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Cytokines and Perinatal Brain Damage

Olaf Dammann, Dr.med., S.M [Research Professor of Pediatrics] and
Tufts University School of Medicine, Director of Clinical Research, Div. of Newborn Medicine, Floating Hospital for Children at Tufts Medical Center, 800 Washington Street, Box 854, Boston, MA 02111 USA, Phone 617-636-0240, Fax 617-636-8943, Email: odammann@tuftsmedicalcenter.org

Michael O'Shea, MD, MPH [Professor of Pediatrics]
Wake Forest University School of Medicine, Winston-Salem, NC 27157, Email: moshea@wfubmc.edu, Phone: (336)-716-2529, FAX: (336)-716-2525

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Introduction

Perinatal brain damage has been implicated in the pathogenesis of both neurodevelopmental impairments and psychiatric illnesses. These conditions constitute an enormous source of human suffering and health care costs. For example, the average lifetime costs for mental retardation(1), cerebral palsy(1), and high functioning autism exceed $1 million, and for individuals with autism and mental retardation, they exceed $5 million(2).

The focus of this chapter is on specific aspects of the pathogenesis of perinatal brain damage in which cytokines and chemokines have been implicated. Epidemiologic studies indicate an association between maternal and neonatal infections and perinatal brain damage, even when the infection is distant from the brain. Experiments in animals indicate that the causal link between these two events probably involves cytokines and chemokines. Further, these inflammatory molecules are produced locally in the brain after exposure to a variety of damage initiators, including experimental hypoxia-ischemia and infection/inflammation. Based on research completed in the past two decades, it seems plausible that interventions can be developed to prevent or attenuate brain damage attributable to the fetal or neonatal response to infection, or some other initiator of inflammation(3-5).

We will begin this chapter by reviewing evidence that infection outside of the brain can damage the brain. Then we will discuss specific cytokines and pathomechanisms that probably mediate the putative effect of remote infection on the developing brain. Next we will describe events associated with increased circulating inflammatory cytokines, chemokines, and immune cells. Finally, studies of genetic variation in susceptibility to cytokine-related brain damage will be reviewed. Possible neuroprotective intervention

Corresponding author: Michael O'Shea, MD, MPH.

strategies for attenuating cytokine-mediated brain damage are discussed elsewhere in this volume.

Infection distant from the brain can damage the developing brain

In a study completed more than 40 years ago, infants who had bacteria recovered from their cardiac blood at postmortem examination were estimated to be 34 times more likely to have histologic white matter damage than infants whose cardiac blood was sterile(6). No bacteria were found in the brain of any infant who had cerebral white matter damage. These observations led to the hypothesis that a circulating, non-infectious product of inflammation could lead to brain damage. The investigators tested their hypothesis by injecting sterile endotoxin into the peritoneal cavity of newborn kittens (7;8), monkeys, and rabbits (8) and found white matter damage. At about the same time, others had shown that the offspring of rats given endotoxin in the days before delivery had reduced white matter volume (9). Further epidemiological support was provided by the Collaborative Perinatal Project (CPP), a study of about 54,000 pregnancies occurring between 1959 and 1966. In that study, chorionitis (i.e., marked neutrophil infiltration of the chorion) was associated with an increased risk of cerebral palsy (10). Further, among the 560 newborns in the CPP cohort who were born alive, died within the first 28 days, and had postmortem examination of the brain, the occurrence of maternal urinary tract infection with fever was associated with a more than 400-fold increase in the risk of white matter damage, and definite or suspect septicemia with a more than 40-fold increase (11).

Over the past thirty years, a large body of epidemiological studies in humans (12) and experimental studies in animals (13) has been added in support of the concept that infection distant from the brain can damage the developing brain (14), that endotoxin initiates a brain-damaging process (15;16), and that inflammatory proteins play a role in mediating the damage (17;18).

