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Chorioamnionitis, IL-17A, and Fetal Origins of Neurologic Disease

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Abstract

The Centers for Disease Control and Prevention estimate that 1 in 323 infants have cerebral palsy. Highly correlated to intrauterine infection and inflammation, the incidence of cerebral palsy has remained constant over the last few decades despite significant advances in neonatal intensive care including improved ventilator techniques, surfactant therapy, maternal steroid administration, and use of intrapartum empiric antimicrobials. Recent advances in our understanding of immune responses to infection and inflammation have identified the cytokine IL-17A as a crucial component of early pro-inflammatory mediators that cause brain injury associated with neurologic impairment. Remarkably, maternal inflammatory responses to *in utero* inflammation and infection can also lead to potentially debilitating neurologic conditions in the offspring, which often become clinically apparent during childhood and/or early adulthood. This review details the role of IL-17A in fetal and maternal proinflammatory responses that lead to fetal brain injury and neurologic sequelae, including cerebral palsy. Recent findings regarding the role of maternal inflammatory responses in the development of childhood and adult neurologic conditions, such as autism, schizophrenia, and multiple sclerosis, will also be highlighted.

Keywords

Chorioamnionitis; IL-17A; Neonates; Cerebral palsy; PVL; Autism; Schizophrenia

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Introduction

Fifteen million neonates are born preterm (<37 weeks completed gestation) around the world annually^{1, 2}. Intrauterine infection remains the leading cause of spontaneous preterm^{3, 4} birth despite the widespread use of intrapartum antibiotics^{5, 6}. By triggering robust maternofetal proinflammatory immune responses against ensuing infection, chorioamnionitis results in early pregnancy termination to preserve the life of the mother, albeit at the expense of the developing brain and vulnerable fetus^{7, 8}. Conversely, preterm birth may prevent or attenuate the development of proinflammatory fetal immune responses, thereby protecting the neonate against future adverse sequelae. The prevalence of chorioamnionitis is inversely proportional to gestational age (GA), ranging from more than 50% at 23–24 weeks' GA to 5% at term gestation (> 37 weeks' GA)^{9, 10}. Remarkably, microscopic examination of placental tissues demonstrates histologic indicators of chorioamnionitis in 65% of extremely preterm infants born at 23–24 weeks' GA and in one-third of neonates born at 29 weeks' GA¹¹.

During fetal development, the amniotic membrane safeguards the maturing fetus against exposure to pathogenic organisms, while providing an immunologically privileged site designed to protect the allogenic fetus from maternal rejection¹⁰. If this membrane is breached, then chorioamnionitis may ensue. Maternal immune responses dominate the early stages of *in utero* infection with maternal leukocytes becoming the “first responders” that are tasked with prompt containment and elimination of the offending microorganisms¹². If the infectious or inflammatory process continues, fetal leukocytes will subsequently infiltrate the chorionic plate and release proinflammatory cytokines and chemokines, such as interleukin (IL)-6, IL-8, and IL-18, in a condition known as *fetal inflammatory response syndrome* (FIRS)^{8, 13, 14}. Classically defined by an elevated umbilical cord plasma IL-6 concentration⁸ with or without the presence of funisitis^{15–17}, the severity and prevalence of FIRS increases with GA of the fetus and intensity of the initial maternal inflammatory response¹⁰.

Recently, the cytokine IL-17A was shown to be a vital component in the initiation of FIRS and a potential contributor to the later development of chronic conditions caused by fetal exposure to *in utero* inflammatory and/or infectious processes^{10, 18, 19}. First discovered in 1993²⁰, IL-17A (aka CTLA8) belongs to a family of six IL-17 cytokines (IL17A-F) and demonstrates diverse biologic functions^{21–23}. IL-17A is produced by a wide spectrum of innate immune cells strategically located in barrier tissues that protect the human body from the outside environment. If breached by pathogenic microorganisms, IL-17A-producing cells become key instigators of early innate immune responses that may negatively impact the future health of the host¹⁹.

