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Postnatal Sepsis, Necrotizing Entercolitis, and the Critical Role of Systemic Inflammation in White Matter Injury in Premature Infants

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Approximately 60 000 infants per year in the United States have a birth weight < 1500 g. About 5% of the nearly 55 000 who survive the newborn period later exhibit the spastic motor deficits categorized as cerebral palsy, and 25% to 50% exhibit cognitive/behavioral deficits. Although the neuropathology underlying this neurologic disability is diverse,[1] the dominant lesion appears to be white matter injury, characterized primarily by microscopic areas of focal necrosis deep within the white matter and more diffuse injury to premyelinating oligodendrocytes (pre-OLs), that is, noncystic periventricular leukomalacia (PVL). Classic cystic PVL, characterized by macroscopic areas of necrosis with subsequent cyst formation, is now rare. Although neuronal abnormalities may accompany the white matter injury,[2] white matter abnormality appears to be the dominant lesion. In this issue of the *The Journal*, Shah et al[3] present data demonstrating that the detection of noncystic PVL by magnetic resonance imaging (MRI) is a common sequela of postnatal sepsis, a very common systemic complication in preterm infants. These findings are of particular value because they define an anatomic substrate for the subsequent neurodevelopmental disability in preterm infants with postnatal sepsis and have important implications for the pathogenesis of noncystic PVL.

Shah et al evaluated 192 unselected preterm infants born before 30 weeks' gestation and found that 68 (35%) experienced at least 1 episode of postnatal sepsis (first positive blood culture at a median age of 8 days). Four of these 68 infants also had necrotizing enterocolitis (NEC), and another 5 had NEC without sepsis. Coagulase-negative staphylococci (CONS) accounted for 81% of all cases of sepsis. This high incidence of postnatal sepsis in preterm infants and the predominance of CONS have been described previously.[4-7] The study of Shah et al has 4 major findings. First, those infants with sepsis/NEC (n = 73) had, by MRI at term equivalent, a high incidence (80%) of white matter abnormalities consistent with noncystic PVL. Second, similarly high incidences of white matter abnormalities were found in infants with any sepsis (with or without NEC), with CONS sepsis, and with sepsis caused by other organisms. Third, at age 2 years, the infants with any sepsis/NEC had an increased risk of having lower Bayley Mental Development Index (P = .05) and Psychomotor Development Index (P = .03) scores, even after adjustment for adverse perinatal/neonatal characteristics. Importantly, when adjusted for white matter abnormalities, the lower scores in the septic infants disappeared. Fourth, the 9 infants with NEC had the poorest outcomes; all had white matter abnormalities, and in 6 the abnormality was moderate/severe. A strong independent relationship between NEC and subsequent neurodevelopmental disability has been described previously.[8-10]

The earlier demonstrations of neurodevelopmental disability after postnatal sepsis in preterm infants raised the important question of the anatomic substrate. Thus, in a large study of more

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than 6000 premature infants (401 to 1000 g at birth), infants with sepsis alone (without meningitis) had 50% to 100% higher rates of cognitive deficits, cerebral palsy, and other neurodevelopmental disabilities compared with uninfected infants.[11] Systematic MRI was not performed in this large and important epidemiologic study. The data of Shah et al indicate that white matter disease, similar or identical to noncystic PVL, is the principal anatomic substrate. A similar white matter abnormality detectable by MRI at term equivalent has been identified as the principal anatomic correlate for neurodevelopmental disability in preterm infants in general.[12] Thus, preterm infants with postnatal sepsis should be considered at high risk for white matter abnormalities, and preventative measures beyond antibiotics should be considered to prevent this pathology (see later).

The data of Shah et al have important implications for the pathogenesis of white matter disease in preterm infants. PVL and its variants appear to be related to 2 major initiating mechanisms, ischemia and infection/inflammation.[1] Concerning the latter, although the early seminal work of Gilles et al[13] noted a relationship among gram-negative sepsis, endotoxin, and PVL, most recent studies have focused on a pathogenetic role of maternal intrauterine infection and fetal systemic inflammation.[14] The hypothesis is that the fetal systemic inflammatory response leads to white matter injury, perhaps through systemic cytokine release. Various difficulties with the cytokine hypothesis have been noted;[15,16] however, neuropathologic studies of PVL have shown a brisk inflammatory response in white matter mediated by the brain's resident immune cells, the microglia.[17,18] Whether this brain inflammatory response is secondary to systemic inflammation, hypoxia-ischemia, or both (see later) remains unclear. Nevertheless, prominent microgliosis is present in the diffuse component of noncystic PVL and is likely associated with the release of compounds toxic to pre-OLs. Available experimental and clinical evidence suggests that these toxic compounds are a combination of free radicals (reactive oxygen and nitrogen species), glutamate, and cytokines.[1] Pre-OLs exhibit a maturation-dependent vulnerability to free-radical attack and glutamate-mediated excitotoxicity, the 2 major downstream mechanisms leading to pre-OL death in PVL.[1] Cytokines in the brain amplify both of these mechanisms, leading to generation of free radicals and changes in glutamate release and uptake that result in enhanced excitotoxicity.[1,19] Interferon-γ and tumor necrosis factor-α appear to be especially important. Because microglia are in particular abundance in normal cerebral white matter during the preterm period as part of normal development,[20] a large microglial population is in the right place at the right time to be activated and lead to white matter injury (see later).

