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Review

Effect of intrauterine infection on brain development and injury

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ABSTRACT

Intrauterine exposure of term and premature infants to infection/inflammation may increase the risk of perinatal brain injury, which may be more serious than that incurred by interpartum exposure to hypoxia–ischemia (HI). Many microorganisms, including certain viruses, protozoa, and bacteria, have been linked to this injury. In regard to the mechanisms of intrauterine infection-triggered brain injury, the inflammatory risk factors such as cytokines play a central role. The inflammation signal is likely transmitted across the blood–brain barrier and initiates a neuroinflammatory response. Studies have reported that polymorphism of cytokine genes also has been implicated in perinatal brain injury. Moreover, inflammation and HI may be synergistically involved in this process. Although the relationship between inflammation and adverse neurodevelopmental outcome in affected infants is slowly being elucidated, the literature contains scant evidence of measures that can improve fetal neurologic outcome. Several pharmacologic molecules such as magnesium sulphate, erythropoietin, and corticosteroids as a neuroprotective agent for the fetus need further investigation.

Contents

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1. Introduction

Despite the exponential increase in the use of continuous intrapartum fetal monitoring, cesarean sections aimed at reducing intrapartum asphyxia, and improvements in neonatal management, the incidences of brain injuries such as white matter damage (WMD) and cerebral palsy (CP) in premature and term infants remain essentially unchanged over the last few decades, and the etiology of CP remains poorly understood (Marret et al., 2008; Longo and Hankins, 2009). In both term and premature infants, intrauterine infection may be a more common antecedent of poor outcome than perinatal asphyxia (Malaeb and Dammann, 2009). These observations suggest that intrapartum hypoxia may play a lesser role in the genesis of neonatal brain injury than other factors such as intrauterine infection. As demonstrated by a variety of recent clinical and epidemiologic studies, intrauterine infection not only directly affects the immature brain but also might aggravate secondary neuronal damage after cerebral ischemia (Yuan et al., 2010; Yang et al., 2013).

The host response induced by intrauterine infection includes the maternal inflammatory response and fetal inflammatory response syndrome (FIRS). Chorioamnionitis represents the maternal inflammatory response, and leukocytes invading the fetal membranes are primarily of maternal origin. Funisitis, fetal vasculitis, and elevated fetal blood cytokine concentrations are now thought to represent FIRS (Malaeb and Dammann, 2009). Recent studies provide evidence that chorioamnionitis initiates a FIRS and the association between FIRS and brain injury has been shown to be much stronger than the association between chorioamnionitis and brain injury (de Vries, 2009). In this paper, we review the evidence for the relationship between intrauterine infection and brain injury in premature and term infants as well as pathologic mechanisms by which this injury can occur. We also provide information for the clinician that might lead to an improved fetal neurologic outcome in these high risk infants.

2. Epidemiology of intrauterine infection in premature and term infants

Intrauterine infection and inflammation complicates up to 32% of premature deliveries (Park et al., 2009). In term infants, the incidence ranging from 8.8% in Indians to 23.5% in Chinese (Becroft et al., 2010). Several studies have reported risk factors for intrauterine infection, including longer duration of rupture of membranes, prolonged labor, multiple vaginal examinations, meconium-stained amniotic fluid, smoking, alcohol or drug abuse, immunocompromised status, epidural anesthesia, colonization with group B streptococcus (GBS), bacterial vaginosis, and periodontitis (Baud et al., 2007; Tita and Andrews, 2010).

3. Pathogens of intrauterine infection

Many microorganisms, including certain viruses, protozoa, and bacteria, have been linked to these infections. These organisms and the resulting clinical syndromes have been categorized as TORCH infections, a useful acronym referring to Toxoplasma, Other microorganisms, Rubella virus, Cytomegalovirus (CMV) and Herpesvirus (HSV) (Hagberg and Mallard, 2000). CMV is the most common congenital infection in developed nations. The incidence of congenital CMV infection varies between 0.2% and 2.5% of all newborn (Gabrielli et al., 2012). Recent studies have shown that adenovirus infection of the placenta is also strongly associated with intrauterine infections (Glass et al., 2009). More than 65% of positive amniotic fluid cultures involve two or more organisms. *Ureaplasma urealyticum* and *Mycoplasma hominis* are the most frequent causative microbes, occurring in up to 47% and 30% of cases, respectively. Other common isolates in women with infection include anaerobes, such as *Gardnerella vaginalis* (25%) and *Bacteroides sp.* (30%), aerobes, including GBS (15%), and gram-negative rods, including *Escherichia coli* (8%) (Bashiri et al., 2006; Tita and Andrews, 2010).

Initially, these microorganisms are considered to be strongly associated with preterm birth (Glass et al., 2009). However, subsequent studies showed that a persistent intrauterine inflammatory state may follow chronic exposure to organisms, perhaps resulting in fetal brain injury (de Vries, 2009).

4. Intrauterine infection and perinatal brain injury

4.1. Toxoplasma

Congenital toxoplasmosis resulting from a primary infection in a pregnant woman is uncommon; however, it often has severe consequences. The literature contains a number of reports that suggest that Toxoplasma infection may alter human behavior and cognitive function; in additon, it may cause cryptogenic epilepsy, headaches, and the onset of schizophrenia (Hermes et al., 2008).

4.2. Rubella

In the last large Rubella epidemic in the USA in 1964–1965, there were thousands of infected infants who went on to have lifelong problems. This virus has a particular affinity for the central nervous system, resulting in encephalitis, mental retardation, cataracts, cochlear atrophy, glaucoma, and central auditory imperception (Plotkin, 2006)

4.3. Cytomegalovirus

CMV infection is the leading cause of congenital viral infection and brain disease in children in developed nations. Thus, it is a major pathogen responsible for congenital illness and subsequent lifelong disabilities, including vision loss, hearing loss, and mental retardation. One study in Japan showed that half of the children with congenital CMV developed hearing loss after 6 months of age (Ogawa et al., 2007).

4.4. Herpes simplex viruses

The incidence of neonatal HSV infection ranges from 1 per 2500 to 1 per 20,000 live births. Manifestations of congenital HSV include skin lesions and scars, chorioretinitis, microcephaly, and hydranencephaly. Neonates with a HSV infection can deteriorate rapidly as a result of respiratory distress, shock, disseminated intravascular coagulopathy, or encephalitis. Infants who survive neonatal HSV encephalitis have high rates of neurological sequelae, consisting of seizure disorders, mental retardation, and visual or motor deficits (Stamos and Rowley, 1994).

4.5. Other diseases: syphilis, GBS, and E. coli

A syphilis infection can only occur in the second trimester. The main manifestations of late congenital syphilis, in which symptoms of the disease do not become apparent until two-to-five years of age, are frontal bossing, short maxilla, high-arched palate, saddle nose, mulberry molars, Hutchinson's incisors, and interstitial keratitis with loss of vision (Glaser, 1996).

GBS is the leading cause of congenital bacterial infection in developed nations. In GBS positive women, the risk of transmission to newborns is about 21% (Kraśnianin et al., 2009). There is no direct evidence of GBS infection playing a role in CP. However,