FIRS is correlated with increased risks of neonatal death and disability due to its direct role in exacerbating common neonatal conditions such as sepsis^{24, 25}, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD)^{26, 27}, and necrotizing enterocolitis (NEC)^{8, 28, 29}. A review of IL-17A in the pathogenesis of these common neonatal conditions is offered in our accompanying review entitled, *IL-17A and Neonatal Disease*. In addition, IL-17A-mediated FIRS can initiate adverse neurologic conditions in the neonate, such as

intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP)³⁰, and/or periventricular leukomalacia (PVL), which can directly injure cerebral white matter and later manifest as cerebral palsy (CP) or other forms of neurodevelopmental impairment^{31–36}. Regrettably, the incidence of prematurity and CP has remained unchanged over the last few decades despite technological advances in ventilator management, widespread use of intrapartum antibiotics for the prevention of early onset neonatal infection, intrapartum maternal steroid exposure, and surfactant administration³⁷. Alternatively, FIRS can act collaboratively with maternal inflammatory responses to exacerbate disease severity relating to multiple sclerosis^{38–40}, autism-associated behaviors^{41, 42}, schizophrenia⁴³, depression^{44, 45}, and post-ischemic phases of stroke^{21, 46–50} in children and adults.

Presently, the administration of intrapartum magnesium sulfate for “fetal neuroprotection” to women at risk for preterm birth is the only known medical intervention that reduces the incidence of CP in surviving offspring⁵¹. However, the incidence of CP is significantly increased in neonates born to women with intact membranes who received magnesium sulfate in addition to prophylactic intrapartum antibiotics⁵¹. Likewise, neurodevelopmental outcomes are unchanged in infants following exposure to maternal magnesium sulfate who are delivered prematurely due to complications relating to chorioamnionitis⁵².

This review will detail our current understanding of IL-17A and its association with common neonatal, childhood, and adult neurologic conditions. Newly discovered associations between maternal inflammatory response syndrome (MIRS) and late-onset neurologic conditions will be highlighted.

Chorioamnionitis and IL-17

Naïve helper T (Th) lymphocytes can differentiate into multiple Th subtypes, but two are emphasized here due to their importance in facilitating inflammation-induced fetal onset of neurologic disease: (i) Th17 cells, which are important in the clearance of extracellular bacteria through production of the cytokine IL-17A and (ii) Regulatory T cells (Tregs), which suppress immune activity^{24, 53–55}. Induction of Th17 cells from naïve helper T lymphocytes is triggered by IL-1 β , IL-6, IL-21, and IL-23 in coordination with transforming growth factor (TGF)- β and RAR-related orphan receptor- γ t^{56–60}. Whereas low levels of TGF- β promote Th17 lymphocyte differentiation, high levels stimulate the transcription factor forkhead box P3 (FOXP3) to generate Tregs^{56, 61}. Because of their opposing immune responses, the Th17/Treg balance is vital for maintaining fetal immune homeostasis.

The cytokine IL-17A is an important component of early host immune responses that target and eliminate extracellular pathogens including Gram-positive, Gram-negative, and fungal microbes^{62–64}. Neonates demonstrate reduced baseline production of IL-17A compared to adults, which may diminish their ability to generate proinflammatory immune responses and increase their susceptibility to infection by group B *Streptococcus*, *Escherichia coli*⁵³, and *Klebsiella pneumoniae*^{24, 65}. Because IL-17A levels are similar between preterm and term neonates, IL-17A production is not dependent upon immune maturation or advancing gestational age (GA)²⁴.

