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Maternal infection and white matter toxicity

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Abstract

Studies examining maternal infection as a risk factor for neurological disorders in the offspring have suggested that altered maternal immune status during pregnancy can be considered as an adverse event in prenatal development. Infection occurring in the mother during the gestational period has been implicated in multiple neurological effects. The current manuscript will consider the issue of immune/inflammatory conditions during prenatal development where adverse outcomes have been linked to maternal systemic infection. The discussions will focus primary on white matter and oligodendrocytes as they have been identified as target processes. This white matter damage occurs in very early preterm infants and in various other human diseases currently being examined for a linkage to maternal or early developmental immune status. The intent is to draw attention to the impact of altered immune status during pregnancy on the offspring for the consideration of such contributing factors to the general assessment of developmental neurotoxicology.

Keywords

Microglia; White matter damage; Inflammation; Oligodendrocyte

1. Introduction

The complex issue of maternal immune status is now being discussed as a possible factor for numerous neurodevelopmental disorders with either infant or adult onset. One initial and continuing areas of study in this area focuses on the effects occurring in the developing brain during the middle trimester of human gestation as a result of maternal infection. Maternal infection and inflammation, fetal compartment infection (chorioamnionitis and vasculitis), and fetal, as well as, perinatal inflammatory responses have been related to very premature birth and its associated neuropathologies, and functional outcomes in infancy and childhood. Given this pathophysiology, mechanisms of immune response in the immature brain, particularly related to microglia activation and susceptibility of oligodendrocytes to inflammatory insult, are discussed. The majority of this paper focuses on early manifestation of damage to white matter tracts in the brain; however, current speculation suggests. Given the current speculation that similar exposures could result in less anatomically gross lesions. Such early insults could contribute to other diseases, such as, schizophrenia and autism which have been linked to maternal infections or immune competence. Thus, relevant data for these diseases are briefly summarized. The nature of developmental neuroimmune toxicity, beginning to emerge from

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recent human and animal studies, is a complex portrait of susceptibility, sensitization, protection, risk, and resilience within the contexts of genetics, age, and environment.

The association of cerebral palsy with white matter damage in very premature infants set the stage for subsequent evaluations of the contribution of intrauterine infection to adverse neurological outcomes. The overall hypothesis is that maternal infection, occurring during specific gestational periods, leads to both a maternal and fetal inflammatory response. This response can then contribute to preterm delivery, white matter damage, and other neurological disorders (Gomez et al., 1998). Studies initially focused on hypoxia/ischemia, alterations in cerebral perfusion, free-radical damage, and release of cytokines and trophic factors (Volpe, 2001; for review). More recent work has focused on the association of maternal infections with preterm birth and the endogenous expression of fetal inflammatory proteins (Arntzen et al., 1998; Dammann et al., 2001; Hagberg, 2003; Hagberg and Malard, 2005; Hansen-Pupp et al., 2005; Martinez et al., 1998). In addition, the concept of maternal infection has expanded from a narrow focus on local infection of the reproductive tract to include remote or subclinical infections, such as, periodontal disease (reviews: Sanchez et al., 2004; Tucker, 2006). This evaluation has currently expanded to include consideration of more subtle functional outcomes in later childhood. From these studies, one begins to conclude that relatively minor insults occurring during the second trimester through the early third trimester (~16–28 weeks gestation) can set in motion processes that eventually alter the structural morphology and functional integrity of the developing brain. Understanding the complexity of immune responses in the fetal brain and interactions with maturing glial and neural networks comprise an area of active inquiry.

In order to begin to understand the impact of a maternal infection on the fetus, we need to remind ourselves of the basic processes involved in early brain development and various cell types that may contribute to an immune response in the fetal brain. The many cell types of the developing CNS regulate an extraordinarily complex structural formation. This is accomplished via an array of cytokines, growth factors, and other signaling proteins occurring in specific temporal and spatial patterns through cell–cell interactions and chemical diffusion gradients. Development of the vertebrate brain involves a tightly regulated sequence of stem cell proliferation, differentiation, and migration outward from the germinal layer surrounding the lateral ventricles. While these processes are largely complete for radially migrating neurons in the telencephalon by 16 weeks, they continue for populations of glia and interneurons throughout the second trimester. Orientation of neurons along tracks established by glial cells, formation of synapses, myelination, and the maturation of specific signaling networks initiated during this period continue well into infancy. In addition, refinement of the final neural network requires that redundant or inappropriate cells and their connections be terminated, thus, requiring a period of apoptosis and neural pruning. Questions are currently being raised as to the more general nature of the immune response during this period and the susceptibility of the developing nervous system to immune-mediated responses given the impact of cytokines and microglia.

2. Immune cells in the brain

The nervous system contains resident populations of ‘‘immune’’ cells in the form of brain mononuclear phagocytes (perivascular macrophages and microglia). Under normal healthy conditions, they support critical regulatory immune and homeostatic functions. With injury, or in disease states, their role expands and both reactive and activated microglia can be supportive or destructive to the brain. depending on additional ongoing processes. The mononuclear phagocyte system is comprised of cells with similar morphology, function, and origin (van Furth et al., 1972). This system includes monocytes and their precursor cells in the bone marrow, macrophages of connective tissue and lymph nodes, Kupffer cells of the liver,

lung alveolar macrophages, osteoclasts, and microglia in the nervous system (van Furth, 1988). The inclusion of microglia was initially based upon observations that, in the development of the CNS, microglia cells can be found only once blood vessels have innervated the tissue (Andersen and Matthiessen, 1966; Hume et al., 1983) and, in pathological conditions, many of the mononuclear phagocytes originate from circulating monocytes. This has been further extended to include the expression of complement and complement receptor on microglia.

