress; however initial studies suggest that both brain immaturity and brain injury may increase the risk of neurodevelopmental impairment in infancy and childhood. Incorporating other measures of brain function in addition to MRI such as clinical exam, or EEG monitoring may help better predict outcomes in this population of patients.

References


