Intrauterine Infection Linked to Cerebral Palsy

by Michael G. Sullivan
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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. “The absence of a puerperal fluid culture in women with oligohydramnios, we see proinflammatory cytokines, prostaglandins, and others.” 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 intratropical infection. In human fetuses, epidemiologic evidence points to a similar association, with infection and brain injury leading to cerebral palsy. Dr. Norwitz said “In normal term and low-birth-weight infants, we see an association between periventricular leucomalacia and both group B strep sep sis and histologic chorioamnionitis.”

The premature labor associated with intrauterine infection appears to be triggered by the fetus’s inflammatory response to escape the contaminated intrauterine environment. “What we are suggesting here is that the infectious agent gets into the baby by 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 prenatal 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, 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-alpha (TNF-a), interleukin 1beta, or interleukin 6 in 88% of cases with the lesions, but only 18% of cases without them (Am. J. Obstet. Gynecol. 1997;177:466-41). Another study of neuronal biomarkers in cases with the lesions concluded that an immune-mediated inflammatory process might play a role in the development of such lesions, with TNF-a, a myelomonoctytic 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 cerebro- palsy (Ann. Neuro. 1999;44:665-75; Am. J. Obstet. Gynecol. 1997;177:19-26). Given these findings, questions arise about the 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 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 intra partum event, he said. But this statistic and the prevailing 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 cases of cerebral palsy are due to birth injury, and could have been avoided if a C-section was performed early enough. It’s very difficult to convince them otherwise, especially when the cause is simply not known.”

The conference was sponsored by Boston University.