33. Raby BA, Silverman EK, Kwiatkowski DJ, Lange C, Lazarus R, Weiss ST. ADAM33 polymorphisms and phenotype associations in childhood asthma. J Allergy Clin Immunol. 2004;113:1071-8.

34. Chen C, Huang X, Sheppard D. ADAM33 is not essential for growth and development and does not modulate allergic asthma in mice. Mol Cell Biol. 2006;26:6950-6.

35. Schedel M, Depner M, Schoen C, Weiland SK, Vogelberg C, Niggemann B, et al. The role of polymorphisms in ADAM33, a disintegrin and metalloprotease 33, in childhood asthma and lung function in two German populations. Respir Res. 2006;7:91.

Systemic infection and brain injury in the preterm infant

Richard A. Polin*

In this issue of Jornal de Pediatria, Silveira et al.[1] investigated risk factors for the development of periventricular leukomalacia (PVL) in a cohort of very low birth weight (VLBW) infants. A significantly greater number of infants with PVL had documented sepsis and/or were ventilated for more than 24 hours. This well-designed study adds supportive evidence for the role of postnatal infection in the pathogenesis of PVL.[2] While the data are provocative, it is unclear from this article how the timing of the sepsis episodes is related to the development of PVL. If the study infants all had early-onset sepsis, it is somewhat surprising that coagulase negative staphylococcus was the most common pathogen recovered. In the USA that microorganism would be a rare cause of early-onset sepsis. If the study infants had late-onset infections, the question of timing of the infectious episode with the onset of PVL is particularly important. A major limitation in this study is the lack of data on the likelihood of antenatal infection. That question is particularly important given the high rate of bacteremia with *Mycoplasma* and *Ureaplasma* in infants born prematurely.[3] A third weakness in this study (as noted by the authors) is the lack of magnetic resonance imaging (MRI) information; MRI is a more sensitive way to diagnose PVL. Given these limitations, however, the authors should be congratulated for addressing this question.

See related article on page 211

PVL is strongly associated with the development of cerebral palsy.[4] The pathogenesis of PVL has been linked with disorders resulting in hypoperfusion of the brain (e.g., hypoxia-ischemia, hypotension patent ductus arteriosus with reversed diastolic flow, etc.) and perinatal (antenatal and postnatal) infection. The final common pathway for both etiologies is likely to include microglial activation, cytokine and glutamate release and free radical production (Figure 1).

Late-onset infections are common among VLBW infants and up to 25% develop a systemic bacterial or fungal infection; 5-10% have documented meningitis.[6] Neurological abnormalities are common among survivors. In a recent prospective observational study by Stoll et al. (n = 6,093)[7] preterm infants with proven systemic infections, clinical infection (negative blood culture), necrotizing enterocolitis (NEC) and meningitis were all more likely to exhibit neurological and growth abnormalities compared with an uninfected control group. Hearing impairment was more common in infants with NEC and in those infected with gram-negative microorganisms. In a case-control study, O'shea et al. also noted an association between clinical chorioamnionitis, sepsis and cerebral palsy.[8]