$\gamma\delta$ T lymphocytes are specialized innate immune cells that are exclusively generated before parturition and strategically located in barrier tissues, which protect the host against the outside environment²³. IL-17A-producing $\gamma\delta$ T cells first appear within the fetal thymus around embryonic day 15 in mice⁶⁶, but are not observed in human embryos until the 8th week of gestation⁶⁷. In the intestinal epithelium, $\gamma\delta$ T lymphocytes increase throughout human embryonic development, while Tregs are not seen until 23 weeks' GA⁶⁸. In prematurely born neonates, the disproportionate quantities of $\gamma\delta$ T lymphocytes in relation to Tregs may predispose these infants to develop proinflammatory fetal conditions. Remarkably, the period between 24–28 weeks' GA in humans is generally referred to as the “window of susceptibility”^{68, 69}. Representing the second trimester of pregnancy, exposure to infection and/or inflammatory conditions during this critical period significantly increases the neonates' risk of developing chorioamnionitis-induced IL-17A pathology, such as sepsis, NEC, and brain injury⁶⁹. The maturing fetal brain may be affected by IL-17A-mediated brain pathology due to impaired migration of immature post-mitotic neurons from the ventricular zone to the neocortex, leading to aberrant cortical development^{53, 70}. In addition, damage to immature oligodendrocytes and microglia in white matter regions may increase the brain's susceptibility to pathologic insults during this important developmental period^{36, 71–73}.

Tregs and Th17 cells share a common lineage regulated by the transcription factor ROR $\gamma\delta$ ⁷⁴. In preterm neonates, chorioamnionitis is associated with increased cord blood quantities of IL-17A-producing Th17 lymphocytes⁷⁵ and Tregs that exhibit Th17-like features²³. Heightened expression of ROR $\gamma\delta$ during acute inflammation converts Tregs into Th17-like effector cells, thereby contributing to the loss of Treg anti-inflammatory actions^{76, 77}. Likewise, cord blood T lymphocytes with effector memory (TEM) can also express Th17-related markers and secrete IL-17A during proinflammatory immune responses⁷⁸. While these permutations can facilitate initial pathogen clearance, they may also initiate chronic immune dysregulation⁷⁵.

Th17 cell differentiation is also transcriptionally regulated by hypoxia-inducible factor 1 α (HIF-1 α) in murine models⁷⁹. HIF-1 α production is stimulated by T cell receptor activation in conjunction with IL-6, TGF- β , IL-1 β , and STAT3-dependent signals. HIF-1 α expression is enhanced by IL-23 and tissue hypoxia caused by oxygen deprivation in infected tissue⁸⁰. HIF-1 α binds to and promotes ROR γ t transcription, thereby facilitating Th17 proliferation and IL-17 production, while concurrently targeting FOXP3 for proteasomal degradation⁷⁹. However, dysregulation of Th17 lymphocytes via an IL-23/IL-17 cytokine axis may occur after prolonged exposure to inflammation or infection and result in severe local tissue damage by unknown mechanisms⁷⁹.

Acute elevations of IL-17A during early inflammation also enable Th17 cells to assume Th1-like effector functions. Th17/Th1 cells can expedite neutrophil recruitment to inflamed tissues and stimulate phagocytes to promote pathogen clearance^{24, 81, 82}. Extremely preterm neonates, however, exhibit clinically relevant deficiencies of Th17 and Th1 cellular responses due to impaired induction of the common p40 subunit, shared by IL-12 and IL-23^{53, 83}. Loss of these cytokines heightens the neonate's risk for early onset sepsis despite increases of other pro-inflammatory cytokines^{53, 83}.

In summary, IL-17-mediated proinflammatory immune responses are important for clearance of extracellular pathogens. Chorioamnionitis-mediate increases of IL-17A in fetal blood and amniotic fluid, however, are associated with cerebral white matter lesions and neurodevelopmental impairments^{32, 44, 46, 47, 84}. Fetal hypoxia and ischemia, commonly associated with chorioamnionitis, enhance fetal inflammatory responses and worsen fetal white matter damage^{7, 13}. This mechanism of fetal brain injury remains the leading cause of neurodevelopmental disability in prematurely born infants⁸⁵. Remarkably, nearly one-half of all infants born before 30 weeks' GA manifest some degree of white matter injury on serial MRI⁸⁵. Infants exposed to chorioamnionitis prior to 28 weeks' GA also experienced depressed patterns on amplitude integrated EEG (aEEG) indicating early brain injury⁸⁶. Recent studies confirm that preterm birth alone is insufficient to cause fetal neuronal aberrations associated with neuroinflammation and white matter injury, but must occur concurrently with *in utero* inflammation^{71, 87}. Conversely, neonates with low serum IL-17A generally demonstrate concomitant elevations of IL-10 and Th2-biased T cell populations, promoting immune tolerance and senescence. Because immune tolerance significantly increases the incidence of neonatal bloodstream infections, however, these infants remain at risk for neuroinflammation, fetal brain injury, and poor neurologic outcomes²⁴.