As noted earlier, ischemia is the other principal upstream initiating mechanism in the pathogenesis of PVL.[1] Could postnatal sepsis lead to ischemia as well as inflammation? Hypotension associated with sepsis is well known, and in the study of Shah et al, approximately 40% of the septic infants required inotropic support.[3] However, a similar proportion of the nonseptic infants required such support as well. More importantly, it is now clear that decreased blood pressure per se is not reliably predictive of decreased cerebral blood flow.[1] The status of cerebrovascular autoregulation is central. Recent work has demonstrated that a pressure-passive cerebral circulation is very common in preterm infants,[21] and that the presence of systemic cytokines appears to be associated with a disturbance in cerebrovascular autoregulation.[22] Both postnatal sepsis and NEC are associated with sharply elevated concentrations of proinflammatory cytokines systemically.[23] Thus, such infants may be more likely to exhibit diminished cerebral blood flow at a given blood pressure due to the presence of cerebrovascular autoregulatory impairment. This possibility is of extreme importance, because abundant experimental data show that infection/inflammation can *potentiate* hypoxic-ischemic insults to the brain and convert a subthreshold insult to a seriously damaging event.[24-28] This critical synergistic interaction between infection/inflammation and hypoxia-ischemia depends in part on the relative timing of the 2 insults, but in general, when hypoxia-ischemia occurs within several hours of the inflammatory insult, pronounced potentiation is

apparent. These observations suggest that a continuous noninvasive assessment of cerebral circulation (by, eg, near-infrared spectroscopy) or of cerebral function (by, eg, conventional or amplitude-integrated electroencephalography) should be done in septic preterm infants.

How might postnatal sepsis, particularly due to CONS (by far the predominant organism in preterm postnatal sepsis), lead to white matter injury? The clinical, pathological, and experimental data related to the link between infection/inflammation and white matter injury has focused on gram-negative infection and lipopolysaccharide (LPS) (or "endotoxin"). The data suggest that systemic LPS results in the expression of thousands of genes in the brain,[29] including those encoding various Toll-like receptors (TLRs), nuclear factor-κB, antioxidants, oxidants, and cytokines.[30] Most of the responses involve brain microglia, and the TLRs are especially important. These specific cell-surface receptors of innate immunity respond to specific molecular motifs (so-called "pathogen-associated molecular patterns" [PAMPs]) shared by the products of entire classes of microorganisms; for example, the LPS motif shared by gram-negative organisms is recognized by TLR4, and the peptidoglycan motif shared by gram-positive microorganisms is recognized by TLR2.[31] The role of TLR4 as a mediator of white matter injury with LPS exposure has been well established in experimental models.[32] Activation of TLR2 in microglia has led to neurodegeneration in a mouse model,[33,34] but white matter or pre-OLs have not been studied explicitly. It is noteworthy that pre-OLs, like microglia, express TLR2. The possible mode of entry of the PAMP for CONS into the brain is unclear. By analogy with LPS, consideration should be given to movement of the bacterial product across a blood– brain barrier that is immature or compromised by cytokine or other toxic insults or across brain regions without a blood– brain barrier (ie, circumventricular organs), or to propagation of the PAMP-mediated immune signal from the systemic circulation to the brain by other cellular or molecular mechanisms.[1,30,35-37]

NEC, which was uniformly associated with white matter injury in the study of Shah et al,[3] likely provokes the aforementioned inflammatory mechanisms. NEC is associated with a particular vigorous systemic inflammatory response that includes not only cytokines, but also sharply elevated LPS concentrations, even in the absence of gram-negative bacteremia.[23] As noted earlier, LPS and its associated PAMP are known to lead to white matter injury through activation of microglial TLR4.[32]

Involvement of TLRs in the amplification as well as the generation of white matter injury may be important. Recently, endogenous ligands for TLRs have been found to be released due to tissue injury.[38] These ligands include heat-shock proteins, which activate TLR2 and/or TLR4, and such extracellular matrix components as biglycan and hyaluronan, which activate TLR2 and TLR4. A role for such ligands in the amplification of ischemic brain injury has been reported recently.[39,40]

What are the implications of these data for intervention? It appears that antibiotic therapy is not sufficient to prevent brain injury with sepsis. Because ischemia and infection/inflammation potentiate each other to cause white matter injury, great care is mandatory to avoid cerebral ischemia in the setting of sepsis. Increased direct monitoring of cerebral hemodynamics and physiological function also may be important. Specific therapies to study include antimicroglial agents (eg, minocycline), interventions that counteract free-radical generation or accumulation (eg, oxygenase and nitric oxide synthase inhibitors, free-radical scavengers, antioxidant enzyme mimetics), antiexcitotoxic agents (eg, topiramate, memantine), and antiapoptotic compounds (eg, erythropoietin, growth factors). Experimental observations support the potential value of these agents.[1] Because endogenous ligands for TLRs are released with tissue injury and activate TLRs to amplify cellular injury, agents targeted to TLRs may be of particular value. All of these are fertile topics for future research.

Glossary

CONS, Coagulase-negative staphylococcus (CONS); LPS, Lipopolysaccharide; MRI, Magnetic resonance imaging; NEC, Necrotizing enterocolitis; PAMP, Pathogen-associated molecular pattern; pre-OL, Premyelinating oligodendrocyte; PVL, Periventricular leukomalacia; TLR, Toll-like receptor.

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