

Commentary

Fetal origin of brain dysmaturation in congenital heart disease – Challenges and opportunities for interventions

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1. Introduction

Congenital heart disease (CHD) severe enough to require corrective surgery in the first weeks – months of life occurs in nearly 1% of all live births in the United States, or approximately 40,000 infants yearly [1, 2]. Remarkable advances in perioperative and operative care have led to rates of survival to adulthood of nearly 90%. However, this increased survival rate has been accompanied by a large burden of neurodevelopmental deficits. Although neurological outcome varies according to types of CHD, for the focus of this Commentary, such severe forms as single ventricle defects (hypoplastic left heart syndrome (HLHS)) or transposition of the great arteries (TGA), cognitive scores are in the mid-80's to low average range and markedly impair school performance and quality of life [2, 3]. Additionally, later behavioral disturbances are very common, and impaired executive functions exacerbate overall deficient cognitive/adaptive abilities [4].

2. Changing spectrum of neuropathological substrate with congenital heart disease

The underlying neuropathologic substrate for the array of cognitive and behavioral deficits in complex CHD has differed in reports published over the past several decades [5–8]. Thus, earlier studies emphasized hypoxic-ischemic lesions, such as cerebral white matter injury (WMI) (including periventricular leukomalacia (PVL)), neuronal loss and gliosis in cerebral cortex (especially hippocampus), thalamus, basal ganglia and brainstem/cerebellum, and cerebral infarcts. These various destructive lesions often were reported to be accentuated or to become more frequent after cardiac surgery and cardiopulmonary bypass. In recent years, with major advances in operative and perioperative care, the destructive lesions have become less frequent. For example, the incidence of overt WMI, such as PVL, has declined from as high as 61% [6] to 6% in a recent neuropathological series [8]. Nevertheless, neurodevelopmental deficits remain common (see earlier). Recent studies suggest that destructive lesions have been displaced in importance by impaired maturation of brain, i.e., dysmaturation (see later). Indeed, this more recent work suggests that dysmaturation was not detected

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in earlier studies, in part because conventional neuropathology cannot detect the abnormalities and advanced MRI, especially of the *fetus* with CHD, was not yet available.

The purpose of this Commentary is to advance the notion that the principal brain abnormalities in CHD have their *onset in utero* and that these abnormalities are largely characterized by *impaired brain maturation*. Moreover, a remarkable recent study based on advanced fetal MRI methodology has identified the likely regional and cellular targets in brain involved in the dysmaturation [9]. The work raises important challenges and opportunities for interventions to ameliorate or prevent the dysmaturation and its deleterious neurodevelopmental consequences.

3. Fetal origin of brain dysmaturation in CHD

Disturbances of brain maturation with onset in utero were suspected initially with CHD by early *postnatal* MRI studies that provided evidence for delayed development of both white matter and gray matter structures [10–19]. The advanced MRI deficits included diminished macrostructural (volumetric), microstructural (diffusion-based measures) and functional connectivity measures.

Establishment of the *fetal origin* of these disturbances of brain maturation awaited development of advanced, motion-corrected MRI studies, applied in utero as early as 25 weeks' gestation [13, 19–25]. The principal intrauterine findings have been progressive decreases in cortical gray matter volume, cortical surface area, cortical sulcation, and “white matter” volume. The changes have generally been observed without evidence of concomitant destructive lesions. Fetal circulatory derangements leading to impaired substrate (oxygen, glucose, other nutrients) delivery to brain appear central to causation. Placental dysfunction may also be critical (see later).

4. Regional and cellular origins of fetal brain dysmaturation

A remarkable recent study of 108 fetuses with CHD with advanced MRI methods *applied twice* between 18–40 weeks' gestation has identified the likely regional and cellular origins of the brain dysmaturation [9]. The investigators utilized innovative acquisition and postprocessing techniques to

delineate regional brain growth trajectories in fetal brain regions, including especially transient fetal brain compartments of particular maturational importance. Simultaneously fetal echocardiographic data was gathered to determine the relationship between fetal cardiac physiology and substrate delivery and brain development.