The role of Chorioamnionitis and IL-17 in cerebral palsy and white matter injury

Early associations between chorioamnionitis and CP were discovered nearly 25 years ago in a study evaluating long-term neonatal outcomes in preterm infants exposed to empiric intrapartum penicillin for preterm rupture of membranes⁸⁸. In this study, CP was significantly reduced in the offspring of mothers randomized to the treatment group due to decreased maternal and neonatal infectious morbidities⁸⁸. Preterm birth complicated by perinatal infection may trigger fetal proinflammatory responses that injure white matter tissues in the brain, leading to the development of cerebral palsy. Periventricular leukomalacia, a specific form of white-matter injury, is the most common brain lesion in preterm infants and is often accompanied by elements of gray-matter impairment^{89–91}.

Cerebral palsy remains the leading cause of motor disability in childhood^{92, 93}, with an estimated prevalence of 1.5 to 4 per 1000 live births^{94, 95}. Remarkably, the incidence of CP is significantly higher in term compared to preterm infants exposed to chorioamnionitis⁹⁶. A recent meta-analysis confirmed a 4.7-fold increase in CP in term vs a 1.9-fold increase in CP in preterm infants following pregnancies complicated by *in utero* infection⁹⁶. In murine models, intrauterine inflammation that was insufficient to induce parturition was sufficient to cause fetal brain injury in an IL-6- independent manner in both preterm and term pups⁹⁷. Despite technological and therapeutic advances in the field of Neonatal-Perinatal Medicine that have improved patient survival at younger gestational ages, the incidence of neurodevelopmental disability, including CP, mental retardation, blindness, and/or deafness, has not declined in this patient population^{98, 99}.

Former preterm infants, who subsequently developed CP, exhibit elevated blood levels of IL-17A in addition to cytokines IL-6, IL-8, IL-12, and tumor necrosis factor (TNF)- β ,

suggesting late perinatal and/or early neonatal inflammatory origins of disease^{98, 100–102}. Utilizing quantitative brain MRI scans, *Anblagan and Colleagues* demonstrated altered microstructures in major white matter tracts of preterm infants at term equivalent age from pregnancies complicated by histologic chorioamnionitis¹⁰³. This effect was independent of known predictors of preterm brain injury and poor neurodevelopmental outcomes (i.e. degree of prematurity, BPD/CLD, and postnatal sepsis) as well as neonatal age at imaging acquisition.

Employing murine models to study the early stages of PVL revealed the pro-inflammatory cytokines IL-1 β and TNF- α , generated during the fetal inflammatory response, mediate brain injury by increasing the permeability of the blood brain barrier (BBB) to cytotoxic proteins^{90, 100, 104}. This alteration in the BBB allows an abundance of stimulated macrophages to infiltrate inflamed brain tissue⁹⁰. Together with elevated levels IL-1 β , and TNF- α , macrophages persist in affected areas from early stages of inflammation until the appearance of cystic cavitation late in disease pathogenesis⁹⁰. Conversely, circumventricular ventricular portions of the brain that are devoid of the BBB allow cytokines and bacterial products from the bloodstream to directly contact cellular elements of the central nervous system (CNS)¹⁰⁵. Because these areas contain high concentrations of macrophages and antigen-presenting cells, robust inflammatory responses can be triggered in a NF- κ B-mediated fashion¹⁰⁶.