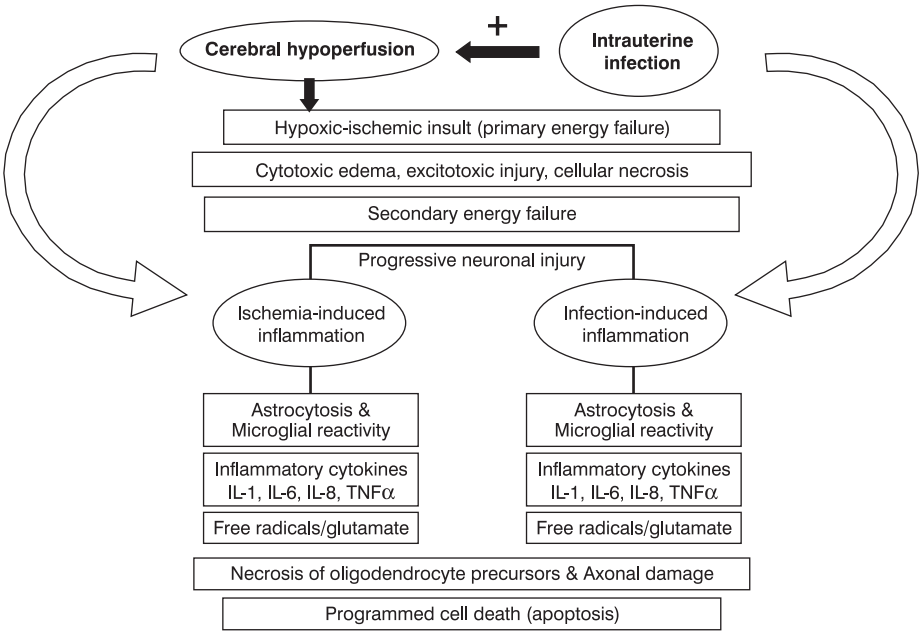
Over the past 10 years, there has been considerable interest in the relationship of antenatal infection and cerebral palsy.

* MD. Professor of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, USA.

No conflicts of interest declared concerning the publication of this editorial.

Suggested citation: Polin RA. Systemic infection and brain injury in the preterm infant. J Pediatr (Rio J). 2008;84(3):188-191.

doi:10.2223/JPED.1784



Modified from Rezaie & Dean.[5]

Figure 1 - Pathogenesis of periventricular leukomalacia

Data from the recent Alabama Preterm Birth Study demonstrated that 23% of preterm infants (23-32 weeks gestation) are bacteremic at the moment of birth with *Ureaplasma urealyticum* or *Mycoplasma hominis*.[4] Infection is more common in preterm infants delivered after spontaneous labor and inversely correlated with gestational age. Importantly, bacteremia is strongly associated with an elevation in systemic interleukin (IL)-6 levels (OR = 5.82, 95%CI 3.15-10.78).

There is a strong association between chorioamnionitis and cerebral palsy in term and preterm infants: however, a cause and effect relationship has not been proven.[9] The possible links between antenatal infection and neurological injury are based upon the following observations: 1) antenatal infection is commonly associated with preterm birth[10]; 2) women with chorioamnionitis delivering preterm infants have elevated serum cytokine levels,[11] as do their infants[12]; and 3) infants who develop PVL and intraventricular hemorrhage have elevated cytokine levels in umbilical cord blood.[13] It is unclear, however, how a systemic cytokine response in a fetus or neonate is capable of injuring the central nervous system. There are several possibilities. First of all, cytokines may be actively transported across the intact blood brain barrier. Data from experimental animals indicate that radiolabeled cytokines are capable of crossing the blood brain barrier; however, most of the radiolabel resides in brain endothelia and does not get into brain parenchyma.[14,15] The second potential mechanism is via activation of the hypothalamic-pituitary axis.[16] Data suggest that responses to low dose endotoxin are partially mediated through the vagus nerve. The third pathway is leakage of cytokines across the blood brain barrier at circumventricular organs.[17] Circumventricular organs (midline structures that border the third and fourth ventricle) have permeable fenestrated capillaries. These "barrier deficient sites" are recognized as important locations for communication between the blood and cerebrospinal fluid. Cytokines may also "leak" across an intact blood brain barrier when the permeability has been altered by inflammation. Stolp et al. demonstrated that there is a restricted period in brain development when the blood brain barrier is susceptible to systemic inflammation.[18] The fourth potential pathway is production of cytokines by cells of the blood brain barrier. In this regard, systemic injection of IL-1 induces intense transcriptional activity in cells of the blood brain barrier, which in turn produce IL-1 and tumor necrosis factor-alpha (TNF-α).[19,20] The fifth possibility is production of cytokines by cells infiltrating the central nervous system.[21] The final possible mechanism is alteration of antenatal or postnatal hemodynamics by systemic inflammation. Yanowitz et al. demonstrated that there is an inverse relationship between systolic, mean and diastolic blood pressures and cord-blood IL-6 levels.[22] Similarly, using an experimental animal model, Garnier et al. demonstrated that when fetal sheep receive intravenous endotoxin, blood flow to the placenta and cerebral oxygen delivery decrease.[23]