The vascularization of the CNS is initiated from the surrounding perineural vascular plexus and continues in a caudal-cephalic gradient. It starts at the myelencephalon and then ascends through the metencephalon, mesencephalon, diencephalon, and telencephalon (Marin-Padilla, 1985). The capillary sprouts perforate the CNS and endothelial cells at the leading edge penetrate through the tissue by focal degeneration of the subadjacent glial endfeet. It is thought that these fragments of degenerating membranes serve to attract monocytes and macrophages from the blood circulation (Marin-Padilla, 1988). During the formation of the brain, the microglia cells and their phagocytic activity may serve a critical role in removal of debris generated from synaptic pruning and remodeling. In addition, this process may serve to recruit additional infiltrating monocytes.

In a normal resting state, microglia exhibit very small cell somas surrounded by fine elongated processes. The cell can morphologically change to a reactive state showing increased number and hypertrophy of processes. These features define the class of reactive microglia, often referred to as nonphagocytic activated microglia (Gehrmann and Kreutzberg, 1995). When the microglial cell assumes a phagocytic phenotype, it displays a round amoeboid morphology and is classified as a fully activated microglia. Both reactive and activated microglia can express cell surface antigens and various proinflammatory cytokines, such as tumor necrosis factor alpha (TNFα). Although these classifications now tend to be applied very loosely, accurate structural and functional differentiation of resting, reactive, and activated microglia is critical for defining the actual contribution of a ‘‘microglia response’’.

An active role for microglial cells in the normal developing brain may be related to the *in vitro* observation that cultured microglia, obtained from the developing brain, exhibit a more activated phenotype and have greater antigen presenting activity than those isolated from the adult brain (Aloisi et al., 2000; Carson et al., 1998). Yet, as in the adult, in the absence of direct injury, the microglia cells do not normally differentiate to an activated amoeboid phenotype. With injury, monocytes can infiltrate the CNS. They have the potential to transform into macrophage-like cells in conjunction with the transformation of the resident microglia. In the adult, it can be difficult to determine a specific role of the microglial cell given that the cells display both injurious and protective properties and provide various growth factors necessary for normal neuronal functioning. During development, such a distinction can be even more difficult with the active process of synaptic remodeling and the need to maintain high levels of growth factors for neuronal maturation.

An association between neuronal loss and microglia activation has been identified in multiple models of brain injury; however, any link to a causal relationship of microglia initiating neuronal degeneration has not been established. Whether the induction of a microglia response in a damaged region is a negative or positive event, or a combination of both, has yet to be determined. The presence of activated microglia displaying a phagocytic phenotype often occurs in the presence of dying neurons; however, microglia displaying a reactive ramified phenotype also can be seen in the absence of any indication of neuronal death. The complex interactions mediated by cytokines in the brain can result in neuroprotection or neurodestruction, depending on the specific signals induced and cell–cell contact. For example, interleukin-6 (IL-6) can be induced by IFNγ and TNFα, as well as, by LPS; yet, it can have

both inflammatory and anti-inflammatory activities within the brain (Gadient and Otten, 1997). After injury, IL-6 can trigger either neuronal survival as a developmental neurotrophic factor or increase neuronal degeneration (Gadient and Otten, 1994; Wagner, 1996). IL-6 has also been linked to immunosuppressive activity in inflammatory demyelinating disorders (Tilg et al., 1997). The same is true for elevations in the proinflammatory cytokine TNFα. Receptors for TNFα can provide cell-death signals or cell-survival signals depending on multiple factors not yet fully understood. These include temporally and spatially regulated expression of its specific receptors during brain development.

While the nervous system retains a relative immune-privileged state from the systemic circulation, communication does exist between the two and recent work suggests active interactions. For example, in the healthy brain, T-cells serve in a monitoring role of the brain parenchyma. In the absence of antigen presentation, the T-cells exit the brain; however, if activated by the presence of antigen on a resident brain cell, an inflammatory response can be initiated. This can lead to a cascade of responses including elevation in the proinflammatory cytokines and chemoattractants. Monocyte infiltration into the brain can then be allowed under conditions of increased blood–brain barrier (BBB) permeability. For example, following a severe systemic inflammatory response, permeability of inflammatory and growth factors across the BBB can be increased. Thus, a clear separation is not always maintained and may be significantly altered under various disease states, exposure conditions, age, and genetic background. Exactly how these processes and interactions are modified in the immature brain, relative to what is known in the adult, continues to be an area of research activity.

3. Infection and preterm birth

Just as brain development is fully orchestrated, the immune system follows a specific pattern of maturation with sequential development of the individual components and cell types. In this developmental process, the fetus becomes capable of mounting an immune response to uteroplacental infection as early as 23 weeks gestation (Duggan et al., 2001). Fetal inflammatory response has recently been considered as a causal factor in preterm birth and neonatal morbidity (Chaiworapongsa et al., 2002; Dammann and Leviton, 1997; Dammann et al., 2005; Elovitz et al., 2006; Gomez et al., 1998; Lu and Goldenberg, 2000; Salafia et al., 1999).