Microglial activation is an essential component for excitotoxic, inflammatory, and free radical damage to cells of the developing CNS^{105, 107}. Activation of microglia¹⁰⁸ and astrocytes⁹⁰ initiate PVL pathology by damaging surrounding axons¹⁰⁰ and inhibiting oligodendrocyte maturation, which causes regional hypomyelination^{100, 109}. Disease progression leads to sensitization of the developing brain to subsequent hypoxic-ischemic (HI) insults^{103, 110} through activation and propagation of the coagulation cascade¹¹¹. This modification enhances neuronal injury, accelerates cell death^{70, 112}, and greatly reduces endogenous stem cell populations required for brain growth¹¹³. The cytokines IL-17 and IL-8 also stimulate quiescent neutrophils and promote their accumulation in cerebral blood vessels, which leads to physical tissue injury via microvascular perfusion obstruction, amplification of inflammatory responses through the release of bioactive mediators^{98, 114}, and increased production of reactive oxygen and nitrogen species¹⁰³.

Hypoxic-ischemic-induced injury to the immature brain bolsters the production of proinflammatory cytokines including IL-17A from a variety of cells, such as macrophages, microglia, T cells, $\gamma\delta$ T cells, and ILCs, and promotes the expression of various genes related to immune responses and inflammation^{90, 115}. Studies utilizing neonatal murine models showed HI drives T cell differentiation towards Th1/Th17-mediated responses. These T cells infiltrate infarcted areas, where they remain for hours to months after the inciting event, thereby contributing to ischemic brain injury, white-matter damage, and general CNS inflammatory demyelination disease^{90, 116–119}. In human patients with periventricular leukomalacia, Th1/Th17-type cytokines, including IFN γ , TNF- α , IL-6, and IL-17A, are highly expressed and contribute to disease pathogenesis^{90, 120}.

In summary, chorioamnionitis-triggered FIRS promotes the development of cerebral palsy in preterm and term infants. However, FIRS is also associated with other common neonatal maladies that can directly cause CP, such as postnatal infection^{89, 97}, necrotizing enterocolitis^{8, 28, 29}, and chronic lung disease^{26, 27}. Moreover, neonates diagnosed with postnatal sepsis and hypotension requiring inotropic support may be at a higher risk of white-matter injury and CP than those with histologic chorioamnionitis alone^{34, 100, 121, 122}. Even though further research is needed to delineate how systemic inflammation, arterial hypotension, hypoxia/ischemia, and impairments of cerebral autoregulation individually contribute to the susceptibility of white-matter injury and cerebral palsy, therapies that target early pro-inflammatory cytokines, including IL-17, may offer new therapies for the prevention of white and gray-matter injuries that cause cerebral palsy and neurodevelopmental impairment¹²³. For example, short treatment with IL-17A-neutralizing antibodies reduced brain injury after a HI by inhibiting neutrophil recruitment to affected sites⁴⁶. Mesenchymal stem cells (MSC), sourced from cord blood and placental tissue, can suppress upregulation of cytokines IL-1 α , IL-1 β , IL-6, and TNF- α within the cerebral spinal fluid and periventricular brain region, resulting in attenuation of swelling and fluid formation around the brain^{124, 125}. Together with endothelial progenitor cells (EPCs), MSCs may have the capacity to limit inflammation-based brain injury, while facilitating neuroreparative processes (such as vascular repair) to improve neurodevelopmental outcomes¹²⁵. More research is greatly needed to determine if similar findings will be demonstrated in human neonates.

Presently, antenatal magnesium sulfate is administered to mothers at risk for preterm delivery to reduce the risks for CP in the offspring, although its mechanism of action remains unknown^{126–128}. In pregnancies complicated by preterm labor and chorioamnionitis, however, the neuroprotective effects of antenatal magnesium sulfate infusion are greatly reduced or absent^{52, 126}. In neonatal murine models, magnesium sulfate decreased maternal serum levels of inflammatory markers (i.e. IL-6, INF- γ , and TNF- α) and prevented fetal neuronal damage after intrapartum systemic LPS exposure^{129–131}. These findings, though, do not appear translatable to human pregnancies and immunologic differences between the two species may explain outcome differences. Alternatively, the protective effects of magnesium sulfate may be dependent upon on the severity of fetal-maternal immune response, magnitude of intrauterine inflammation, and virulence of the causative pathogen⁹⁷. The timing of magnesium sulfate administration may also be an important factor with irreversible neonatal brain damage occurring quickly after intrauterine inflammation/infection exposure but prior to initiation of magnesium sulfate treatment^{126, 132}.