Another possibility is that the systemic cytokine response is only a marker for local production of cytokines within the central nervous system. Elovitz et al. have shown that the

magnitude of the cytokine response to injection of endotoxin in a mouse fetus varies considerably between organs.[24] In a study of preterm infants (< 33 weeks gestation with and without PVL), Viscardi et al. observed that only cerebrospinal fluid levels of IL-6 and TNF-α correlated with development of PVL; systemic cytokine levels did not.[25] Similar observations were made by Ellison et al.[26] These data suggest that locally produced brain derived cytokines may be more important in the pathogenesis of brain injury.

There are many animal models indicating that white matter injury may be induced in the fetus by injection of endotoxin or bacterial cell products.[27] However, it must be emphasized that the patterns of cytokine elevation associated with infection are complex and thousands of inflammatory genes are upregulated.[28] Moreover, cytokines play a critical role in normal brain development and depending on the local milieu cytokines can be neuroprotective or neurotoxic. This suggests that a single anti-cytokine therapy is likely to be ineffective in the prevention of brain injury. Proteomics offers the possibility of identifying women with chorioamnionitis before their infants are born.[29] Early identification of women with subclinical chorioamnionitis and treatment offer the best opportunity to reduce the likelihood PVL.

References

1. Silveira RC, Procianoy RS, Dill JC, da Costa CS. Periventricular Leukomalacia in very low birth weight preterm neonates with high risk for neonatal sepsis. J Pediatr (Rio J). 2008;84:211-6.
2. Drougia A, Giapros V, Krallis N, Theocharis P, Nikaki A, Tzoufi M, et al. Incidence and risk factors for cerebral palsy in infants with perinatal problems: a 15-year review. Early Huma Dev. 2007; 83:541-7.
3. Goldenberg RL, Andrews WW, Goepfert AR, Faye-Petersen O, Cliver SP, Carlo WA, et al. The Alabama Preterm Birth Study: umbilical cord blood Ureaplasma urealyticum and Mycoplasma hominis cultures in very preterm newborn infants. Am J Obstet Gynecol. 2008;198:43.e1-5
4. Volpe JJ. Neurology of the newborn. 4th edition. Philadelphia, PA: WB Saunders; 2001.
5. Rezaie P, Dean A. Periventricular leukomalacia, inflammation and white matter lesions within the developing nervous system. Neuropathology. 2002;22:106.
6. Carey A, Saiman L, Polin RA. Hospital-Acquired infections in the NICU: Epidemiology for the new millennium. Clin Perinatol. 2008; 35:223-49.
7. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz S, Vohr E, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA. 2004;292:2357-65.
8. O'Shea TM, Klinepeter KL, Meis PJ, Dillard RG. Intrauterine infection and the risk of cerebral palsy in very low-birth weight infants. Paediatr Perinat Epidemiol. 1998;12:72-83.
9. Wu YW, Escobar GJ, Grether JK, Croen LA, Greene JD, Newman TB. Chorioamnionitis and cerebral palsy in term and near-term infants. JAMA. 2003;290:2677-84.
10. Romero R, Mazor M, Wu YK, Sirtori M, Oyarzun E, Mitchell MD, et al. Infection in the management of preterm labor. Semin Perinatol. 1988;12:262-79.
11. Greig PC, Murtha AP, Jimmerson CJ, Herbert WN, Roitman-Johnson B, Allen J. Maternal serum interleukin-6 during pregnancy and during term and preterm labor. Obstet Gynecol. 1997;90:465-9.