In 2000, a meta-analysis of 19 studies concluded that clinical chorioamnionitis is associated with both cerebral palsy as well as cystic periventricular leukomalacia (i.e., cerebral white matter damage on neuroimaging studies). (19) It is estimated that about 11% of all cases of cerebral palsy in term and near-term infants are attributable to chorioamnionitis, assuming that it is a causal factor (20). Studies of neonatal encephalopathy also are relevant, because term neonates with encephalopathy have a risk of cerebral palsy that is 100 times that of neonates without encephalopathy. In a population-based study, infants with encephalopathy accounted for 24% of all cases of cerebral palsy in term infants (21). Maternal pyrexia (22;23) has been associated with a 3- to 4-fold, and chorioamnionitis with a 5-fold (24), increase in the odds of neonatal encephalopathy.

Maternal infection, including that evidenced only by neutrophil infiltration of the placenta (25), is a frequent antecedent of preterm delivery, resulting from either preterm labor or preterm rupture of the fetal membranes (26). Among preterm infants, maternal chorioamnionitis is associated not only with evidence of brain damage on cranial ultrasound examination, but also with cerebral palsy (27). These observations lead to the hypothesis that the link between prematurity and cerebral palsy is attributable, at least in part, to their being causally related to maternal infection (28;29).

It would appear that both prenatal, as well as postnatal, infection is potentially harmful to the developing brain. As mentioned above, postnatal sepsis was associated with white matter damage at autopsy (6). In a large cohort of extremely low birth weight infants, sepsis and sepsis with necrotizing enterocolitis were associated with an increased risk of delayed mental development at 18 months adjusted age, even when adjusting for 18 potential confounders (30).

While the larger body of research relates maternal infection to white matter injury, inflammatory processes may present a hazard also to the cerebral cortex. In an autopsy study, polymicrogyria was found in 78% of infants with evidence of infection of the placenta, but in none of those without this finding (31). Maternal influenza infection during the second trimester has been associated with an increased risk of schizophrenia (32). Among very low birth weight infants, maternal fever at birth was associated with an almost 4-fold increase in the risk of non-verbal intelligence at 9 years of age in a cohort of very low birth weight infants (33).

Which cytokines might be involved?

Cytokines, chemokines, and growth factors are ubiquitous signaling molecules that help orchestrate almost all bodily functions of growth and development, as well as acute responses such as fever and inflammation. An important aspect of cytokine biology is the high degree of overlap in source, target cell, and function. This redundancy makes it very difficult to identify individual cytokines as "most important" in specific settings. In addition, some cytokines can have apparently contradicting functions. For example, interleukin (IL)-6 is considered both a pro- and anti-inflammatory cytokine (v.i.).

Which cytokines, chemokines and growth factors might be involved in the process of perinatal brain damage and repair is context-specific. Three context levels, among others, are of utmost importance when considering the role of cytokines in brain-damaging processes.

First, fetal and neonatal inflammatory responses to the various perinatal challenges are likely to occur at multiple levels. At the systemic level, the so-called acute phase response (34) involves molecules synthesized mainly in the liver (e.g., CRP, IL-6), by white blood cells and the endothelium. At the local (brain) level, the neuroinflammatory response is of crucial importance.

Second, the relative importance of individual molecules is likely to vary by level and characteristics of the insult. Obviously, most research on the roles for cytokines in perinatal brain damage that focuses on one or a few individual molecules in the setting of defined insults comes from bench science groups, most of which focus on hypoxia-ischemia, inflammation, and excitotoxicity (35), or on combinations of multiple challenges (36;37).

Third, timing of the insult(s) during brain development is certainly an effect-modifier. Although the well-known differences between term and preterm infants could be due to different challenges (exposure to intrauterine infection in preterm and perinatal energy failure in term infants), at least part of the neuropathological differences between the two groups of newborns is likely to be due to their different developmental stages.

In what follows, we highlight a few examples of molecules that have been investigated over the past years. For the purpose of structure, we have deliberately chosen to present these data in functional groups. We are fully aware, however, that some molecules overlap in function and/or belong to multiple groups. For example, IL-6 is considered both anti- and pro-inflammatory, and IL-2 is both a cytokine and a growth factor.