Fetal origins of childhood and adult disease caused by maternal inflammatory response syndrome

Maternal inflammatory responses (MIR) to *in utero* infection and inflammation can also increase IL-17A production by biasing naïve Th cell differentiation towards Th17 subtypes in the mother and her offspring¹²². This maternal adaption, though, can influence the risks that her offspring will develop a chronic neurologic disorder. Surprisingly, the timing and

microbial source at the center of the maternal inflammatory response can greatly influence the type of future neurologic impairment. That is, maternal infections occurring during the first or second, but not the third, trimester can increase the risk of schizophrenia¹³³. Mid-gestation maternal infection generally results in suppressed exploratory behaviors, while late gestation infection usually causes perseverative behavior, such as autistic spectrum disorders (ASD)¹³⁴, addictive behavior, and obsessive-compulsive disorder^{71, 90}. In this section, neurologic conditions that originate from *in utero* fetal exposure to maternal inflammatory responses, but primarily present in childhood and adulthood, will be discussed including autism, schizophrenia, and multiple sclerosis (MS).

Autism

An estimated 1 in 68 children residing in the United States displays behaviors consistent with ASD¹³⁵. Although genetic and environmental factors may influence ASD risks, exposure to intrauterine inflammation may also contribute to the development of ASD⁴². Unlike previously discussed neonatal conditions, alterations within the developing fetal brain predisposing newborns to ASD appears to be caused by maternal, not fetal, inflammatory responses to *in utero* infection or inflammation in murine models of disease¹³⁶. The cytokine IL-17A is implicated in ASD pathogenesis, with the gene *il17a* directly linked to ASD susceptibility and elevated levels of IL-17A observed in the blood of children with ASD¹³⁶.

The role of IL-17A in ASD pathogenesis was established using a murine model of MIR that induced maternal proinflammatory responses by injecting pregnant dams with polyinosinic-polycytidylic acid (poly(I:C)), a TLR3-agonist that mimics viral infection⁴¹. This intervention increased IL-17A levels by expanding the number of circulating maternal Th17 cells, resulting in MIR-mediated disorganized cortical phenotypes and ASD-like behaviors in the offspring⁴¹. These effects were dependent upon IL-17A synergy with IL-6, as IL-6-deficient mice failed to demonstrate MIR-induced ASD phenotypes¹³⁷. To prove maternal origins of disease, these investigators deleted one or both copies of *il17ra* in the mother and found the offspring were rescued from MIR-induced sociability deficits⁴¹. Additionally, pretreatment with IL-17A blocking antibodies suppressed the MIR-mediated up-regulation of IL-17A gene expression in fetal brains, restored normal behavior in the offspring, and reduced maternal serum concentrations of IL-17A⁴¹.

Schizophrenia

In addition to genetic predisposition and environmental factors, perinatal viral and bacterial infections play a major role in the development of schizophrenia in young adults¹³⁸. Affecting 1% of the world's population, or approximately 21 million people, schizophrenia has an estimated incidence rate of 0.2 per 1000 live births per year^{133, 138}. Remarkably, fetal consequences of MIR exposure typically remain behaviorally silent until at risk individuals reach young adulthood, thus demonstrating that pathophysiologic mechanisms involved in the genesis of schizophrenia are progressive in nature¹³³.

Patients diagnosed with schizophrenia have increased serum and CSF concentrations of proinflammatory cytokines, including IL-6, IL-1 β , IL-17A, and TGF- β ^{138–141}, and recent

findings confirm an association between the IL-23/IL-17 immune axis and schizophrenia^{141, 142}. Circulating peripheral T lymphocytes, including Th17 cells, can directly influence CNS immune homeostasis and promote neuroinflammation^{141–143}. IL-17 and its receptor, IL-17R, are also produced by glial cells, which function as a central regulators of brain inflammation¹⁴¹. Once Th17 lymphocytes transmigrate the BBB, they secrete IL-17A and granzyme B leading to CNS inflammation and neuronal destruction^{31, 141}. BBB endothelial cells can also express IL-17A and IL-22, as well as their receptors, which disrupts tight junctions and the integrity of the BBB¹⁴¹. Impairment of the BBB allows entry of peripheral immune mediators into the CNS, further heightening the severity of proinflammatory reactions within the CNS^{141, 144}.