Some of the initial interest, with regards to altered brain development, was based upon observations of diverse neurological deficits in children born prior to full gestation of 37–40 weeks. In 2002, 12% of US births occurred prematurely (<37 weeks completed gestation); 2% of all infants were born very premature at <32 weeks (80%) completed gestation (Martin et al., 2003). Infections are now believed to contribute to about 40% of all preterm births, and up to 70% of very preterm birth (Creasy and Resnik, 2004). Approximately 85% (50,000/year) of these highly vulnerable infants survive annually (Volpe, 1998). While ~10% of very premature survivors have major developmental impairments, principally cerebral palsy and mental retardation, an additional 25–64% demonstrate mild to moderate functional impairments such as learning disabilities, coordination problems, and/or social and attention deficits at school age (Bennett and Scott, 1997; Dammann et al., 2002; Hack et al., 2005; Kuban and Leviton, 1994; Lefebvre et al., 1996; Resnick et al., 1998; Volpe, 1998; Wood et al., 2000). The most severe neuropathology (hemorrhage and/or white matter lesions) is usually diagnosed during the first month of life; however, the more subtle effects take longer to manifest and represent disturbances in CNS development perhaps unrelated to early lesions.

As compared to term-born or low birth weight infants, very premature infants demonstrate a decrease in intelligence scores of 0.5–1.0 standard deviations below the population mean (Hack et al., 2005; Olsen et al., 1996; Vohr and Msall, 1997; Wood et al., 2000). Peterson et

al. (2000) concluded that very preterm birth is associated with regionally specific reductions in brain volume and that consequent morphological abnormalities are associated with poorer cognitive outcome. Abernethy et al. (2002) longitudinally studied 87 children who were born at <1500 g. From results at 15–17 years of age, the authors concluded that learning disorders, attention deficits, and dyspraxia do not correlate with perinatal structural injuries, such as, hemorrhage from the germinal matrix into the ventricles and periventricular leukomalacia. It was considered that functional changes may be related to global brain growth or development of key structures such as, the caudate and hippocampus (Abernethy et al., 2002).

Magnetic resonance imaging (MRI) of 32 weeks gestation premature infants showed that brain abnormalities at birth, such as severe white matter injury, ventriculomegaly, and intraventricular hemorrhage were associated with adverse neurodevelopmental outcome measured at 18 months (Miller et al., 2005). In addition, this study identified postnatal infection as a risk factor in these children. In teenagers born at very low birth weight (defined as <1500 g), MRI detected a persistent pathology in cerebral white matter (Skranes et al., 2005). While white matter damage has been the outcome most studied by MRI, in preterm-born low birth weight children between 7 and 11 years of age, MRI imaging also showed enlarged parietal and frontal gray matter and reduced temporal and subcortical gray matter volume as compared to control subjects (Kesler et al., 2004).

In addition to morbidity, infection/inflammation during pregnancy and the perinatal period has been associated with a spectrum of adverse neurodevelopmental outcomes and structural alterations in the brain. While normal pregnancy in itself is linked with inflammatory changes, recent work has demonstrated that several circulating proinflammatory cytokines are elevated in the mother after preterm birth (Gucer et al., 2001), as well as, in the child (Dammann et al., 2001; Hagberg, 2003; Hagberg and Malard, 2005; Martinez et al., 1998). These include TNFα, IL-1β, IL-6, and IL-8 and may contribute to subsequent brain damage. Acute neuropathology and later functional deficits in infants have been correlated with an elevation of IL-6 after preterm birth. A recent study by Hansen-Pupp et al. (2005) demonstrated that circulating cytokine levels change rapidly over time, often with a peak occurring during the first 6 h after premature birth, followed by a decrease over the next 72 h. This suggests that systemic inflammatory activity over the first 3 days of life are initiated *in utero* and that any singular time point assessment could easily fail to detect relevant associations between inflammatory response and morbidity (Hagberg, 2003; Harding et al., 2003). This observation has led to the speculation that the actual relationship between preterm birth and inflammatory response has been underestimated.

4. White matter abnormalities/damage and perinatal infection

Oligodendrocytes (OLGs) are a polymorphic family of glia cells that make and maintain myelin (white matter) in the central nervous system. These cells are responsible for forming a sheath around the axon. This sheath may be a simple cytoplasmic sheath or comprised of multiple wrappings of myelin lamella. In fully myelinated axons, the myelin sheath allows for efficient conductance of signaling along the axon via nodes of Ranvier in fully myelinated axons. Multiple interactions occur between the myelin and the axon it ensheaths that maintain the integrity of the neuron and signaling processes. In addition to their myelin related activities, certain oligodendrocyte/myelin related proteins contribute to the growth and maintenance of axons within white matter (Edgar et al., 2004; Lappe-Siefke et al., 2003) and synapses in gray matter (Kaifu et al., 2003).

For myelinating OLGs, a relatively small soma produces and supports many more times its own volume of membrane and cytoplasm given the number of myelin nodes produced on multiple axons. Morphologically these cells can be categorized as type I to type

IVoligodendrocytes. Type I OLGs can be found in the forebrain, cerebellum, and spinal cord, where they are clustered around blood vessels, neurons, and fiber tracts. Type II OLGs are seen only in white matter in close proximity to nerve fibers. Type III OLGs are localized in the cerebral and cerebellar peduncles, the medulla oblongata, and the spinal cord. Type IV OLGs adhere directly to the nerve fibers at the entrance of nerve roots into the CNS. These cells constitute a heterogeneous population that can be expressed not only in their morphology but also, in their interactions with axons. Under normal conditions, not all OLGs form myelin. For example, the perineuronal OLGs do not form myelin; however, these cells have the potential to form myelin under pathological conditions (Ludwin, 1984).