Pro-inflammatory cytokines

Pro-inflammatory cytokines have been at the forefront of clinical and laboratory investigations of fetal and neonatal brain damage in the past decade. Initial suggestions were that pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α can affect the developing brain and blood-brain barrier (38) and that intrauterine infection and a pro-

inflammatory cytokine response are involved in the pathogenesis of preterm brain white matter damage (28;29). Since then, the theory has come of age (14;39;40) and is now close to reaching the status of "received knowledge." (13;16;41-45;45-47) At the center of the paradigm is the notion that fetal exposure to a strong pro-inflammatory challenge (intrauterine infection) elicits a fetal inflammatory response that contributes to both preterm delivery (48) and brain damage in the preterm newborn(40), without leading to brain infection (14).

TNF-α, interferon (IFN)-gamma, interleukin (IL)-1, -6, [11] and -18(49) are the pro-inflammatory cytokines that have been studied frequently in term (50-56), preterm (57-61;61-66), and mixed populations (67). Most, but not all of these studies have found elevated levels of these mediators in newborns with evidence of perinatal brain damage compared to controls. A role for the pro-inflammatory cytokines is further suggested by reports (68-70) supporting the hypothesis (71) of an association between single-nucleotide-polymorphisms (SNPs) in the genes that encode for such cytokines and brain damage.

The major role for experimental studies in attempts to prevent or attenuate perinatal brain injury by interfering with the cytokine cascade is in the realm of blocking individual cytokines. For example, in one study, co-administration of LPS with IL-1 receptor antagonist, but not with TNF-α antibody, significantly attenuated LPS-induced white matter injury in one study(72).

Anti-inflammatory cytokines

Cytokines that function as immuno-modulatory regulators by antagonizing pro-inflammatory responses are sometimes called "anti-inflammatory" cytokines. Soluble receptors for pro-inflammatory cytokines can have similar function. Major anti-inflammatory cytokines include IL-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11, and IL-13, and transforming growth factor (TGF)-β (73).

Only a few of these anti-inflammatory/immunomodulatory cytokines have been studied clinically in relation to perinatal brain damage. Probably the best studied is IL-10, which has protective properties in microglial culture studies after a pro-inflammatory insult (74) and in rat pups born to E.coli infected dams (75). In newborn mice subjected to intracerebral injection of the excitotoxic stimulus ibotenate (which by itself induces white matter lesions similar to those seen in periventricular leukomalacia), pretreatment with intraperitoneal IL-10 alone had no detectable effect, while IL-10 co-administered with IL-1-β reduced the toxic effects of interleukin-1-β, suggesting that exogenous IL-10 might be neuroprotective mainly in inflammatory contexts(76). This result is in keeping with our clinical observation that infants homozygous for the high IL-10 producer - 1082 G-allele were significantly less likely to develop ultrasound-defined periventricular echodensities(77).

Transforming growth factor-β3 was found expressed in the brains of neonatal rats with post-hemorrhagic hydrocephalus(78) and in cerebrospinal fluid of preterm infants with this condition(79). If TGF-β turns out to be part of an endogenous protection factor derived from astrocytes(80), it might reduce damage, e.g., by blocking IL-1-induced activation of microglia cells(81). However, in an excitotoxicity context, TGF-β appears to help orchestrate IL-9/mast cell interactions that lead to exacerbation of excitotoxic brain damage via increased extracellular histamine concentrations(82). In the adult rat, cerebroventricular administration of TGF-β improves only short-term, but not long term neuropathology and neurologic function (83).

Chemokines

The central role for chemokines in immunity is to help orchestrate leukocyte trafficking, thereby "engendering the adaptive immune response." (84) Chemokine biology offers a variety of linkage points for intervention in neurological diseases (85), including those with a neuroinflammatory component (86).

The chemokine nomenclature recently underwent revision (87). In our subsequent discussion of examples for chemokine functions in perinatal brain injury, we use the new and old chemokine names side by side.

The "oldest" and probably best studied chemokine is CXCL8 (IL-8), well known to neonatologists as one of the serum biomarkers of neonatal sepsis (88). In term newborns, serum levels of CXCL8 (IL-8) are elevated among those with MRI-defined neuroabnormalities and adverse neurologic outcome (89). It is also associated with intraventricular hemorrhage in preterm infants (66), with levels being comparatively higher in cerebrospinal fluid than in serum (90), which might indicate its production inside the CNS, where microglial cells are one potential production site of CXCL8 (IL-8)(91). Indeed, the crucial role of microglia cells in the neuroinflammatory process leading to developmental disability is now widely acknowledged (92).