In humans, influenza H1N1 maternal infection during the first trimester is associated with an increased risk of schizophrenia in the offspring^{138, 145}. Similar findings are found in murine models, with significant gene, protein, and brain structural abnormalities in the pups of dams infected with influenza N1H1¹³⁸. Neuroanatomical abnormalities associated with schizophrenia include tissue loss associated with ventricular enlargement, as well as reduced hippocampal, parahippocampal gyrus, and temporal lobe volume^{138, 146}. Additionally, oxidative stress associated with neuroinflammation can cause neurodegeneration, apoptosis, and reduced neurogenesis of brain structures^{138, 147, 148}. Influenza-induced CNS malformations associated with schizophrenia also include abnormal neuronal migration, reduced synaptic plasticity¹⁴⁹, astrogliosis and reactive nerve injury¹⁵⁰, decreased axonal growth, and impaired neurotransmitter release¹³⁸.

Rat and murine models of MIR demonstrate specific alterations of brain development leading to neurodevelopmental disorders, including schizophrenia¹³³. *Oskvig and Colleagues*¹⁵¹ employing a rat model of disease discovered that neutralizing IL-6 and IL-1 β prevented these alterations and inhibit MIR-induced behavioral and physiological consequences in the offspring^{151–153}. Gene expression studies also demonstrated a significant downregulation of fetal genes critically important to CNS maturation and development¹⁵¹. The greatest fold reduction was observed for genes regulating neuronal migration and maturation of GABAergic interneurons¹⁵¹. Failure to demonstrate gene expression differences in the fetal brain for key mediators, such as TNF α , IL-1 β , and IL-6, between chorioamnionitis exposed and non-exposed pups lead these authors to conclude that increased serum and CSF cytokine levels were derived from maternal, not fetal, sources¹⁵¹. Conversely, a murine study by *Burd et al.* demonstrated heightened fetal brain gene expression of IL-1 β , and IL-6 following LPS-induced chorioamnionitis, resulting in decreased neuronal cytoskeleton development, altered neuronal morphology, and delayed neurotoxicity¹⁵⁴. Differences in animal model and gestational age for LPS-induced chorioamnionitis may explain these differences.

Multiple Sclerosis

Worldwide, an estimated 2.3 million people are living with multiple sclerosis and females have a higher prevalence than males^{155, 156}. The diagnosis of MS is based on the distribution of inflammatory lesions throughout the CNS, which develop over time. The initial stages of MS are typically described as relapsing-remitting in nature, followed by sporadic episodes

of acute neurologic dysfunction¹⁵⁶. Early stages typically demonstrate full recovery in most (85%) cases. After 10–20 years, though, most patients convert to a debilitating, progressive course of MS¹⁵⁶.

Historically, MS was thought to be a Th1-mediated disease due to high levels of IFN- γ in MS lesions, increased serum concentrations of IL-12, and worsening of disease following IFN- γ administration^{156–158}. Mice lacking critical components of the IL-12/Th1/IFN- γ pathway, however, were still susceptible to disease onset^{156, 159, 160}. Involvement of IL-17A, however, was discovered in knockout models of the p40 subunit common to IL-12 and IL-23 because animals became resistant experimental forms of MS^{156, 161}. This finding allowed investigators to focus their attention on IL-23 and the IL-23/IL-17 immune axis.

Studies utilizing standard animal models of MS, known as experimental autoimmune encephalomyelitis (EAE), demonstrated greater severity of EAE in adult offspring of dams who received intraperitoneal LPS versus sham injections¹⁶². In this model, IL-6 played a primary role in maternal Th17 lymphocytes differentiation and IL-17 production. The involvement of Th17 cells in EAE and MS is complicated, because IL-17-deficient mice are not immune against EAE but display delayed onset and reduced severity of disease^{163, 164}. GM-CSF deficient mice, on the other hand, are resistant to EAE and demonstrate the importance of this cytokine in MS pathogenesis¹⁶⁵.

