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Review: Neuroinflammation in intrauterine growth restriction

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ABSTRACT

Disruption to the maternal environment during pregnancy from events such as hypoxia, stress, toxins, inflammation, and reduced placental blood flow can affect fetal development. Intrauterine growth restriction (IUGR) is commonly caused by chronic placental insufficiency, interrupting supply of oxygen and nutrients to the fetus resulting in abnormal fetal growth. IUGR is a major cause of perinatal morbidity and mortality, occurring in approximately 5–10% of pregnancies. The fetal brain is particularly vulnerable in IUGR and there is an increased risk of long-term neurological disorders including cerebral palsy, epilepsy, learning difficulties, behavioural difficulties and psychiatric diagnoses. Few studies have focused on how growth restriction interferes with normal brain development in the IUGR neonate but recent studies in growth restricted animal models demonstrate increased neuroinflammation. This review describes the role of neuroinflammation in the progression of brain injury in growth restricted neonates. Identifying the mediators responsible for alterations in brain development in the IUGR infant is key to prevention and treatment of brain injury in these infants.

Contents

1. Introduction

Intrauterine growth restriction (IUGR) is a major cause of perinatal morbidity and mortality and occurs in approximately 5–10% of pregnancies [1,2] with even higher rates (21%) reported in the

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developing world [3]. IUGR is generally defined as a fetus that fails to achieve appropriate growth potential due to genetic or environmental factors. It is characterised by fetal weight dropping over time across growth percentiles; by birth most IUGR infants weigh less than the 10th percentile for gestational age. Chronic placental insufficiency is a common cause of IUGR. Placental insufficiency or utero-placental dysfunction results in insufficient blood flow to the placenta during pregnancy and inadequate supply of nutrients and oxygen to support normal growth of the fetus. Thus, the fetus develops in a chronic hypoxic environment. Placental insufficiency can result in changes fetal metabolism, hormones, hematology, immunology and cardiovascular function.

The adverse fetal environment can significantly affect the developing brain. In a chronic hypoxic environment, fetal circulatory redistribution occurs; blood flow is selectively redirected to the brain and away from other organs to maximise oxygen and nutrient supply. This type of growth restriction is referred to as 'brain-sparing' or asymmetric IUGR because the body is disproportionately smaller than the head. Asymmetrical IUGR is the most common form of growth restriction affecting 70–80% of all IUGR infants with disruption to fetal growth occurring mainly in the third trimester. Symmetric IUGR accounts for 20–25% of all IUGR fetuses and is characterised by a global growth restriction throughout pregnancy. Brain-sparing has been regarded as a protective mechanism in the IUGR fetus to protect and promote brain development but recent evidence has challenged this idea (reviewed in Ref. [4]). Several studies have demonstrated that asymmetric IUGR infants i.e. those with 'brain-sparing', have worse neurodevelopmental outcomes than symmetric IUGR infants [5–10].

2. Brain injury in IUGR

The fetal brain is particularly vulnerable to the effects of IUGR [11]. Long-term neurological disorders such as cerebral palsy (CP) and epilepsy, as well as learning and attention difficulties, neurobehavioural disabilities, and other cognitive issues have been attributed to restricted growth of the fetus [12–15]. A four-to six-fold increase in CP has been shown in IUGR neonates [14] with others reporting up to a 30-fold increase [16]. The long-term care of a child with compromised brain development is associated with emotional stress for families and a direct cost on society. Currently there are limited treatments to prevent neurological impairment in the IUGR neonate. Research is addressing IUGR health problems from different angles; both the preventative aspect *in utero* as well as interventions from birth. As many growth restricted fetuses may not be detected until after birth (especially in the case of asymmetric IUGR) it is important to examine the vulnerable IUGR brain to best determine treatment options to prevent long-term adverse neurological outcomes.