Chemokines are upregulated in immature rat brain after hypoxic-schemic challenge (93) and in mature rodents after a systemic bolus of lipopolysaccharide (94). This upregulation was followed by a transient neutrophil invasion of the infarct region and an activation of microglia/macrophages, CD4 lymphocytes, and astroglia for up to at least 42 d of postnatal age implicating a chronic component of immunoinflammatory activation in the immature animals (93). These findings support our suggestion that white cell invasion might be part of the pathogenesis of perinatal white matter damage (95).

Growth factors

A vast variety of growth factors are implicated in brain development and damage/repair mechanisms. For the sake of brevity, we focus on only four in this section.

IL-2 is the major cytokine/growth factor for T-lymphocytes by stimulating their clonal expansion. We have previously argued(96) that its toxicity to oligodendrocytes and myelin(97) and the fact that IL-2 and its receptor have been identified in areas of cerebral white matter damage in human newborns in the absence of lymphocytes(98) raises the possibility that the IL-2 originated outside the brain.

In adult models of stroke, vascular endothelial factor (VEGF) has neuroprotective properties as a reducer of apoptosis (programmed cell death) and initiation of neurogenesis and maturation of heterologous newborn neurons in adult rat brains after stroke(99). VEGF is expressed in hypoxic neonatal rodent white matter(100) and reduces excitotoxic brain lesions in the developing mouse(101). This supports the hypothesis that VEGF is part of an endogenous protection response(3).

Inflammation at birth appears to be associated with a systemic up-regulation of Insulin like growth factor (IGF) and a down-regulation of its binding proteins(102). Since IGF improves oligodendrocyte survival after hypoxic insult(103) and reduces hypoxia/ischemia-induced brain damage in fetal sheep(104) and newborn rats(105), it would be interesting to know whether IGF might also be part of the developing organisms' anti-inflammatory response geared towards brain protection in experimental models using LPS challenge.

One most interesting growth factor involved in multiple developmental processes is neuregulin (NRG). Our recent proposal that NRG is a potential endogenous protector of the perinatal brain(106) is based on its role in brain development(107), particularly in oligodencrocyte development(108), its neuroprotective effects in the setting of ischemia(109-112), and its involvement in the pathogenesis of neuropsychiatric disorders such as schizophrenia(113), which shares with perinatal brain injury an antenatal infection/inflammation-related etiology(114).

Proposed mechanisms

Just as context is important for which cytokine are involved in perinatal brain damage causation, it is also important for how they might be involved. By this we refer to the experimental paradigm used to study cytokine actions in animal experiments of perinatal brain damage causation.

The following are examples of intricacies that should be kept in mind. First, the cytokine cascade in experimentally-induced ischemia might differ both in quality and in quantity from the cytokine response to intracerebrally injected lipopolysaccharide (LPS). Second, responses might differ between paradigms of direct cerebral LPS exposure and remote systemic/transplacental exposure(13), which does not even implicate the presence of LPS in the brain. On the other hand, different paradigms might have some central aspects in common, such as microglia activation as one key pathomechanisms and the premyelinating oligodendrocyte (pre-OL) as the major cellular target in white matter damage(47). Third, differences in species, timing, dosage, and definition experimental study endpoint are clearly non-trivial. Finally, some general issues of causal inference(115) deserve consideration when integrating experimental results with other sources of evidence.

Cytokine upregulation

Both hypoxia-ischemia and exposure to infection/LPS(13) are followed by a prominent neuro-inflammatory response in the immature brain. Inhibition of such neuroinflammatory cascades might help reduce brain injury(5). For example, intravenous melatonin reduces microglial activation and apoptotic cell death in a fetal ovine umbilical cord occlusion model(116). Similarly, administration of glycine 2-methyl proline glutamate (G-2mPE) leads to reduced IL-6 expression and reduced brain damage in a neonatal rat model of hypoxia-ischemia with treatment starting 2h after the insult(117). The immunomodulatory cytokine IL-10 reduces the inflammatory response of microglial cells after LPS challenge(74) and is neuroprotective in a mouse model using intracerebral ibotenate injection(76). Although it does not reduce damage in the developing piglet brain if administered after the onset of inflammation(118), it appears to be protective when administered concomitantly(118).

