

Maternal Infection and Neurodevelopmental Disorders in the Offspring

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Abstract: Problem statement: Neurodevelopmental disorders such as schizophrenia and autism have been attributed to both genetic and environmental factors. Whether and how maternal infection as an environmental factor contributes to the development of neurological abnormalities in the offspring remains to be clearly defined. **Approach:** The literature was reviewed to examine the relationship between maternal infection and neurological disorders such as schizophrenia and autism. **Results:** Both epidemiological and experimental animal studies had found strong support for maternal infection as a significant risk factor for neurodevelopmental disorders. There was also accumulating evidence that inflammatory cytokines and glucocorticoids might be important mediators of maternal infection-induced effects on the offspring. Other factors such as oxidative stress and hypoxia might also aggravate neurodevelopmental damages. **Conclusion:** Studies are accumulating to support the link between maternal infection and neurodevelopmental disorders. Mechanisms underlying the link are also unfolding. Future studies examining how maternal infection contributes to the development of different neurodevelopmental disorders can help in developing effective intervention strategies.

Key words: Neurodevelopmental disorder, maternal infection, virus, bacteria, neuroinflammation, glucocorticoids, Herpes Simplex Virus (HSV), Gestational Days (GDs)

INTRODUCTION

Pregnant women have been reported to experience virus infections, such as influenza (Irving *et al.*, 2000), parasitic infections, such as filariasis (Malhotra *et al.*, 2003), gastric infections, such as *Helicobacter pylori* (Kitagawa *et al.*, 2001), periodontal diseases (gingivitis and periodontitis) (Boutigny *et al.*, 2005; Boggess, 2005; Goepfert *et al.*, 2004) and reproductive infections, such as bacterial vaginosis (Cottrell and Shannahan, 2004). Many studies have reported that maternal infections can have serious and diverse consequences on the health of the fetus, including spontaneous abortions, preterm birth, intrauterine growth retardation, innate immune and neuroimmune functions and other development-related functional outcomes in the offspring (Pararas *et al.*, 2006; Rasmussen and Hayes, 2005; Harry *et al.*, 2006; Brown *et al.*, 2004; Vidaeff and Ramin, 2006; Andrews *et al.*, 2000; Lasala and Zhou, 2007; Hodyl *et al.*, 2008). In fact, more than 70% of the placental tissues from newborn infants with systemic illness and poor neonatal outcome have positive test results for viral or bacterial infections (Genen *et al.*, 2004; Satorar *et al.*, 2004). There is increasing evidence that maternal infection is a major risk factor for neurodevelopmental brain damages (Chen *et al.*, 2006;

Ashdown *et al.*, 2006; Golan *et al.*, 2005). The objective of this review is to examine the relationship between maternal infection and neurological abnormalities during the later life of the offspring.

Maternal infection and schizophrenia: Schizophrenia is a complex brain disorder involving alterations in cognition, perception, emotion and behavior. At the psychopathological level, schizophrenic subjects often demonstrate deficits in Pre-Pulse Inhibition of startle (PPI) and endogenous sensitization such as increased amphetamine-induced dopamine release (Braff *et al.*, 2001; Laruelle, 2000). The etiology of schizophrenia has been attributed to combinations of genetic and environmental factors. It has been reported that there is a 5-8% increased risk of schizophrenia among those born in the winter-spring months when infectious diseases are more prevalent and at times when other infections (measles, varicella and poliomyelitis) show increased activity (Yolken, 2004). Epidemiological studies have also found strong association between the development of schizophrenia at later life and maternal infections with viruses such as rubella, influenza and Herpes Simplex Virus (HSV)-2, bacteria such as diphtheria and pneumonia and parasites such as toxoplasmosis (Brown and Susser, 2002; Bresnahan *et*

al., 2005; Babulas *et al.*, 2006; Limosin *et al.*, 2003; Ebert and Kotler, 2005; Tamer *et al.*, 2008; Buka *et al.*, 2008; Mortensen *et al.*, 2010).