When the cell approaches an axon to initiate myelination, the cell displays an undifferentiated ultrastructure (Remahl and Hildebrand, 1990). Questions remain as to whether the fate of such precursor cells to become a specific type of OLG subtype is predetermined by genetic programming and/or influenced by the microenvironment. During maturation, OLGs progress through several stages that are characterized by the expression of myelin-related genes and cell surface markers. Among the first to be expressed are DM20, a splice form of the proteolipid protein, and 2′,3′-cyclic nucleotide phosphodiesterase (CNP) (see Baumann and Pham-Dinh, 2001, for review). This expression is then followed by myelin basic protein, then proteolipid protein, and myelin-associated glycoprotein. The mature myelinating oligodendrocyte expresses myelin oligodendrocyte glycoprotein.

In the human telencephalon, at mid-gestation (17–23 weeks), early OLG precursor cells (platelet derived growth factor receptor $(PDGFR)^{+}/NG2^{+}$) populate all layers of the cerebral cortex and sub-ventricular zone (Jakovcevski and Zecevic, 2005). At the end of the second trimester in humans, the primary source of telencephalic pre-OLGs is the germinal center located at the tips of the lateral ventricles (Richardson et al., 2006). These areas are among the last cortical regions for small blood vessels to become fully arteriolized; thus, they are most susceptible to alterations in cerebral perfusion pressure, intraparenchymal hemorrhage, and local hypoxic/ischemic damage (Volpe, 2001). Pre-OLG migration, differentiation, and survival appear to differ as a function of growth factors such as platelet derived growth factor and fibroblast growth factor (FGF) in the microenvironment (Chandran et al., 2003; Kessaris et al., 2004; Richardson et al., 2006, for review). The myelination process, initiated during late gestation, peaks in the first postnatal year and continues in certain cortical fiber tracts until approximately 20 years of age.

The pathophysiology of white matter (WM) damage and abnormalities that occur in preterm infants is multifaceted with intrauterine or postnatal hypoxia/ischemia or infection and inflammation playing an important role (Robinson, 2005; Volpe, 2001). Damage to myelin and/or loss of pre-OLGs, and OLGs is associated with loss of functional capacity in clinical conditions of clear perinatal origin. These include a full spectrum of cerebral palsy, periventricular leukomalacia (white matter focal cystic lesions), and diffuse myelination disturbances. These various periventricular white matter injuries are believed to be the result of damage to oligodendrocyte progenitors and the disruption of their full maturation to myelinating cells (Back and Rivkees, 2004; Folkerth, 2005; Haynes et al., 2005; Kinney and Back, 1998; McQuillen and Ferriero, 2004; Takashima et al., 1995). These clinical conditions are correlated with maternal infection and markers of inflammation in the fetus (reviews: Blumenthal, 2004; Folkerth, 2005; Haynes et al., 2005; McQuillen and Ferriero, 2004; Volpe, 2001). The lesion of cerebral white matter, periventricular leukomalacia, occurs when white matter is immature and there is a dominance of OLG precursors. This timing is suggestive of damage to the precursor cells as the primary target for the lesion. The potential link between WM abnormalities and intrauterine or early postnatal infection is an area of active inquiry. Infection during pregnancy, including chorioamnionitis, fetal vasculitis, elevated amniotic fluid, or cord blood proinflammatory cytokine concentrations, has been correlated with white

matter damage (Nelson and Willoughby, 2000; Saliba and Henrot, 2001; Saliba and Marret, 2001; Spinillo et al., 1998; Yoon et al., 1997).

Baud et al. (1999) examined patients in which pregnancy was complicated by chorioamnionitis and birth occurred before 32 weeks of gestation. Serum C-reactive protein level was used as a marker for maternal infection. Cytokine levels in the amniotic fluid were used as an estimate of the impact on the fetus. This endpoint was based upon previous studies identifying amniotic fluid IL-6 as a sensitive and specific marker for intrauterine infection in patients in preterm labor, especially those maintaining an intact membrane (Greig et al., 1993; Yoon et al., 1995). A significant correlation was found between the serum and the amniotic fluid measurements of the various cytokines, with TNFα the better predictor of severe neonatal infection. However, no association was found between the cytokine levels and the development of periventricular leukomalacia, as determined by magnetic resonance imaging (MRI).

Yoon et al., however, found that amniotic fluid concentrations of TNFα, IL1β, and IL6 (Yoon et al., 1995, 1997) were higher in mothers who delivered newborns with white matter lesions, as detected by ultrasonography. In addition, histologic chorioamnionitis was more likely to be detected in the placentas of neonates with white matter lesions, as compared to those without lesions. Children with white matter lesions were delivered at a lower mean gestational age and birth weight and overall had a higher rate of significant complications inclusive of infection, respiratory distress syndrome, and intraventricular hemorrhage. No association was found with amniotic fluid concentrations of IL1 receptor antagonist.

A recent study by Miller et al. (2005) used MRI to identify brain abnormalities in a cohort of premature infants and found persistent noncystic white matter injury in more than half of the infants examined. WM abnormalities and postnatal infection were associated independently with adverse neurodevelopmental outcomes. An earlier MRI study (Inder et al., 2003), conducted with a more representative cohort of infants, reported WM abnormalities in ca. 20% of extremely immature infants. Perinatal infection, particularly maternal fever and infant sepsis were identified as risk factors for WM abnormalities. A more recent study (Counsell et al., 2006) showed that the diffuse, excessive, high signal intensity observed by conventional MRI in a majority of preterm infants represents an abnormality in oligodendrocytes or axons distributed throughout the cerebral white matter. Abnormalities were not limited to the WM, as cortical grey matter abnormalities and delayed gyral development were seen in association with WM abnormalities.