Of note, pro-inflammatory cytokines directly exert deleterious effect in the developing brain. For example, injection of IL-1 leads to neuronal death and delayed myelination in neonatal rats(119). Tumor-necrosis factor-α induces cell death in mature oligodendrocytes, probably via apoptosis inducing factor (AIF)(120). In developing oligodendrocytes, exposure to TNF appears to be associated with increased apoptosis(121) and reduced staining for myelin basic protein (MBP)(122), which helps explain the reduced myelination that is considered a hallmark of inflammation-associated diffuse white matter damage in fetal rodents(123) and preterm infants(124).

Extracerebral exposure to LPS

Our conceptual model of remote infection as a damage initiator(14) assumes that the fetus (and its brain) are not directly exposed to bacterial antigen. Indeed, much of our proposal

that cytokines are involved in neonatal brain damage after exposure to intrauterine infection was based on the assumption that damage can develop in the absence of bacterial antigen in the brain, with cytokines playing the role of the "dangerous messenger", being both a secondary pro-inflammatory signal in the brain and a direct cause of cell death and delayed myelination(39). This scenario has been modeled in animal studies that have shown that exposure of the dam to intraperitoneal LPS leads to upregulation of IL-1(125;126), TNF(125;127-129) and neurotrophic factors BDNF and NGF(130) in neonatal rat brain. In some of these and closely related models in fetal sheep(131), rabbits(132;133), and guinea pigs(134) the remote infection results in fetal brain damage. In mice, the remote infection paradigm of maternal intraperitoneal LPS exposure leads to up-regulation of chemokine CCL2 (MCP-1), IL-6 and IL-1β, and growth factor VEGF, among other growth and differentiation factors, and the down-regulation of genes involved in axon guidance and neurogenesis(135). It also leads to longterm memory changes(136) and behavioral changes in the adult offspring of mice exposed to intraperitoneal LPS challenge such as increased anxiety and reduced aggression(137). Recent studies suggest a potential role for oxidative stress in brain damage induced by antenatal remote infection scenarios(138-140). In sum, these observations support the hypothesis that intrauterine exposure to an extracerebral inflammatory stimulus can lead to brain damage in the immature animal without bacterial antigen gaining access to the brain. The finding that antenatal exposure to inflammation might not only affect brain well-being, but also suppresses the neonatal inflammatory response(141), adds an interesting level of complexity to the recently developed "multiple-hit" models(36;37), which in themselves offer intriguing opportunities for future studies of cytokine patterns in dual paradigm scenarios.

Intracerebral endotoxin binding and microglial activation

What if LPS does gain access to the fetal/neonatal brain? Although we still lack evidence that this is actually the case in human perinatal brain damage, some experimentalists have already modeled this interesting scenario.

When injected into the rat brain at postnatal day 5, LPS induces white matter rarefaction and necrosis, ventricular enlargement, and a prominent neuro-inflammatory response(142). Microglial cells appear to be the only brain cells that possess LPS-binding TLR4-receptors and seem to be necessary for LPS-induced oligodendrocyte death(143) and neurodegeneration(144). TLR-dependent pathways involving intracellular heat shock protein signaling of microglia activation might help explain the bidirectional relationship between brain damage and neuroinflammation in multiple inflammatory contexts(145). Minocycline, an inhibitor of microglia activation, reduces both inflammatory response and brain damage after intracerebral LPS challenge(146). Similar effects were observed in experiments that employed hypoxia-ischemia as the damage-inducer(147), indicating that microglial activation might be an important mediator of damage induction in both LPS- and energy failure-related paradigms.