Impaired fetal growth trajectories became apparent before 32 weeks' gestational age and involved the subplate zone, the intermediate (“white matter”) zone, and the ganglionic eminence and subventricular zone [9]. The *subplate zone* is crucial for brain development via the role of subplate neurons (SPN) in development of cerebral cortex. This transient population of neurons during the period of 24 to 32 weeks' gestation elaborate a dendritic arbor which receives synaptic inputs from thalamus and distant cortical sites [26] and extend axon collaterals to overlying cortex to promote cortical differentiation and to guide ascending axons to cortex. Although in neonatal rat models of severe hypoxia-ischemia SPNs may undergo cell death [27, 28], perhaps a more representative experimental model, i.e., transient hypoxemia in third trimester fetal sheep, showed impaired dendritic development of SPNs, without cell death [29]. These features are consistent with primary dysmaturation (i.e., dysmaturation not secondary to cell death of SPNs), and the consequences would include underdevelopment of cerebral cortex, thalamus and white matter axons. Notably, ischemia was not necessary for the deleterious neuronal effects, thus raising the important possibility that correction of fetal hypoxemia, e.g., by maternal hyperoxygenation, could prevent the dysmaturation. In the identical sheep model of transient fetal hypoxemia impaired maturation of hippocampal neurons also was noted [30]. Whether this effect is caused by a disturbance of SPNs or reflects a separate instance of primary neuronal dysmaturation is not clear.

The involvement of the *intermediate zone* shown in the fetal MRI study of Rollins et al. [9] is of importance because this region in the last 16 weeks of gestation is the site of differentiating premyelinating oligodendrocytes (pre-OLs), rapidly growing axons, and late migrating GABAergic neurons. These vulnerable cells are important, respectively, for subsequent white matter development, including myelination, for development of axonal connectivity between thalamus and overlying cerebral cortex, and for incorporation of GABAergic neurons into upper layers of cerebral cortex. Pre-OLs are especially vulnerable to hypoxia and impaired substrate delivery

and perhaps could undergo cell death in utero, as appears to occur postnatally in the premature infant under conditions of hypoxia-ischemia and inflammation, as reviewed elsewhere [26]. In the premature infant subsequent replenishment of the pre-OL pool by proliferation of progenitors in the subventricular zone occurs, but these cells fail to mature into myelin-producing cells. This failure of pre-OL differentiation results in failure of ensheathment of axons, which in turn leads anterogradely to impaired maturation of neuronal targets, e.g., cortical neurons, and retrogradely to impaired maturation of neurons of origin (e.g., thalamus). Similarly, the injury to developing axons also likely leads to a failure of their maturation [26] and consequently the maturation of their neurons of origin and their neuronal targets. On balance, it seems most likely from the MRI data that in CHD the pre-OLs and developing axons are not destroyed but, rather, undergo primary dysmaturation, i.e., failure of maturation in the absence of cell death.

A disturbance of the third major cellular element in the intermediate zone in the latter half of gestation, i.e., GABAergic neurons, likely contributes to the disturbance of the intermediate zone seen on MRI, since these differentiating cells are migrating in large numbers in the last trimester toward the cerebral cortex (peak concentration in cortex occurs at term) [31]. In an excellent animal model of fetal hypoxia-ischemia, dysmature GABAergic (somatostatin positive) interneurons were prominent in cerebral cortex [32]. Thus, as with pre-OLs and growing axons, primary dysmaturation of migrating GABAergic neurons seems the most likely underlying mechanism affecting this cellular element.

