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Editorial

Necrotizing Enterocolitis: Neurodevelopmental ''Risky Business''

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From the neonatal gut to the postnatal brain — what is the connection, above and beyond the obvious? Certainly, optimal nutrition for extremely premature infants enhances a baby's potential for a good neurodevelopmental outcome. Yet, pathophysiologic conditions such as neonatal necrotizing entercolitis (NEC) continue to be an ''albatross around our neck'' in the neonatal intensive care unit (NICU). Although NEC was first described in the 19th century, this disorder has progressed to be a major neonatal problem since the advent of NICUs in the 1960s. Despite multiple descriptive studies, clinical reports, and intense basic science study, the etiology of NEC remains relatively undefined, although common multiple risk factors implying a multifactorial etiology have been suggested. These commonly identified ''risk factors'' for NEC — hypoxia, enteral non-breast milk feeding, bacteria and prematurity — all potentially provide ''substrate'' for possible development of NEC.[1] Unfortunately, the disease can strike without warning, and these risk factors are nonspecific and ubiquitous.

In this issue of the Journal, Salhab et al.[2] document serious and problematic neurodevelopmental morbidities in short-term follow-up in extremely low-birth-weight infants with documented NEC. Utilizing a retrospective case–control analysis, the author described the clinical courses and neurodevelopmental outcomes of a cohort of extremely low-birth-weight infants with ''medical'' NEC that did not require surgical intervention (clinical illness characterized by hematochezia, pneumatosis intestinalis, etc.), and a group of infants for whom acute surgical intervention was needed.

Although NEC may initially express itself within the context of a variety of clinical circumstances (e.g. the most common perhaps is that of simply being a premature infant), the ''final common pathway'' of the disorder is that of localized or diffuse intestinal injury with ultimate progressive mucosal transmural necrosis in the most severe of cases. (Note that NEC should not be considered just a gut ''injury'' secondary to some direct primary insult, but likely is the end-result of the GI tract's *response* to pathophysiologic stress.) A detailed and scientific understanding of NEC still rests ''below the water surface'', and is not in clear view.

Salhab and colleagues describe a group of infants with NEC and age-matched controls who were born at an average gestational age of 26 weeks with a birthweight of approximately 770 to 780 g, and received close neurodevelopmental follow-up at 18 to 22 months corrected age. A substantial portion of infants with NEC were noted to have significant psychomotor delay, along with an abnormal neurologic examination. The diagnosis of NEC was made according to Bell's criteria[3] and included only those infants with Stage 2 disease (characterized by hematochezia, pneumatosis intestinalis or portal venous gas), and more advanced cases (Stage 3) in which there was more profound cardiovascular collapse with pneumoperitoneum. (The authors were wise to exclude infants with Bell's Stage 1 since it is not clear that such infants with nonspecific symptoms (such as abdominal distension and ileus) are appropriately identified as having NEC in the first place.)

The ''take home message'' from the authors is a sobering one — if an infant develops NEC, there is a significant likelihood of major neurologic morbidity. We all have experience with low-birth-weight infants who develop NEC (some of us with less experience; others, unfortunately, with more; such is the nature of the disease). In particular, consider those infants who do not have a fulminant life-threatening course but present with a bilious aspirate or two, a blood-streaked stool, and evidence of pneumatosis intestinalis on one or two abdominal radiographs, which then resolves. We may see an increase in apnea and bradycardia in these infants, and many babies may not even require initiation of mechanical ventilation at the time of onset of NEC. Frequently, these infants have concomitant bacteremia with a positive blood culture at the time of their acute illness. Likely, the bacteria are not causative of the initial disease, but merely a multiplying (noninnocent) bystander, which gains access to the bloodstream due to a breakdown in the intestinal mucosal defenses. We routinely treat these infants for 10 to 14 days with parenteral antibiotics and gut rest, and then cautiously reinitiate enteral feeds in a slow but progressive manner. Such infants may reachieve full enteral feeds within 10 days to 2 weeks except for the occasional infant who

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develops a stricture or short gut syndrome. The majority of infants with NEC will seemingly weather this illness and be discharged from the NICU along with their non-NEC compatriots.