White cell tissue migration

A few years ago, we proposed that recruitment of white blood cells might play a role in perinatal white matter damage(95). Multiple intraperitoneal LPS injections over the first 8 postnatal days induce an acute inflammatory response, a prominent breakdown of the blood-brain barrier for proteins in the white matter, and white matter paucity(148). Even short-term disruption of blood-brain barrier integrity can contribute to LPS-induced inflammatory brain damage in 35 day old rats(149). Indeed, macrophage-like cells appear in the close vicinity of blood vessels in the white matter of fetal sheep after a single, low-dose intravenous LPS challenge(150). It will be interesting to learn from future research whether blocking blood-

brain transfer of white cells can attenuate neuroinflammation and brain damage in the remote infection paradigm.

Sustained activation

Along the lines of white cell involvement, we further propose that an interplay between the innate and adaptive components of immunity is highly likely to be part of white matter damage pathogenesis(96). This argument is based on the multiple linkage points between the two systems, created by crosstalk between dendritic cells, natural killer cells, and monocytes/macrophages on the innate side, and T-cells on the adaptive side of immunity. (We further expand on the importance of T-cells in the next section). One exciting potential implication for intervention designers might be the window of opportunity opened by prolonged and possibly persistent inflammation generated by such innate-adaptive immune interactions(151).

Two faces of neuroinflammation

What has recently been called the "dual role of inflammation in CNS disease"(152) incorporates aspects of what we refer to as the interplay between pro-inflammatory challenge and endogenous protection response(s)(3). Multiple aspects of neuroimmune responses in the brain might help explain the purported ambivalent role of inflammation in the CNS, which is still not unanimously accepted in the neuroimmunology community(153). First, it is increasingly recognized that the immune system and the CNS overlap in expression of both inflammatory cytokines and neurotrophic factors. Indeed, brain derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF) are not only produced in the CNS, but also by immune cells(152). Conversely, B-cell activating factor (BAFF) is not only a product of white blood cells, but is also produced by astrocytes and appears to play a role in multiple sclerosis(154). Second, "classic" pro-inflammatory neurotoxic signals such as TNF also appear to elicit potentially protective effects. For example, TNF-receptor knock-out mice sustain greater damage after focal ischemia than wild-type animals(155). Moreover, TNF stimulation of astrocytes leads to BDNF production by these cells(156). Third, T-cells specific to myelin basic protein (MBP) appear to contribute to damage limitation after initial damage(157). Such "protective neuroimmunity" mechanism is likely to involve microglial cells(158), who were suspected more than a decade ago to not only exert potentially damaging, but beneficial effects(159). The possibility to enhance protective neuroimmune responses via "T cell-based vaccination" in neurodegenerative disorders is tempting(160). Fourth, immune signals are involved in adult hippocampal neurogenesis(161). In essence, T cells appear to be necessary for spatial learning and the production of BDNF in the adult brain(162). It will be interesting to learn from groups who will pursue such studies in the developing brain. What follows from the above points is that links between the innate and adaptive immune systems might not only contribute to perinatal brain damage(96), but might also offer target points for the design of neuroprotective intervention.

Potential initiators of inflammation in fetuses and neonates

As described above, some of the earliest experiments linking infection and cerebral white matter damage involved exposure of immature animals to endotoxin, or lipopolysaccharide (LPS). LPS binding to specific toll-like receptors (TLR) constitutes an early molecular event leading from endotoxin exposure to inflammation. The binding of endotoxin to TLR activates signal-transduction pathways that induce the expression of genes coding for a variety of immune-response proteins, such as inflammatory cytokines. TLR and other pattern recognition receptors may be secreted or located on the surface of phagocytes and serve to recognize molecules produced by microbial pathogens(163). Organisms recognized

by TLR include Group B Streptococcus, Listeria monocytogenes, Mycoplasm hominis, Candida albicans, cytomegalovirus, and Enterobactericeae(164). Based on the frequency with which these organisms are implicated as pathogens in neonates, it is not surprising that multiple antecedents have been identified which could induce the production of effectors of innate immunity. Clinical events associated with a fetal inflammatory response include chorioamnionitis(54;165-167), while those associated with a neonatal inflammatory response include sepsis(168-172), necrotizing enterocolitis (NEC)(173), and pulmonary infections.

