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Review article

Blocked, delayed, or obstructed: What causes poor white matter development in intrauterine growth restricted infants?

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ABSTRACT

Poor white matter development in intrauterine growth restricted (IUGR) babies remains a major, untreated problem in neonatology. New therapies, guided by an understanding of the mechanisms that underlie normal and abnormal oligodendrocyte development and myelin formation, are required. Much of our knowledge of the mechanisms that underlie impaired myelination come from studies in adult demyelinating disease, preterm brain injury, or experimental models of hypoxia-ischemia. However, relatively less is known for IUGR which is surprising because IUGR is a leading cause of perinatal mortality and morbidity, second only to premature birth. IUGR is also a significant risk factor for the later development of cerebral palsy, and is a greater risk compared to some of the more traditionally researched antecedents – asphyxia and inflammation. Recent evidence suggests that the white matter injury and reduced myelination in the brains of some preterm babies is due to impaired maturation of oligodendrocytes thereby resulting in the reduced capacity to synthesize myelin. Therefore, it is not surprising that the hypomyelination observable in the central nervous system of IUGR infants has similarly lead to investigations identifying a delay or blockade in the progress of maturation of oligodendrocytes in these infants. This review will discuss current ideas thought to account for the poor myelination often present in the neonate's brain following IUGR, and discuss novel interventions that are promising as treatments that promote oligodendrocyte maturation, and thereby repair the myelination deficits that otherwise persist into infancy and childhood and lead to neurodevelopmental abnormalities.

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Abbreviations: AHDS, Allan-Herndon-Dudley syndrome; Axin2, Axis inhibition protein 2; APC, adenomatous polyposis coli; BMP, Bone morphogenetic protein; CNP, 2′,3′-cyclic nucleotide 3′-phosphodiesterase; CNS, Central nervous system; D2/3, Deiodinases 2 and 3; E, Embryonic day; GABA, gamma-aminobutyric acid; GFAP, Glial fibrillary acidic protein; HDAC, Histone deacetylase; HIE, Hypoxic-ischemic encephalopathy; IGF, Insulin-like growth factor; IGFBP, Insulin-like growth factor binding protein; IUGR, Intrauterine growth restriction/restricted; IL, interleukin; MBP, Myelin basic protein; MCT8, Monocarboxylate transporter 8; MCT10, Monocarboxylate transporter 10; miRNA, Micro-ribonucleic acid; mitoK$_{ATP}$, mitochondrial potassium ATP; MOG, Myelin oligodendrocyte glycoprotein; Olig2, Oligodendrocyte transcription factor 2; OPC, Oligodendrocyte progenitor cell; P, Postnatal day; PDGFRα, Platelet-derived growth factor receptor alpha; PLP, Proteolipid protein; PR, Progesterone receptor; PVL, Periventricular leukomalacia; T_3, triiodothyronine; T_4, thyroxine; TNFα, Tumor necrosis factor alpha; TRα, Thyroid hormone receptor alpha; TRβ, Thyroid hormone receptor beta.

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1. Introduction

Intrauterine growth restriction (IUGR) is a significant health issue worldwide. In developed countries, up to 9% of all pregnancies are complicated by IUGR, which equates to approximately 30 million newborns worldwide. IUGR is defined as the failure of a fetus to reach its genetic growth potential, and is second only to prematurity as a leading cause of perinatal death (Bernstein et al., 2000). It is commonly caused by poor placental function, a condition known as placental insufficiency, which leads to chronic hypoxemia and reduced nutrient supply to the fetus, and ultimately impacts on organogenesis and fetal body growth in general. The placental dysfunction that underlies IUGR is itself not always detectable, and the problem is usually revealed only when the fetus fails to meet the expected growth profile, or the baby is born with asymmetrically small body proportions. Clinical management of an IUGR pregnancy involves fetal monitoring and preterm delivery if indicated, however there is currently no treatment to prevent the placental insufficiency, the restricted fetal growth or the brain injury that ensues.

Surviving IUGR infants have a greatly heightened risk of neurodevelopmental impairment (Geva et al., 2006b) and a 10–30-fold increase in the risk of developing cerebral palsy (Blair and Stanley, 1990; Jacobsson and Hagberg, 2004; MacLennan et al., 2015; McIntyre et al., 2013); indeed, the risk of cerebral palsy is positively correlated with the severity of IUGR (Jacobsson et al., 2008), and IUGR is a greater risk factor for the development of cerebral palsy than is birth asphyxia and inflammation combined (McIntyre et al., 2013). White matter injury and reduced myelination as a consequence of IUGR is more strongly associated with the later development of cerebral palsy than any other neuroimaging finding (e.g. infarction, hypoxic-ischemic brain injury) (Wu et al., 2006b). However, our understanding of the mechanisms that underlie the association between IUGR, cerebral palsy and poor white matter development is incomplete, even though much emphasis is placed on studies of white matter injury induced by hypoxia-ischemia and/or endotoxin-induced fetal inflammation. Recent reviews have discussed the issue of disorders of myelination in relation to preterm birth (van Tilborg et al., 2016) and adult demyelinating disease (Fancy et al., 2011a; Kotter et al., 2011). In this review we specifically focus on the impact of IUGR on the developing white matter, and discuss some of the mechanisms thought to underlie impaired myelination, particularly in relation to IUGR, drawing upon knowledge gained in studies of preterm birth and demyelinating disease in the adult brain. We will propose and discuss putative therapies that could be exploited in future preclinical studies to either prevent poor myelination in the growing brain, or promote its appropriate development.

2. Impact of intrauterine growth restriction on the brain

2.1. Neuroanatomical and neuropathological changes

In IUGR infants, the brain is relatively less affected in terms of size compared to the body as a whole, leading to the concept of brain ‘sparing’, but there is clearly an attrition of central nervous system (CNS) development in terms of both structure and function observable even in the fetus. For example, while brain growth in the IUGR baby is “spared” relative to other organs, key neurodevelopmental processes (e.g. myelination) are affected and this can lead to significant neurological impairment. Neurofunctional deficits have been attributed to grey and white matter alterations in the IUGR brain (Batalle et al., 2012), and neuroimaging studies have shown significant reductions in cerebral cortical grey matter (Tolsa et al., 2004) and hippocampal volumes (Lodygensky et al., 2008), as well as delayed cortical development and reduced cortical expansion and gyrification in preterm IUGR babies (Dubois et al., 2008). For the white matter, post-mortem studies show reduced myelination in the brain of IUGR infants (Chase et al., 1972), and *in vivo* imaging shows reduced white matter volume and delayed myelination without evidence of overt cystic lesions in preterm IUGR infants at term age (Ramenghi et al., 2011).

Importantly, the myelination deficits at term in IUGR (Eixarch et al., 2016; Eikenes et al., 2012) and preterm IUGR (Eixarch et al., 2016; Esteban et al., 2010; Padilla et al., 2011, 2014) infants do not normalise after birth, with disrupted white matter integrity detected at 12 and 18 months of age (Eixarch et al., 2016; Esteban et al., 2010; Padilla et al., 2011, 2014) and in adulthood (Eikenes et al., 2012; Fischi-Gomez et al., 2015). The advent of advanced imaging of whole structural brain networks now allows for the assessment of brain connectivity in IUGR infants, and studies show that connectivity in motor and cortico-striatal-thalamic networks in IUGR children at 1 and 6 years of age is altered, and these alterations correlate with poorer outcomes in motor, cognitive and socio-emotional performance (Eixarch et al., 2016; Fischi-Gomez et al., 2015). Hence, imaging biomarkers may predict the neurodevelopmental outcomes for IUGR infants.