However, as pointed out by the authors, the residua of NEC extends well beyond the gut. Although the numbers of infants in this study are relatively small, the infants described were at increased risk for a host of serious post-NEC medical issues, including chronic bronchopulmonary dysplasia, and a higher rate of subsequent culture-proven nosocomial sepsis. In particular, these episodes of sepsis, which were distant in time to the initial episode of NEC, were primarily associated with Gram negative bacilli and a smaller proportion with the Gram positive cocci. This observation suggests that once an infant with NEC ''heals'' his/her gut (as grossly evidenced by tolerating reinitiation of enteral feeds), there may continue to be a subclinical deficit in the intestinal mucosal defense barrier, which later evidences as Gram negative sepsis.

It is precisely this group of infants, who on follow-up, had a significantly lower psychomotor developmental index along with a greater incidence of an abnormal neurologic examinations. It is important to note that on follow-up, the number of infants with relative microcephaly (frontal–occipital head circumference less than the 5th percentile) was nearly one-quarter of the NEC cohort vs 0% in the controlled infants.

It is clear from this study and others[4] that NEC is not just an acute disorder limited to the confines of the NICU, but one that leaves its lasting mark with ongoing neurodevelopmental problems long after discharge. Not only did these infants have problems once they were home, but while in the hospital, they required a significantly longer intubation and mechanical ventilation time, and had longer hospital lengths of stay.

The particular abnormalities noted on neurologic examination in the NEC infants (spastic diplegia, spastic quadraplegia) suggest injury to periventricular white matter. Although these areas of the brain are known to be particularly sensitive to states of hypoperfusion, and these findings are certainly not limited to babies with NEC, the brain injury in the described infants with NEC, along with the history of infections, also suggests that other incriminating pathologic mechanisms, such as cytotoxic inflammatory mediators could be operative. There is an increasing body of evidence demonstrating a causal relationship between Gram negative infections, lipopolysaccharide, and subsequent white matter disturbance.[5] Thus, some of the lasting brain injury sustained by these infants may be cumulatively related to subsequent infection above and beyond any primary insult (such as hypotension), which preceded the initial bowel disorder. Given that the multifactorial etiology of NEC includes a critical role for inflammatory mediators such as platelet activating factor, endothelin-1, oxygen radicals, and tumor necrosis factor,[6] then release of these chemical intermediates in infants with NEC may then result in receptor-mediated brain white matter injury.

Despite its relative infrequency, NEC has clearly developed into an important public health issue because of its profound long-lasting effects on the health of premature infants, including neurodevelopmental function. As we counsel families and care for infants with NEC, we need to be cognizant that the effects of NEC are just not limited to time spent in the NICU. Along with a multitude of other issues that affect neurodevelopmental outcome (intraventricular hemorrhage, periventricular ischemic disease, etc.), the infant who develops NEC is at high risk for serious neurodevelopmental sequela.

Although not specifically discussed in this article, importance of human milk as a primary nutrition for premature infants is paramount. NEC is characterized by a profound impairment in local gastrointestinal mucosal integrity. Nutrition with fresh human milk has been observed to reduce the incidence of NEC in preterm infants.[7] Milk contains a variety of cellular and biologically active humoral components (e.g. immunoglobulins, prostaglandins) which enhance gastrointestinal mucosal integrity.[8] Optimizing the outcomes of infants with NEC will likely be more successful with prevention strategies rather than development of new treatment modalities. The ill preterm infant who is fed non-human milk nourishment may be at risk for ''nutritionally induced/related inflammation'' via release of endotoxin and vasoactive substances related to the intestinal proliferation of pathogenic bacteria with resultant gut and central nervous system injury.

NEC is a profound, life-altering event with major posthospitalization sequelae. Unfortunately, as we counsel parents whose infants have NEC, we may not be able to say ''all will be well'' just because the gut seemingly has healed. It is sometimes difficult to predict the eventual courses of preterm infants with grade II and III intraventricular hemorrhages, and severe chronic bronchopulmonary dysplasia because we know that there is wide variation in neurologic outcome. Can we say the same for NEC?

Knowing that an infant recovering from NEC may have nearly a 25% chance of developing microcephaly and serious developmental delay should make us pause as we sit down with families and discuss prognosis. As we care for the families of premature infants, we have an obligation to provide information as realistically (and sensitively) as possible. Our families need to hear the whole story, and not simply unfounded optimism, which may have little basis in fact. Hopefully, the future will bring scientific discoveries, which will further elucidate the etiology of NEC, result in bedside clinical advancements, and hopefully prevent the disease. Until that time, the unfortunate infant with NEC may pay a price for the rest of his/her life. As we take into account other complicating medical factors, counseling families that their infant should do well since he/she has recovered from a bout of NEC and now resumed full feeds is ''risky business''.

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