As compared to uninfected controls, very preterm neonates with either confirmed or suspected sepsis have higher umbilical cord blood levels of Il-6, but not TNF-α. Infants born to mothers with more severe grades of chorioamnionitis and infants with funisitis have higher umbilical cord blood levels of IL-6(166;167) and CXCL8 (IL-8)(167) than those without these histological findings. Infants born to women from whose placenta Ureaplasma urealyticum was cultured were more likely to have this organism in their blood cultures and were three times more likely to have elevated levels of IL-6(174). Histological chorioamnionitis also has been associated with increased levels of CXCL8 (IL-8) in blood(54) and tracheal aspirates, (165) and increased levels of the chemokine CCL5 (RANTES) in blood(54). In a study of infants suspected of having early onset sepsis, levels of IL-6, CXCL8 (IL-8), and TNF-α were elevated at the time when sepsis was initially suspected (< 48 hours of age). Twenty-four hours later, CXCL8 (IL-8) and TNF-α levels were similar to uninfected controls, but IL-6 remained elevated(168). In a study of very low birth weight infants suspected of having late onset sepsis, the levels of multiple chemokines, IL-6, IL-10, IL-12p70, and TNF-α were higher among infants with confirmed infections. All of the chemokines as well as IL-6 and IL-10 remained elevated 24 hours later(169). Also elevated in late onset systemic infections are anti-inflammatory cytokines, such as IL-4 and IL-10(170).

In a study of infants with necrotizing enterocolitis, those with the most severe disease (stage 3) had higher levels of CXCL8 (IL-8) than either infants with milder NEC or controls without NEC, and the level of CXCL8 (IL-8) continued to rise over the 72 hours when serial measurements were made(173). Differences were not found when comparing infants with sepsis and NEC and infants with NEC only. IL-10, an anti-inflammatory cytokine, also was higher in infants with stage 3 NEC, when compared to controls and to infants with milder NEC. Significant group differences were not found for either IL-1β or the anti-inflammatory protein IL-1ra.

Among term infants, elevated blood levels of inflammatory cytokines have been associated with indicators of perinatal asphyxia, infection, and encephalopathy. In a group of 20 infants with fetal acidemia, respiratory depression, and low Apgar scores, cerebrospinal fluid levels of IL-6 were higher among those with infants with more severe neonatal encephalopathy(50). This elevation in IL-6 could be attributable to brain damage manifesting as neonatal encephalopathy and/or to antecedents of encephalopathy, which as discussed above, include chorioamnionitis(175). Blood levels of IL-6, as well as IL-1β(56;89), TNF-α(56), CXCL8 (IL-8) (89), and IL-12(89) also are elevated in infants with encephalopathy. This association was found even among infants born to mothers who were not diagnosed with chorioamnionitis(89). Thus, antecedents of neonatal encephalopathy other than chorioamnionitis (e.g., hypoxia-ischemia) might lead to elevated levels of inflammatory cytokines in the blood. Higher levels of IL-1β, IL-6, TNF- α, and CXCL8 (IL-8), in the blood of neonates with encephalopathy have been associated with increased anaerobic brain metabolism, as assessed with magnetic resonance spectroscopy, as well as with abnormal neurodevelopmental outcome(89).

Lung injury, which occurs in many critically ill neonates, and even in otherwise healthy premature infants, has been consistently associated with elevations in inflammatory cytokine and chemokine levels in respiratory tract secretions. CXCL8 (IL-8) and IL-6 are found in tracheal aspirates of preterm infants treated with mechanical ventilation for respiratory distress syndrome, and as early as the first day of life, levels of CXCL8 (IL-8) are higher among those who eventually will develop bronchopulmonary dysplasia (BPD)(176). These infants have, by the second day of life, higher levels of TNF-α(177;178), IL-6(178), and IL-β(177;178), macrophage inhibitory protein-1α (MIP1α -) activated macrophages(177). That mechanical ventilation may be an inducer of inflammation is suggested by the finding that within hours after birth, preterm infants who required mechanical ventilation had significantly higher numbers of activated phagocytes in their blood as compared to preterm non-ventilated controls(179) (and no difference was found comparing umbilical cord blood specimens from these two groups). Although not studied in vivo, increased pressure in lung venular capillaries, as would be expected when a patent ductus arteriosus leads to excessive pulmonary blood flow, has been found, in vitro, to cause proinflammatory responses in endothelial cells (e.g., expression of P-selectin)(180).