2.1. Grey and white matter injury in IUGR

Brain injury in the IUGR infant may be due to a combination of grey matter and white matter disruption and disorganisation in the development of the brain. Clinical imaging studies of preterm IUGR infants have demonstrated significant alterations in white and grey matter volume and structure [17–19] including decreased cortical thickness, delayed cortical development and altered brain connectivity [17–19] in comparison to non-IUGR preterm infants. In IUGR infants cortical grey matter volume is 28% less than that of age equivalent healthy term-born infants [17]. Reduced cerebral cortical grey matter volume in the term IUGR neonate has been shown to correlate with attention disorders [17]. Furthermore, such grey matter structural changes in the term IUGR infant that persist at 1 year of age have been found to be associated with developmental disabilities [18,20]. These alterations are also evident in animal models of growth restriction with demonstrated neuronal and white matter disruption [21–30]. Neuronal loss and disruption are observed in IUGR animal models throughout many regions of the brain including the hippocampus [29,31]. A decrease in proliferation and differentiation of oligodendrocytes are also evident in many growth restricted animal models [21,24,25,27] with some demonstrating postnatal restoration of myelin depending on the severity of injury [25,26,30]. Miller et al. (2014) showed decreased myelination with fragmentation and disorganisation of the white matter tracts in growth restricted sheep [29]. They postulated these abnormal patterns may result in abnormal neuronal activity and functionality in the IUGR brain. Even though characterisation of white matter injury has been a major avenue of investigation in IUGR animal models, neuronal disruption is also a critical neuropathological feature and brain injury in the IUGR neonate is a combination of white and grey matter injury. As discussed above, grey matter injury is a predominant neuropathological feature observed in human studies [17,18,20], therefore further emphasis on mechanisms of neuronal injury in growth restricted animal models studies are vital.

3. Mechanisms of neuronal injury

Few studies have focused on the detailed mechanisms of brain injury in the IUGR neonate which is surprising given the high proportion of IUGR infants who exhibit adverse long-term neurological outcomes [18,19]. There is a considerable paucity of data from human autopsy tissue of the pathology of the human IUGR brain. A classical study of six term IUGR infants demonstrated a reduction in myelin lipids and DNA content (used as an estimate of cell number) in cerebrum-brainstem and cerebellum fractions [32]. More recently in nine IUGR fetuses a significant decrease in cell number in the developmental zones of the cortex has been reported [33]. It is extremely challenging to acertain mechanisms of IUGR injury from post-mortem human brain tissue. Difficulty in estimating the timing of an IUGR insult as well as untangling variables of gestational age on brain development, insults such as pregnancy hypertension and other factors confound intepretation from human IUGR autopsy findings. Therefore animal models of IUGR are necessary to adequately explore mechanisms of injury in the IUGR brain. It is likely that key normal developmental processes are affected during the growth of the fetal brain and these may underlie the adverse neurodevelopmental outcomes in the IUGR infant. Understanding the mechanisms behind grey matter and white matter loss, and impairment in the IUGR infant is essential to identifying therapeutic targets for intervention or prevention of brain injury. The mechanisms leading to neuronal injury in the IUGR neonatal brain are complex and not well understood. Although the IUGR fetal brain is often referred to as hypoxic-ischemic (HI) [34], the IUGR fetal brain is not generally regarded as globally ischemic as blood flow is actually increased to many regions of the brain [35–37]. However, the IUGR fetus is relatively hypoxic due to chronic placental oxygen deprivation. The chronic IUGR insult leads to a reduction in oxygen delivery to the brain and concomitant reduction in delivery of glucose and amino acids with potential effects on immature neurons and neuroglia [34]. When cerebral oxygen is reduced, a cascade of cellular and biochemical events occur in the fetal brain causing cellular injury that can lead to cell death [36]. Many of these events result in mitochondrial disruption and immediate or delayed cell death [34]. The major putative mechanisms that may underpin the cellular death and injury in IUGR brains are excitotoxicity, oxidative stress, necrotic and apoptotic degeneration and neuroinflammation [34,38].