The disturbance of late migrating GABAergic neurons likely plays an important role in some of the deficits of cerebral cortical development observed on fetal and neonatal MRI (see earlier). As noted earlier, these neurons are destined for the upper layers of the cerebral cortex, where their arrival and differentiation lead to expansion and increase in surface area of these layers [26]. This increase in outer cortical surface area leads to the inward buckling of cortex, i.e., gyral formation, a *process found to be deficient in studies of cortex in fetuses and newborns* with CHD (see earlier).

The third region affected in the fetal study of Rollins et al. is *the ventricular-subventricular zone* [9]. These germinative sites in the last 16 weeks of gestation give rise to the GABAergic neurons destined for cerebral cortex, as just described, as well as progenitor cells for pre-OLs. The origin of the late

generated GABAergic neurons is approximately 65% from the dorsal subventricular zone and 35% from the ventral ganglionic eminence [33–35]. Two excellent experimental models of fetal hypoxia designed to mimic CHD identified vulnerability of these progenitor cells, associated with reduced neurogenesis and abnormal cortical development [36, 37]. A similar reduction in neuroblasts was identified in the subventricular zone of human infants born with CHD [36].

5. Intrauterine disturbances leading to brain dysmaturation in CHD

The anatomic observations of brain dysmaturation, as delineated by fetal and neonatal MRI, have been correlated with intrauterine disturbances in substrate delivery to brain with CHD (see, for review, ref. 38). These disturbances relate to three major factors, i.e., the *nature of the severe cardiac defects* involved, e.g., TGA and HLHS, the increasing substrate demands of the rapidly growing fetal brain, and placental abnormality. During the third trimester of gestation, the blood supply to the brain increases prominently and represents fully 25% of the ventricular output [38]. With d-TGA, in which the aorta arises from the right ventricle and the pulmonary trunk from the left ventricle, the oxygen-rich blood from the left ventricle is directed toward the body (through the pulmonary trunk and ductus arteriosus). Relatively deoxygenated blood from the superior vena cava streams through the right ventricle and, via the aorta, to the brain. With HLHS, oxygenated blood from the placenta and deoxygenated venous return mix in the right atrium. Because of the hypoplastic left ventricle and aorta, the fetal brain is underperfused and with hypoxic blood.

In addition to the effects of the severe cardiac defects, as just noted, *placental abnormality* also appears important in contributing to the deficient substrate delivery in pregnancies with severe CHD [4]. Support for this contention emanates from both functional and structural placental studies. These studies have utilized advanced MR imaging allowing definition of placental growth, blood flow, and oxygen extraction [39–43]. Taken together, the findings suggest that in CHD, the placenta is abnormal, with disrupted microvasculature and impaired oxygen extraction, resulting in decreased cerebral oxygen delivery and impaired brain development [4]. Although the structural substrate for the placental

deficits requires further study, recent data show that the placentas with severe CHD have failed branching of the villous tree, decreased terminal villi and vascular immaturity [4, 44]. Inflammation, fetal thrombotic vasculopathy and infarction may also be present [45].

6. Therapeutic implications of fetal onset of brain dysmaturation in CHD

In the past several decades, the principal focus of attempts to prevent brain disturbance in CHD has been the neonatal period, i.e., the preoperative, operative and postoperative periods, with a particular emphasis on hypoxic-ischemic injury. This emphasis is understandable because the disturbances in cellular maturation during the fetal period render the neonatal brain particularly susceptible to subsequent hypoxic-ischemic events occurring during these postnatal periods. Marked improvements in neonatal intensive care, cardiac surgery, and cardiopulmonary bypass have led to improved survival rates, a decrease in overt hypoxic-ischemic injury and improved neurological outcomes. However, the recent data concerning the *fetal* origin of brain *dysmaturation*, as described above, suggest that an emphasis on novel interventions applied *in utero* is necessary to diminish or eliminate the persistent cognitive defects.

Fetal interventions will require insights into the nature of the factors leading to brain dysmaturation. Impaired fetal brain blood supply (ischemia) and blood oxygenation (hypoxemia) appear to be the principal initiating factors. Whether deficiencies of other substrates are crucial during the fetal period is not known, but hypoxia-ischemia does seem central. Thus, detection of the severity of their disturbances *in utero* is important.