WM abnormalities and damage usually develop in infants born at less than 32 weeks gestation when specific brain areas are populated by the myelin forming oligodendrocyte and the immune system has reached a critical landmark in development. In these cases, the most common WM sites for the development of perinatal CNS lesions include the optic pathways, the auditory radiation in the internal capsule, myelinated fibers of the corpus callosum, cortical association pathways, and the periventricular white matter below the sensorimotor cortex. In many cases, the pattern of WM damage suggests a primary insult to the oligodendrocyte cell lineage. For example, a portion of premyelinating OLGs normally express interferon gamma (IFNγ) receptor. Elevated levels of IFNγ and subsequent toxicity to these immature OLGs have been suggested to contribute to the WM abnormalities found in cerebral palsy (CP), given the IFNγ immunoreactivity associated with macrophages and astrocytes in postmortem brain of patients (Folkerth et al., 2004). The chronic nature of the myelin damage in CP suggests alterations in the oligodendrocyte cell lineage that are sensitive to elevated interferon gamma levels possibly via a receptor mediated toxicity (Folkerth et al., 2004).

While it is not clear if elevated levels occur within the brain, circulating levels of the Th1 cytokine, IFNγ, are increased in infants developing WM damage (Hansen-Pupp et al., 2005).

IFNγ is a pleiotrophic cytokine with anti-proliferative and immunomodulatory effects and antiviral activity. As an immunomodulator, IFNγ activates macrophage induction of major histocompatibility complex (MHC) antigens and promotes leukocyte adhesion. Expressed by infiltrating T-cells (Kennedy et al., 1992; Renno et al., 1995), it induces the release of proinflammatory cytokines such as, TNFα and IL-1. Although IFNγ is not normally expressed in the nervous system, it can be detected following disruption of the blood–brain barrier and infiltration of activated T cells. Once in the brain, IFNγ is a potent modulator of MHC antigen expression in astrocytes, oligodendrocytes, and microglia (Suzumura et al., 1986; Wong et al., 1984). It is possible that a common stimulus such as, a severe systemic infection, could initiate activation of immune cells along the vascular walls either compromising the permeability of the blood–brain barrier or initiating a signaling event to glia in the brain parenchyma via the perivascular microglia or T-cells.

A complex circuitry of interactions is mediated by cytokines; thus, in the brain, cytokines can be either neuroprotective or neurodestructive depending on the full cascade of signals and cell–cell contact. While many studies have focused on demonstrating a potential linkage between elevated IFNγ levels and brain damage, this is only a part of a larger cascade of Th1 and Th2 cytokines. It is the overall interaction between these pro- and anti-inflammatory signals that determines the final outcome. In the preterm infant exposed *in utero* to maternal inflammatory stimuli, circulating levels of IFNγ, IL-10, and IL-12 are simultaneously increased (Hansen-Pupp et al., 2005). In this case, IL-10 has modulating effects on IFNγ by shutting down inflammatory reactions (Choe and Choi, 1998) and preventing the death of oligodendrocytes (Molina-Holgado et al., 2001); while, IL-12 can induce IFNγ production (Romagnani, 2000). Interestingly, the work previously mentioned of Hansen-Pupp et al. (2005) and the results of Duggan et al. (2001) showing that the elevation of T-cell activation in umbilical cord blood was associated with early cerebral damage in very preterm births, lead to the suggestion of a greater risk for WMD if birth does not occur immediately upon the induction of an inflammatory response *in utero*. This implies that the length of exposure may significantly modulate effects.

5. Animal models of immune-mediated white matter damage

To allow more direct examination of the linkage between immune system activation and WM alterations and damage, animal studies have administered the immune stimulator, lipopolysaccharide (LPS), during gestation or the early postnatal period (Hagberg and Malard, 2005; review). In fetal sheep, exposure to systemic endotoxemia by intraperitoneal injection of lipopolysaccharide (LPS) at either 65% or 85% of gestation, representing preterm and near-term infant, respectively, produced a microglia response in the subcortical white matter and a decrease in neurofilament staining (Svedin et al., 2005). In rodents, cerebral white matter shows an increased sensitivity to systemic LPS exposure when the dam is exposed during mid-gestation (Duncan et al., 2002; Mallard et al., 2003). Dam exposure to LPS (total dose of 1–4 mg/kg) at gestation days 16–18 results in an increase in IL-1β and TNFα in the fetal brain (Cai et al., 2000; Urakubo et al., 2001). With cervical administration of 0.1 mg/kg LPS to the dam on gestational day 15, fetal brain TNFα and INFγ are increased (Bell et al., 2004). However, with the same dose delivered to the dam intraperitoneally at this gestational time, Gayle et al. (2004) reported no changes in fetal brain cytokine levels but, rather, an upregulation in corticotropin-releasing factor. A direct intracerebral injection of LPS (1 mg/kg) in rat pups at postnatal day 5 produced sub- and periventricular cell death, loss of oligodendrocyte and myelin basic protein immunoreactivity, and ventricular enlargement that could be attenuated by minocycline and the suppression of microglial cells (Fan et al., 2005).