Many experimental studies using animal models have directly tested if maternal infection results in psychosis-related abnormalities in brain and behavior relevant to schizophrenia in later life. Bacterial products such as lipopolysaccharide (LPS) or viral mimic polyinosinic:polycytidylic acid (poly I:C) have been commonly used to treat pregnant animals to model maternal infection. When LPS is subcutaneously administered to pregnant rats on alternate days during pregnancy, the offspring exhibit deficits in PPI at adulthood (Borrell *et al.*, 2002). Intraperitoneal administration of LPS into pregnant rats on Gestational Days (GDs) 18 and 19 leads to enhanced locomotor response to amphetamine in the adult offspring (Fortier *et al.*, 2004). Intranasal administration of influenza virus on GD 9 causes abnormal corticogenesis in adult mice (Fatemi *et al.*, 2002). The offspring born to poly I:C-treated rats display impaired object recognition memory, loss of latent inhibition and increased sensitivity to the locomotor-stimulating effects of MK-801, a non-competitive antagonist of the N-Methyl-D-Aspartate (NMDA) receptor (Wolff *et al.*, 2011; Zuckerman and Weiner, 2005). Taken together, both epidemiological and experimental animal studies suggest that maternal infection represents an important environmental risk factor for the development of schizophrenia in the offspring at later life.

Maternal infection and Autism Spectrum Disorders (ASDs): ASDs are another group of neurodevelopmental disorders with both genetic and environmental etiological factors (Rapin and Tuchman, 2008; Johnson and Myers, 2007). The hallmark symptoms of ASDs include deficits in social interaction and language and the presence of repetitive/stereotyped behaviors. Although the causes of ASDs remain to be defined, several areas of studies support maternal infection as a risk factor for ASDs. A link between autism and congenital rubella infection has been suggested by Chess in early 1970s (Chess, 1971) and Ivarsson *et al.* (1990) reported two cases of autistic children with congenital cytomegalovirus infections in Ivarsson *et al.* (1990). More recent epidemiological analyses have also shown that maternal infection is associated with diagnosis of ASDs in the offspring (Brown *et al.*, 2008; Atladottir *et al.*, 2010).

The animal models have also provided important insight into the relationship between maternal infection and pathogenesis of ASDs in later life of the offspring. Male offspring mice born to dams treated with poly I:C on GD 10.5 exhibit deficient social and communicative

behavior as well as high levels of repetitive behaviors (Malkova *et al.*, 2012). Female rat pups born to dams treated with LPS on GDs 15 and 16 exhibits impaired nest-seeking behavior and odor-stroke associative learning, suggesting that maternal infection affects the social/communicative behavior in the neonate offspring (Baharnoori *et al.*, 2010). Taken together, the animals born to dams treated with LPS or poly I:C exhibit symptoms relevant to autism, suggesting that maternal infection may contribute to the development of ASDs in later life.

Besides schizophrenia and ASDs, Cerebral Palsy (CP), a group of permanent disorders of the development of movement and posture, has also been linked with maternal infection by many epidemiological and experimental studies (Zhou, 2008). It is still unclear how the same insult could contribute to various neurodevelopmental abnormalities. There is some evidence suggesting that the stage of brain development during which the insult is inflicted may play an important role. For example, epidemiological studies by Sorensen *et al.* (2009) have found that the effects of maternal bacterial infection on offspring risk of ICD-8 schizophrenia is somewhat stronger with an earlier stage of pregnancy (Sorensen *et al.*, 2009). Furthermore, challenge of poly I:C on GD 9 suppresses spatial exploration, impairs sensorimotor gating, reduces prefrontal dopamine D1 receptors and leads to marked enlargement of lateral ventricles in adult mice offspring whereas the same treatment conducted on GD 17 leads to perseverative behavior, impaired working memory, potentiated locomotor reaction to the NMDA-receptor antagonist dizocilpine, reduced hippocampal NMDA-receptor subunit 1 expression and expanded volume of the 4th ventricle without disrupting sensorimotor gating, suggesting that the timing of maternal immune challenge plays a critical role in determining the patterns of behavioral abnormalities offspring display at a later life (Meyer *et al.*, 2006; 2008).