12. Shalak LF, Laptook AR, Jafri HS, Ramilo O, Perlman JM. Clinical chorioamnionitis, elevated cytokines, and brain injury in term infants. Pediatrics. 2002;110:673-80.
13. Goepfert AR, Andrews WW, Carlo W, Ramsey PS, Cliver SP, Goldenberg RL, et al. Umbilical cord plasma interleukin-6 concentrations in preterm infants and risk of neonatal morbidity. Am J Obstet Gynecol. 2004;191:1375-81.
14. Banks WA, Kastin AJ, Broadwell RD. Passage of cytokines across the blood brain barrier. Neuroimmunomodulation. 1995;2: 241-8.
15. Hashimoto M, Ishikawa Y, Yokota S, Goto F, Bando T, Sakakibara Y, et al. Action site of circulating interleukin-1 on the rabbit brain. Brain Res. 1991;540:217-23.
16. Quan N, Herkenham M. Connecting cytokines and brain: a review of current issues. Histol Histopathol. 2002;17:273-88.
17. Blatteis CM, Hales JR, McKinley MJ, Fawcett AA. Role of the anteroventral third ventricle region in fever in sheep. Can J Physiol Pharmacol. 1987;65:1255-60.
18. Stolp HB, Dziegielewska KM, Ek CJ, Habgood MD, Lane MA, Potter AM, et al. Breakdown of the blood-brain barrier to proteins in white matter of the developing brain following systemic inflammation. Cell Tissue Res. 2005;320:369-78.
19. Brady LS, Lynn AB, Herkenham M, Gottesfeld Z. Systemic interleukin-1 induces early and late patterns of c-fos mRNA expression in brain. J Neurosci. 1994;14:4951-64.
20. Quan N, Whiteside M, Herkenham M. Time course and localization patterns of interleukin-1b messenger RNA expression in brain and pituitary after peripheral administration of lipopolysaccharide. Neuroscience. 1998;83:281-93.
21. Del Maschio A, De Luigi A, Martin-Padura I, Brockhaus M, Bartfai T, Fruscella P, et al. Leukocyte recruitment in the cerebrospinal fluid of mice with experimental meningitis is inhibited by an antibody to junctional adhesion molecule (JAM). J Exp Med. 1999;190:1351-6.
22. Yanowitz TD, Jordan JA, Gilmour CH, Towbin R, Bowen A, Roberts JM, et al. Hemodynamic disturbances in premature infants born after chorioamnionitis: association with cord blood cytokine concentrations. Pediatr Res. 2002;51:310-6.
23. Garnier Y, Coumans A, Berger R, Jensen A, Hasaart TH. Endotoxemia severely affects circulation during normoxia and asphyxia in immature fetal sheep. J Soc Gynecol Investig. 2001; 8:134-42.
24. Elovitz MA, Mrinalini C, Sammel MD. Elucidating the early signal transduction pathways leading to fetal brain injury in preterm birth. Pediatr Res. 2006;59:50-5.
25. Viscardi RM, Muhumuza CK, Rodriguez A, Fairchild KD, Sun CC, Gross GW, et al. Inflammatory markers in intrauterine and fetal blood and cerebrospinal fluid compartments are associated with adverse pulmonary and neurologic outcomes in preterm infants. Pediatr Res. 2004;55:1009-17.
26. Ellison VJ, Mocatta TJ, Winterbourn CC, Darlow BA, Volpe JJ, Inder TE. The relationship of CSF and plasma cytokine levels to cerebral white matter injury in the premature newborn. Pediatr Res. 2006;57:282-6.

27. Duncan JR, Cock ML, Scheerlinck JP, Westcott KT, McLean C, Harding R, et al. White matter injury after repeated endotoxin exposure in the preterm ovine fetus. Pediatr Res. 2002;52: 941-9.

28. Eklind S, Hagberg H, Wang X, Sävman K, Leverin AL, Hedtjärn M, et al. Effect of lipopolysaccharide on global gene expression in the immature rat brain. Pediatr Res. 2006;60:161-8.

29. Gravett MG, Novy MJ, Rosenfeld RG, Reddy AP, Jacob T, Turner M, et al. Diagnosis of intra-amniotic infection by proteomic profiling and identification of novel biomarkers. JAMA. 2004;292: 462-9.