The basis for these conflicting data is unclear. It may be related to distinct populations of OLGs contributing to myelination in the cortical gray matter and subcortical white matter in the mouse

(Ivanova et al., 2002). The first wave of OLGs originate from precursors in the ventral ventricular zones between embryonic day E9.5 and E13. These OLG precursors are believed to be largely responsible for myelination in the cortex and do not migrate into the subventricular zone. A second population of OLG precursor cells are present in the subventricular zone by E18 and may be primarily responsible for myelinating subcortical white matter. However, the differences may also reflect complex alterations in the balance of protective versus destructive molecules induced by the immune response over the course of gestation and thus, related to the age of the fetus. At an earlier gestational age, days 14–16, maternal LPS (0.5 mg/kg, i.p.) induced an elevation in brain-derived neurotrophic factor, which may serve in a protective fashion (Gilmore et al., 2003). Experimental animal studies have demonstrated an increase in fetal brain IFNγ protein following LPS (0.1 mg/kg)-induced intrauterine inflammation at gestation day 15 (Bell et al., 2004). IFNγ induces the release of TNFα that along with TNFβ, has potent cytotoxic effects toward oligodendrocytes (Selmaj et al., 1991). The role for IFNγ as an important effector molecule in T-cell-mediated demyelinating disorders has been supported by the observation of hypomyelination in a line of transgenic mice expressing IFNγ under the transcriptional control of the myelin basic protein gene (Corbin et al., 1996). These mice also exhibit reactive gliosis and increased MHC class I and class II mRNA levels in the brain.

Collectively, these animal studies are consistent with the clinical data and suggest that maternal infection can significantly contribute to WM damage in the offspring. However, the recent study by Inder et al. (2005) suggests that maternal infection, while of importance in initiation of preterm birth, may not be the primary neurological insult in the primate. In humans, preterm birth at <32 weeks gestation requires additional intervention for survival. The level of intervention ranges from simple support to rather intensive pharmacological and mechanical interventions. During this time, a vast array of modifying events occurs, simply as a function of infant care. Using a nonhuman primate (baboon) model of preterm birth (gestation day 125) and neonatal intensive care (2–4 weeks) mimicking that used with human infants, Inder et al. (2005) showed a resulting neuropathology characterized by white matter damage, reactive astrogliosis, activated microglia, and ventricular enlargement. These changes occurred in the absence of maternal infection and were associated with the neonatal intensive care protocol. This study raises additional questions with regards to the impact of maternal health, post-birth environment, and the interactions of the stress response with immune and endocrine systems with regards to human brain pathology.

6. Maternal infection and neurological disorders

Any long term clinical manifestation of WM damage is the result of disruptions to the neural network that integrate cortical function. Thus, depending on the type of insult, the target cells, and the timing and duration of the insult, multiple possibilities for adverse outcomes can be predicted. Neurodevelopmental processes that alter WM may result in a slow progressive change in the neuronal population and the manifestation of symptomatology. In addition to acute gross damage to the WM, infection occurring in the mother during the gestational period has been implicated in multiple neurological conditions. Some of these conditions may be mediated by white and gray matter damage, as seen with premature birth; however, a more direct relationship between maternal immune status and altered neurodevelopment may also exist. Alterations in maternal infectious and immune status and other types of perinatal adverse events are currently being examined for childhood disorders such as autism (Fatemi et al., 2002; Juul-Dam et al., 2001; Patterson, 2002; Shi et al., 2003), while other studies are examining the possible association with risk for disorders that manifest later such as schizophrenia.

6.1. Autism spectrum disorders

Autism spectrum disorders includes a very broad group of patients manifesting an array of clinical presentations. In children with autistic disorders, both genetic factors and various immune system abnormalities have been reported (for review; Korvatska et al., 2002; Krause et al., 2002), including autoimmunity and defects in different subsets of immune cells. Reported abnormalities include a decreased response to T-cell mitogens (Stubbs and Crawford, 1977; Warren et al., 1986), reduction in natural killer cell activity (Warren et al., 1987), and selective depletion of CD4+ T helper cells (Warren et al., 1986). With regard to autoimmune responses, patient-derived activated T cells (Plioplys et al., 1994) and lymphocytes (Denney et al., 1996) showed less expression of IL-2 than that seen in normal control subjects. This finding would suggest an incomplete activation of these cells that is also known to occur in various autoimmune diseases. While a proposed link between autism and a number of viral infections has existed in the literature for over 20 years (Chess et al., 1978; Fombonne, 1999; Gillberg, 1991; Stubbs et al., 1984), confirmation of this link with markers in the blood and cerebral spinal fluid of patients has produced less than consistent results (van Gent et al., 1997).

With regard to the nervous system, most of the current studies have focused on the neuroimmune state of the patient rather than determining the causal role of early developmental infection. However, it is possible that early exposure to infectious agents could alter the neuroimmune state of the offspring. Consistent with these initial reports of altered immune function, the work of Zimmerman et al. (2005) raises questions regarding the ability of autism patients to mount an appropriate immune response. This recent study examined the cerebrospinal fluid from 12 children with autism as compared to samples from control subjects with other neurological disorders. Both quinolinic acid and neopterin were used as markers of inflammation in the cerebrospinal fluid (CSF; Azumagawa et al., 2003) and both were decreased in children with autism. In addition, a number of pro- and anti-inflammatory cytokines, reflective of an activation of the proinflammatory cytokine cascade, were examined in both the cerebral spinal fluid and in the serum using high sensitivity enzyme-linked immunosorbent assays. The only change detected in the autism patients was an elevation in serum protein levels of soluble tumor necrosis factor receptor II. The authors raise the possibility that changes in the CSF may not be reflective of localized responses in the brain, but also that the pattern of changes may be reflective of an alteration in the ability of the system to mount a host response to injury. Their hypothesis would be consistent with the previously mentioned findings of deficits in immune cell function in patients.