Therefore, maternal infection during different stages of fetal development may lead to distinct brain and behavioral pathologies in adulthood. Further examination and evaluation of maternal immune challenge at different periods of gestation may provide important new insight into the neuroimmunological and neurodevelopmental mechanisms by which different neurological abnormalities arise. Besides the precise timing during pregnancy, the differing neurodevelopmental vulnerabilities and abnormalities following maternal infection may also be associated with the virulence, strain and severity of infection as well as the insults that occur in later life.

Mechanisms of maternal infection-induced neurodevelopmental disorders: How does maternal infection lead to neurodevelopmental disorders in the offspring? There is still no definitive answer to this question. However, it is known that normal brain development involves precisely timed cellular and molecular events including proliferation, migration, differentiation, myelination, synaptogenesis and elimination of cells and synapses. Disruption of any of these processes could potentially lead to neurotoxicity and long-term brain damage. A common pathway has been suggested to be shared by infecting pathogens considering the diversity of infectious agents during pregnancy that have been linked with neurodevelopmental disorders and inflammatory cytokines and glucocorticoids are among the suggested mediators.

Inflammatory cytokines as a mediator: There are several lines of evidence that support the neuroinflammatory hypothesis. Firstly, as important mediators of immune response, cytokines such as IL-1 β , IL-6 and TNF- α are induced in maternal and/or fetal tissues during maternal infection (Ashdown *et al.*, 2006; Beloosesky *et al.*, 2006; Burton *et al.*, 2012; Oskvig *et al.*, 2012) and these cytokines are also involved in various aspects of brain development including lineage commitment, proliferation, survival and differentiation of both neuronal and glial cells (Marx *et al.*, 2001; Gilmore *et al.*, 2004; Yang *et al.*, 2002; Mehler and Kessler, 1997; Wang *et al.*, 2002). These cytokines may potentially cross placenta and affect fetal brain development during maternal infection. Consistently, administration of IL-2 into pregnant mice significantly influences the immunological profiles and neurobehavioral patterns in the offspring (Ponzio *et al.*, 2007). Transgenic mice overexpressing IL-6 or TNF- α in the brain also develop severe neurologic diseases (Wang *et al.*, 2002).

Secondly, administration of anti-inflammatory cytokines is able to attenuate maternal infection-induced toxicity. For example, coadministration of IL-1 receptor antagonist (IL-1ra) alleviates maternal LPS-induced placental inflammation, fetal mortality and motor behavioral alterations in the offspring rats (Girard *et al.*, 2010). NF- κ B inhibitor pyrrolidine dithiocarbamate (PDTC) suppresses the cytokine increases in the early pregnant rats induced by poly I:C administration and reduces the severity of neurodevelopmental defects in adult offspring (Song *et al.*, 2011). Pretreatment with the Nonsteroidal Anti-Inflammatory Drug (NSAID) Carprofen, a Cyclooxygenase (COX) inhibitor, abrogates maternal poly I:C induced inhibition of neuronal stem cell proliferation (Miranda *et al.*, 2010). Treatment with IL-10, an anti-inflammatory cytokine, significantly reduces

the extent of maternal infection-induced fetal brain damage (Rodts-Palenik *et al.*, 2004; Pang *et al.*, 2005).

Thirdly, case studies have shown a strong association between fetal exposure to elevated maternal IL-8 and structural neuroanatomic alterations in schizophrenic patients, suggesting that *in utero* exposure to elevated IL-8 may partially account for brain disturbances commonly found in schizophrenia (Ellman *et al.*, 2010). Furthermore, an increased maternal level of TNF- α in late gestation period of pregnancy has been associated with cases of psychosis including schizophrenia compared to pregnancies leading to healthy offspring (Buka *et al.*, 2001). Taken together, these findings suggest that cytokines may play a role in the maternal infection-associated neurodevelopmental disorders.