Several approaches provide insights into *fetal oxygenation and perfusion*. Placental studies by advanced MR techniques are now possible. Thus, placental volume can be assessed by 3D-volumetric MRI, diffusion-weighted imaging can provide information about placental microstructure, arterial spin labeling MRI can measure placental perfusion, and blood oxygen level-dependent (BOLD) imaging can assess oxygenation [46]. Placental hemodynamics can be interrogated by functional MR imaging, and *serial measurements* can provide insight into progression of impairments [4]. Doppler ultrasound measures of umbilical artery and middle cerebral artery pulsatility indices can provide insight into

fetal hemodynamics. Blood oxygen saturation in fetal brain can be studied *in utero* with the blood oxygen level-dependent MRI approach. This signal has been shown to be reduced in brains of fetuses with CHD, principally due to the desaturation of fetal blood delivered to brain [4]. Although these studies are limited by high cost and logistical issues, they are crucial to identify the timing of onset and progression of the disturbances in brain maturation and the causative factors thereof. Delineation of such timing can identify the optimal use of targeted interventions. For example, currently underway are multiple clinical trials treating fetuses with single-ventricle CHD with maternal hyperoxygenation from the second trimester to term [4]. Interventions with other neuroprotective agents await further research.

Other maternal interventions may be of particular importance for the brain of the fetus with CHD. Avoidance of well-established factors deleterious to developing brain, e.g., exposure to alcohol, nicotine, opioids and other CNS-active drugs, is obvious. However, of particular note are the adverse effects of maternal stress and anxiety. In one careful study of fetuses with CHD, levels of maternal stress, which are higher in pregnant women with CHD fetuses, correlated with volumetric reductions in bilateral hippocampi and cerebellum [47, 48]. These areas have high concentrations of glucocorticoid receptors that are considered to be mediators of the vulnerability to stress. Additionally, prenatal maternal anxiety has been associated with alterations of the fetal functional connectome [49]. Thus, particular attention to amelioration of maternal stress in CHD should benefit the developing fetal brain.

Postnatal interventions to counteract the impact of neuronal dysmaturation, as observed in infants with CHD, have been discussed in detail elsewhere in relation to the premature infant [26, 50]. Experimental work suggests benefit for postnatal erythropoietin in mitigating the impaired cortical development caused by subplate neuron loss from prenatal hypoxia-ischemia, a scenario suggested by studies of the fetus with CHD (see earlier) [51]. Important additional approaches include avoidance of undernutrition, minimization of pain and stress, environmental enrichment, and optimization of parenting behavior (particularly maternal affective involvement, parent-child synchrony and positive and responsive parenting). Admittedly, some of these approaches are difficult to accomplish because of the circumstances involved in the care of a critically ill child with complex CHD.

7. Conclusions

Recent remarkable technological advances applied to the fetus with CHD have documented progressive impairments of brain development with onset over the last trimester of gestation (or earlier). The findings indicate that the developmental defects involve maturation of multiple structures and cellular components, including subplate neurons, cerebral cortical neurons, late migrating GABAergic neurons, developing pre-OLs, and proliferating neural precursors. Impaired maturation of these structures leads to deficits in development of cerebral cortex, myelin, deep nuclear structures and connectivity. The defects are detectable to a considerable extent by remarkable advances in MRI study of fetal brain and placenta. The principal pathogenetic factor, impaired oxygen and substrate delivery to brain, can be identified in utero.

Management of the fetus with CHD should begin with careful, serial assessments of placental structure and function, fetal oxygenation and perfusion, and of brain development. Neuroprotective interventions to be applied in utero are under study. Postnatal interventions, proven useful versus neuronal and pre-OL dysmaturation in preterm infants, should be applied vigorously to the infant with CHD.

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