Using autopsy brain tissue and CSF from patients with autism, Vargas et al. (2005) reported an increased immunostaining of microglial cells displaying ramified hypertrophic morphology suggestive of a reactive phenotype. These cells were prominent in cortex, cerebellum, and in white matter. Macrophage chemoattractant protein-1 (MCP-1) can be produced by both microglia and astrocytes and was evident in both the brain and in the CSF. Tumor growth factor-β1 was elevated in the brain tissue; however, both growth and neuroprotective features have often been attributed to this cytokine. Given the association between perinatal infection and WM damage established in the preterm infant, the identification of WM abnormalities in individuals with autism may provide a basis for investigation of perinatal disruptions with maternal or perinatal infection (Barnea-Goraly et al., 2004). However, in contrast to the consistent finding of reduced white matter and regional gray matter in preterm infants, recent MRI studies on autistic brain development implicate a period of excessive growth during infancy/early childhood followed by restrictive growth of later-developing regions and circuits (for review; Courchesne and Pierce, 2005; Lainhart, 2006).

6.2. Schizophrenia

In recent years, there has been increasing recognition that schizophrenia reflects a disruption of early neurodevelopmental events combined with the protracted postnatal maturation of critical brain regions that extends through adolescence in humans. Schizophrenia has been linked with a major genetic component; family and twin studies indicate that schizophrenia is a heritable disorder, although specific causative genes have yet to be identified (Harrison and Weinberger, 2005). However, the heterogeneity of the disease has suggested that nongenetic (i.e., environmental) factors and interactions between genes and nongenetic factors play a role as well (Gottesman, 1991; Mortensen et al., 1999; Tsuang and Faraone, 1995). In either case, a disruption of neurodevelopment may play a key pathogenic role (Waddington et al., 1998).

This disease involves multiple pathological processes at various neurodevelopmental stages, on the background of both genetic and nongenetic risk factors (Gottesman and Shields, 1967; McGuffin et al., 1995; Pantelis et al., 2005). Primary evidence for nongenetic influences in schizophrenia is provided by studies reporting a significant association between obstetric complications, including maternal infection, during pregnancy as a major risk factor (Adams et al., 1993; Brown and Susser, 2002; Brown et al., 2004a; Dalman et al., 1999; Falkai et al., 2003; Suvisaari et al., 1999; Yolken et al., 2000). This increased risk has been linked with an increase in circulating proinflammatory cytokines in the mothers of patients with schizophrenia (Brown et al., 2004b; Buka et al., 2001b) and supports the hypothesis of maternal immune status altering neurodevelopment in the offspring (Gilmore et al., 2004; Kronfol and Remick, 2000; Nawa et al., 2000). A series of studies from Buka et al. (2001a,b) examined this possible association. In a nested case-control study of 27 adults diagnosed with psychotic illnesses, stored maternal blood samples were found to have elevated IgG and IgM immunoglobulin-albumin ratios and antibodies to herpes simplex virus type 2 glycoprotein. Any association of infection with psychotic illness was somewhat specific, in that there was no significant association with serum levels of IgA class immunoglobulins, specific IgG antibodies to herpes simplex virus type 1, cytomegalovirus, toxoplasma gondii, rubella virus, human parvovirus B19, Chlamydia trachomatis, or human papillomavirus type 16. In a study examining monozygotic twins, Rapaport et al. (1993) showed that schizophrenic subjects had higher levels of serum soluble interleukin-2 receptors thus, supporting the role of immune modulation in the disease process. The work of Brown et al. (2000) identified respiratory infections occurring during the second trimester of pregnancy as increasing risk of schizophrenia. No association could be found with respiratory infections occurring during either the first or third trimester.

The current neuroanatomical models of schizophrenia are based upon the assumption that the disease involves an aberrant integration of neuronal circuitry involving the frontal lobe and association cortex, as well as their connections to the limbic and other subcortical structures (Pearlson, 2000). These altered connections are proposed to occur at synapses within the frontosubcortex (Pantelis et al., 1992), frontal temporal cortex, and within the circuitry of the cerebello-corticosubcortical loop (Andreasen et al., 1998) or via interhemispheric connections of the corpus callosum (Crow, 1998). More recently, the role of WM in this altered connectivity has been proposed based upon both imaging and genetic methodologies (Bartzokis, 2002; Davis et al., 2003; Walterfang et al., 2005). Neuroimaging of the prefrontal cortex has identified functional and structural abnormalities in schizophrenia (McCarley et al., 1999). A meta-analysis of data sets on WM volume shows a small reduction in the whole brain of schizophrenic patients (Wright et al., 2000). Alteration in myelinated fibers in layer VI of the prefrontal cortex has been reported (Aston et al., 2004; Katsel et al., 2005a; Tkachev et al., 2003; Uranova et al., 2001). Histopathological examination of brains from patients has demonstrated a decrease in neuronal size in the prefrontal cortex (Rajkowska et al., 1998) and an increase in neuronal density (Selemon et al., 1995).

These effects have been linked primarily in regards to oligodendrocytes both in acute damage (Flynn et al., 2003; Hof et al., 2003; Stark et al., 2004; Tkachev et al., 2003; Uranova et al., 2001, 2004) and gene expression related to myelin development, maintenance, and repair (Åberg et al., 2005; Hakak et al., 2001; Katsel et al., 2005a,b,c). In postmortem samples, histological examinations have documented abnormal distribution, number, and density of oligodendrocytes in the cortex. Oligodendrocytes are more severely damaged as compared to other cell types in the prefrontal cortex (Uranova et al., 2001). In layer VI of the prefrontal cortex, a 25% reduction in numerical density of oligodendroglial cells has been reported, as well as, reduced glial density in the neocortex (Cotter et al., 2002), a 29% decreased number of oligodendroglial satellites of pyramidal neurons in layer III (Uranova et al., 2004), and, in area 24, a 20% reduction (Cotter et al., 2001). While the primary focus has been on the oligodendrocyte, many of these changes may be a more generalized glial response given that a 40% decrease in density for both oligodendrocytes and astrocytes in the thalamus (Pakkenberg, 1990) has been reported. The microglia response in the prefrontal cortex has been reported to be both increased (Radewicz et al., 1998) or unchanged.