Glucocorticoids as a mediator: Many bacterial and viral infections are known to activate the Hypothalamic-Pituitary-Adrenal (HPA) axis, which ultimately leads to elevated circulating levels of Glucocorticoids (GCs), anti-inflammatory hormones that play a crucial role in restraining and shaping immune responses (Webster and Sternberg, 2004; Bailey *et al.*, 2003; Beishuizen and Thijs, 2003). Under normal conditions, fetal exposure to maternal glucocorticoids is maintained at a low level (Benediktsson *et al.*, 1997). However, the elevated maternal blood level of glucocorticoids induced by maternal infection could expose the fetus to high levels of glucocorticoids, which may influence the offspring's neurodevelopment.

This hypothesis has been tested in experimental animal models. Maternal LPS treatment has been reported to elevate the basal plasma corticosterone level, decrease level of glucocorticoid receptor in the hippocampus of adult offspring rats which exhibit a deficit in Prepulse Inhibition (PPI) and enhanced amphetamine-induced locomotor activity (Reul *et al.*, 1994; Basta-Kaim *et al.*, 2011). Offspring born to pregnant rats treated with dexamethasone on GDs 6-8 exhibit decreased juvenile social play and a blunted acoustic startle reflex in adolescence and adulthood (Kleinhaus *et al.*, 2010). Male offspring mice exposed to stress early in gestation display increased sensitivity to selective serotonin reuptake inhibitor treatment and increased HPA axis responsivity (Mueller and Bale, 2008). Stressful manipulations during the third week of pregnancy have also been shown to reprogram the HPA response in young and adult offspring rats (Henry *et al.*, 1994; Koehl *et al.*, 1999; Ward *et al.*, 2000; Koenig *et al.*, 2005). However, one study by Hauser *et al.* (2006) reported that male rats prenatally exposed to dexamethasone between GDs 15 and 21 exhibit increased PPI in one of the two replications with

normal latent inhibition (Hauser *et al.*, 2006; Cambonie *et al.*, 2004). It remains to be determined whether the disparate observations in separate studies could be accounted for by the differences in treatment regimen. Overall, increased fetal exposure to glucocorticoids during maternal infection may contribute to altered neurodevelopmental disorders in the offspring.

It should be noted that other mechanisms may also aggravate maternal infection-induced neurodevelopmental damages in the offspring. For example, bacterial or viral infection-induced oxidative stress may affect neurodevelopment in the fetus (Schwarz, 1996; Cambonie *et al.*, 2004; Lante *et al.*, 2007; Saito *et al.*, 1997). Consistently, post-treatment with N-Acetylcysteine (NAC), an antioxidant, after the maternal LPS challenge is able to prevent the drop in the glutathione content in hippocampus and protect Long-Term Potentiation (LTP) in CA1 area of the hippocampus in male offspring (Lante *et al.*, 2008). Infection-induced maternal hypoxia may also impact fetal brain development since maternal hypoxia may lead to fetal hypoxia (Dalitz *et al.*, 2003). Aberrant expressions of neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) in the fetal brain during maternal infection may also affect the development of the offspring's brain (Golan *et al.*, 2005; Gilmore *et al.*, 2003).

CONCLUSION

In this review, we examined the relationship between maternal infection and neurodevelopmental disorders in the offspring. A growing body of evidence suggests that inflammatory cytokines and glucocorticoids produced during maternal infection may be primarily responsible for the neurodevelopmental effects that maternal infection has on the offspring. Gestational timing is an important factor to determine the susceptibility and extent of injury of the immature brain to maternal infection. The genetic vulnerabilities of the host and the virulence, strain and severity of infection may also play a role. In addition, the effects of maternal infection may interact with insults that occur in later life to account for the development of neurological symptoms.

Despite the fact that much progress has been made over the years, there are still many questions to be answered. For example, what is the extent of severity and duration of maternal infection that would lead to developmental damage in the fetus? What are the exact mechanisms by which cytokines and/or glucocorticoids affect neurodevelopment? How do cytokines and/or glucocorticoids produce differing effects at different gestational windows? Furthermore, much research is clearly needed to be able to translate results obtained from

animal model studies to human development. It will also be of significant benefits if a panel of inflammatory markers in maternal or fetal tissues could be used as a profile to predict neurodevelopmental defects at a later life. Future research addressing these issues may help in developing effective new anti-inflammatory interventions and clinical decision-making.

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