Genetic susceptibility to inflammation-related brain damage

As alluded to above, there is increasing evidence that inherited cytokine or chemokine polymorphisms influence the risk of pre- and perinatal brain damage(181). Included are polymorphisms of genes regulating expression of both pro-inflammatory cytokines and chemokines as well as anti-inflammatory cyokines. Increased production of TNF-α is associated with a single nucleotide polymorphism (SNP) at position -308 in the promoter region of the TNF- α gene. Patients with this SNP have a 7-fold increase in the risk of central nervous system malaria(182) and of preterm delivery(183). In a study of 27 infants born before 32 weeks gestation, the TNF-α promoter -308 was associated with severe intraventricular hemorrhage (Papile grade 3 or 4)(184)), although the association was statistically significant only among males(70). In a study of 119 very low birth weight infants, TNF-α promoter -308 was associated with an almost 2-fold increase in the risk of all grades of intraventricular hemorrhage(185). Although in one study of children born before 32 weeks' gestation, those with cerebral palsy were not more likely to have the TNF-α promoter -308 gene(186); this association was found in a much larger study (443 cases and 883 controls)(187). In analyses stratified by gestational age and clinical type of cerebral palsy, the association with TNF-α promoter -308 was strongest among children with quadriplegia who were born at term and those with hemiplegia born prior to 32 weeks. Further, a SNP in the gene for mannose-binding lectin (which is involved in complement activation) was associated with an increased risk of diplegia(187).

An SNP in the IL-6 gene promoter at position -174 (CC genotype) has been associated with enhanced production in lipopolysaccharide-stimulated monocytes of neonates, but not adults. Among infants born before 32 weeks' gestation, this polymorphism has been associated with an increased risk of periventricular hemorrhage and cerebral white matter damage on cranial ultrasound, although no association was found with developmental scores at 2 and 5 years of age (188). In another study of very preterm infants, another polymorphism associated with higher IL-6 synthesis (-572 C allele) found no difference in the frequency of cranial ultrasound abnormalities but worse cognitive development(69).

Further (albeit indirect) evidence that genetic variation influences the risk of brain damage related to inflammation comes from studies of genetic variation in apolipoprotein E, a lipid transport protein that also plays a role in repair after cell injury. The three common alleles of this protein differ only of the basis of one or two amino acids. Among infants who underwent cardiopulmonary bypass for repair of congenital heart disease, the ε2 allele of

apolipoprotein E was associated with lower scores on a standardized measure of psychomotor development at one year of age(189). In another study, early cognitive functioning at two years of age was worse among infants with ε2 or ε3 allele(190).

Finally, as mentioned above, a polymorphism which results in increased production of the anti-inflammatory cytokine IL-10, has been associated with a marked decrease in the risk of cerebral white matter damage. In a study of 39 very low birth weight infants(191) and another study of 15 very preterm infants(77) with the GG allele for Il-10(-1082) genotype, none had cerebral white matter damage, as compared to 10% (30/313) of infants with the GA- or AA-allele. Of 15 infants with the GG-allele for whom developmental follow-up data were available, none had cerebral palsy, as compared to the expected 10% of those children without this allele(77).

Summary

More than 30 years ago, evidence from epidemiological studies and experiments in animals indicated that infection remote from the brain is a potential cause of cerebral white matter damage in human neonates. Since that time, a large body of evidence has accumulated suggesting that the link between infection and brain damage involves various mediators of inflammation, including cytokines, chemokines, and immune cells. Inflammatory mediators also are involved in brain-damaging processes that follow energy deprivation, as may occur with intrapartum asphyxia. Equally important is the role of cytokines in modulation of inflammation and repair after inflammation-related brain damage. Genetic polymorphisms in genes coding for inflammatory mediators could explain, at least in part, genetic susceptibility to pre- and peri-natal brain damage. Strategies to reduce the frequency and extent of pre- and perinatal brain damage may derive from therapeutic interventions which either enhance the production or activity of certain "damage protectors" (e.g., anti-inflammatory cytokines), or inhibit the production or activity of specific "damage mediators" (e.g., inflammatory cytokines).

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