An autoimmune component has been proposed in the etiology of the disease in which an autoimmune attack on the brain occurs. In schizophrenic patients, a number of immune aberrations have been reported including elevated serum immunoglobulin levels, decreased mitogen responses, altered ratios of CD4+ T cells and CD8+ T cells, morphologically abnormal lymphocytes, and increased antibodies to nuclear factor (Noy et al., 1994). The recent work of Kipnis et al. (2006) suggested that while an active immune system is present in schizophrenic patients, there is a selective depletion of autoimmune T-cell clones specific to CNS myelin proteins that may contribute to the alteration of WM. Many of the immunologic abnormalities seen in schizophrenic patients are strongly associated with chronic administration of benzodiazepines and carbamazepine (Cosentino et al., 1996); thus, it is difficult to determine the actual disease contribution to these outcome measures.

Schizophrenic patients are often characterized by elevated levels of neurotransmitters. Based primarily on our understanding of these changes occurring with the pharmacological regulation of the disease, the hypothesis of maternal infection increasing the risk for neurodevelopmental disorders related to the neurotransmitter dopamine has been tested in animal models. In these models, it was demonstrated that prenatal immune challenges result in both structural and functional nervous system abnormalities in dopaminergic neurotransmission (Borrell et al., 2002; Majde, 2000; Ozawa et al., 2006; Shi et al., 2003; Traynor et al., 2004; Zuckerman et al., 2003). Linking these studies back to the human disease of schizophrenia and determining how these studies can establish a link with early infection requires additional research and model development.

7. Susceptibility, protection, and sensitization by inflammation

Ischemic preconditioning was identified initially in the cardiovascular system (Murry et al., 1986) and refers to the phenomenon where a sub-lethal exposure prior to a lethal insult can render the organ less susceptible or possibly enhance and promote repair capabilities. More recently, this concept has been applied to the nervous system in understanding outcomes from specific insults and has expanded to include remote preconditioning and cross-exposure resistance or tolerance (Belayev et al., 1996; Hack and Zeerleder, 2001; Hagberg et al., 2004; Ikeda et al., 2006; Meng et al., 1998; Nandagopal et al., 2001; Takaoka et al., 1999). If such a pre-exposure results in an increased vulnerability, it is referred to as ‘‘sensitization’’. While both phenomena have been characterized outside of the nervous system, they have more recently been observed with reference to an inflammatory mediated response in the brain. However, the basis for the responses and the ability to predict outcome from pre-exposure is not currently available. Currently, we are limited to animal models to address many of these

questions. For example, in the immature rodent brain, a sensitization can be seen following a low dose of LPS accompanied by an increase in mRNA levels for CD14 and decreased mRNA levels for the LPS associated toll like receptor-4 (TLR-4; Eklind et al., 2001, 2005). Hypoglycemia has been proposed as one possible event contributing to sensitization by LPS (Eklind et al., 2004).

In a series of studies, Ling et al. (2002, 2004) demonstrated that a high dose of LPS (10,000 endotoxin U/kg body weight, i.p.) to the gravid dam at gestational day 10.5 decreased tyrosine hydroxylase+ neurons in the substantia nigra and midbrain region of 21-day-old offspring. The cell loss continued into adulthood and was accompanied by MHCII+ microglia cells displaying a reactive but not activated morphology. This early LPS exposure, however, appeared to alter the baseline for similar responses, such that, a second focused neurotoxic insult later in life resulted in an exacerbated response of neuronal loss and an approximate 20% elevation in TNFα protein (Ling et al., 2004). When LPS was injected to pregnant rats on embryonic days 18–19, offspring showed an enhanced behavioral response to amphetamine in both locomotor activity and startle response (Fortier et al., 2004). If the pregnant dam was repeatedly administered LPS, the adult offspring showed a deficit in sensorimotor gating (Borrell et al., 2002). The involvement of the dopaminergic system was confirmed with the attenuation of these effects with haloperidol and clozapine (Borrell et al., 2002) and an increase in tyrosine hydroxylase immunoreactivity in the nucleus accumbens.

8. Summary

A growing body of evidence indicates that many adult-onset human diseases may have their origins in the prenatal period. This idea has been pursued most vigorously for reproductive diseases, obesity and diabetes. In order to determine the broad effect of maternal immune status and adverse effects on the offspring, additional studies are required that truly focus on these specific questions. For example, human studies that incorporate reliable measures of prenatal infections and other exposures to enable analysis of subsequent risk are sorely needed to establish the relevance to adverse neurological outcomes. The spectrum of neurodevelopmental disorders, for which there is an indication of perinatal infection, suggests that effects are probably related to a combination of genetic vulnerabilities, severity of the infection, developmental timing of the infection, and any additional environmental factors occurring simultaneously, as well as, the early postnatal growth environment. In addition, the use of experimental animal models to examine complex exposure scenarios will be of great benefit both in determining the extent of the effect and to dissect the molecular mechanisms underlying such responses in the offspring. Gaining a better handle on these processes will be of assistance not only in the area of human infection but also in determining the impact of immune-mediated responses that can occur with various environmental exposures.

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