Intrauterine Infection Linked to Cerebral Palsy

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RIVIERA MAYA, MEXICO — Prenatal exposure to intrauterine infection is emerging as a possible cause of many cases of cerebral palsy previously classified as idiopathic, Dr. Errol Norwitz said at a conference on obstetrics, gynecology, perinatal medicine, neonatology, and the law.

"Recent data suggest that it is the fetus's inflammatory response which causes problems both in terms of preterm labor and neuronal injury," said Dr. Norwitz, director of maternal-fetal medicine at Yale–New Haven Hospital, Conn. "Even in the absence of a positive amniotic fluid culture in women with chorioamnionitis, we see proinflammatory cytokines, prostaglandins, and other markers of infection."

Animal studies have demonstrated direct brain injury from such infections. Fetal rabbits exposed to intrauterine *Escherichia coli* infections develop white matter injuries, while fetal rhesus monkeys demonstrated brain injuries associated with chronic group B streptococcus intrauterine infections.

In human fetuses, epidemiologic evidence points to a similar association, with infection and brain injury leading to cerebral palsy, Dr. Norwitz said. "In normal- and low-birth-weight infants, we see an association between periventricular leukomalacia and both group B strep sepsis and histologic chorioamnionitis."

The premature labor associated with intrauterine infection appears to be triggered by the fetus's inflammatory response, as a way to escape the contaminated intrauterine environment. "What we are suggesting here is that the infectious agent gets into the baby by the ascending route or, rarely, across the placenta, and the baby's inflammatory response leads independently to preterm birth," Dr. Norwitz said. "It's a protective mechanism, because if the baby didn't do this, it would probably die in utero due to overwhelming sepsis."

The exact mechanism of neuronal damage remains unknown, he said. "There appears to be a fetal vasculitis with activation of leukocytes. This causes a huge surge in proinflammatory cytokines, with an imbalance between the proinflammatory and the anti-inflammatory cytokines. Some of the activated cells appear to cross the blood-brain barrier and cause damage to the brain."

In fact, he said, some studies have shown that elevated proinflammatory cytokines are common in the brains of patients with cerebral palsy and periventricular leukomalacia. A 1997 study found tumor necrosis factor–α, interleukin-1 β, or interleukin-6 in 88% of cases with the lesions, but only 18% of cases without them (Am. J. Obstet. Gynecol. 1997;177:406-11). Another study of neonatal brains with and without the lesions concluded that an immune-mediated inflammatory process might play a role in the development of such lesions, with TNF-α, a myelinotoxic factor, perhaps playing the major role (Neurology 2001;56:1278-84).

Interestingly, higher levels have also been noted in the serum and amniotic fluid of neonates who later developed cerebral palsy (Ann. Neuro. 1999;44:665-75; Am. J. Obstet. Gynecol. 1997;117:19-26).

Given these findings, questions arise about a possible protective effect of immediate cesarean delivery in mothers with intrauterine infection, Dr. Norwitz said. "Right now, intrauterine infection is an absolute indication for delivery, but in some cases, it can take 18-36 hours to get these babies delivered. Are these kids, sitting in this infected environment for all that time, at increased risk? Once we make the diagnosis, should we be getting that baby out immediately by cesarean? Currently there is no indication for this, but I wouldn't be surprised if this changes in 5-10 years, as our understanding of this area develops."

Estimates are that only 10% of cerebral palsy cases are due to an identifiable intrapartum event, he said. But this statistic and the evolving understanding of the possible role of infection don't ease the difficulty of defending such cases in court, cautioned John Scully, a defendant's lawyer from Dallas. "The jury comes in with a preconceived notion that all CP is due to birth injury, and could have been avoided if a C-section was performed early enough. It's very difficult to convince them that in 90% of the cases, the cause is simply not known."

The conference was sponsored by Boston University. ■