Upon IL-23 exposure, Th17 lymphocytes co-express IFN- γ , GM-CSF, TNF- α , IL-22, and granzyme B, transforming them into a Th17/Th1 phenotypic hybrid cell that is highly pathogenic for MS disease^{156, 165–168}. In EAE models, GM-CSF promotes the activation, survival, and recruitment of potent proinflammatory neutrophils^{165, 169–171} and macrophages into the CNS, leading to tissue injury and destruction via cell-mediated acute inflammatory responses. Exposure of microglia cells to GM-CSF results in IL-6 production¹⁷², which may enhance cross-presentation of exogenous MHC class I peptides and propagation of autoimmune properties of the disease^{156, 173}. In addition, IL-17A and Th17 lymphocytes can cross the fetal blood brain barrier and facilitate recruitment of fetal immune cells, such as macrophages, Th1, and Th17 cells, which can exacerbate gliosis and cause cortical disorganization pathognomonic for MS¹⁵⁷.

Conclusion

IL-17A-mediated proinflammatory fetal and maternal immune responses can result in a broad array of debilitating neurologic diseases. Symptoms of disease may present in infancy or lie dormant, revealing themselves in young adulthood. Despite major advances in the field of Neonatal-Perinatal Medicine, the incidence of neurologic disease remains unchanged, particularly in regards to cerebral palsy. Understanding the biology behind IL-17A and pathways involved in disease pathogenesis may facilitate the development of novel interventions and/or therapeutics which may either prevent, cure, or alleviate neurologic symptoms often associated with these chronic, debilitating conditions.

Animal models are often utilized in the study of complex human disease, including neurologic conditions discussed in this review. Replicating human neurologic disease in

animal models remains challenging because study designs must account for variances in early brain developmental timelines when modeling fetal or progressive human brain pathologies¹⁷⁴. Moreover, disparities in brain size and complexity, as well as genetic variations, between species remain compounding factors. For example, the amount of white matter in humans is roughly $4 \times 10^6 \text{ mm}^3$ compared with 10 mm^3 in the mouse^{174, 175}. Our ability to sufficiently replicate neonatal brain injury in an animal model is, therefore, a “moving target”¹⁷⁶. Presently, only 1 in 3 animal studies are estimated to be translatable at the level of human randomized trials and only 10% of therapeutic interventions are subsequently approved for clinical use in patients¹⁷⁷. Correct identification of the timing and pathology involved in human brain injury, as well as the proper translation of medical therapies that provide more benefit than harm in an appropriately suitable animal model, continues to confound investigators. While a more precise scientific method is needed to adequately investigate human disease, the standard use of animal models remains a cornerstone of scientific investigation and provides valuable information regarding disease pathogenesis.

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Abbreviations

ASD	Autism spectrum disorder
BPD	Bronchopulmonary dysplasia
CLD	Chronic lung disease
CNS	Central nervous system
CP	Cerebral palsy
EAE	Experimental automimmune encephalomyelitis
EPC	Endothelial progenitor cell
FIRS	Fetal inflammatory response syndrome
FOXP3	Forkhead box P3
GA	Gestational age
GM-CSF	Granulocyte-macrophage colony stimulating factor
HI	Hypoxic ischemic insult
HIF-1α	Hypoxia-inducible factor 1 α
IL	Interleukin
ILC	Intestinal group 3 innate lymphoid cell

iNKT	Invariant natural killer T cells
IVH	Intraventricular hemorrhage
LTi	Lymphoid-tissue inducer cells
LPS	Lipopolysaccharide
MIR	Maternal inflammatory response
MS	Multiple sclerosis
MSC	Mesenchymal stem cell
NEC	Necrotizing enterocolitis
Poly(I:C)	Polyinosinic-polycytidylic acid
PVL	Periventricular leukomalacia
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of prematurity
RORγt	Retinoic acid receptor-related orphan receptor-gamma t
TEM	T lymphocytes with effector memory cell
TGF-β	Transforming growth factor β
Th	Helper T lymphocyte
TNF	Tumor necrosis factor

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