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Neurodevelopment of extremely preterm infants who had necrotizing enterocolitis with or without late bacteremia

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Abstract

Objective—To evaluate neurodevelopment following necrotizing enterocolitis (NEC) and late bacteremia, alone and together.

Study design—Sample included 1155 infants born at 23–27 weeks' gestation. NEC was classified by the Modified Bell's staging criteria and grouped as medical NEC or surgical NEC. Late bacteremia was defined as a positive blood culture after the first postnatal week. Neurodevelopment was assessed at 24 months corrected age. Multivariable models estimated the risk of developmental dysfunction and microcephaly associated with medical or surgical NEC with and without late bacteremia.

Results—Children who had surgical NEC unaccompanied by late bacteremia were at increased risk of Psychomotor Developmental Indices <70 [OR=2.7 (1.2, 6.4)], and children who had both surgical NEC and late bacteremia were at increased risk of diparetic cerebral palsy [OR=8.4 (1.9, 39)] and microcephaly [OR=9.3 (2.2, 40)]. In contrast, children who had medical NEC with or without late bacteremia were not at increased risk of any developmental dysfunction.

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Conclusion—The risk of neurodevelopmental dysfunction and microcephaly is increased in children who had surgical NEC, especially if they also had late bacteremia. These observations support the hypothesis that bowel injury might initiate systemic inflammation potentially affecting the developing brain.

Keywords

Infant, premature; necrotizing enterocolitis; sepsis; neurodevelopment

Among preterm infants followed to almost two years corrected age, those who had necrotizing enterocolitis (NEC) were at higher risk for poor cognitive and psychomotor development than infants without NEC.⁵⁻⁸ The risks were especially high for children who had an advanced stage of NEC or needed surgery.^{1, 7, 9}

Poor neurodevelopment might be a primary consequence of NEC or secondary to comorbidities of NEC such as bacteremia. Like preterm infants with NEC, infants with bacteremia are more likely than those without to have impaired cognitive and motor development at two years of age.¹⁰ Among infants with NEC, 30-60% also have a diagnosis of bacteremia during their stay in the neonatal intensive care unit (NICU).^{1, 5, 7, 11} Due to the significant overlap of these two diagnoses, the contribution to neurodevelopment of NEC alone versus NEC with bacteremia has been difficult to evaluate. The ELGAN Study provided us with an opportunity to evaluate the developmental correlates of NEC with and without accompanying bacteremia in a cohort of more than 1000 infants born before the 28th week of gestation.

METHODS

The sample for this analysis is a subset of the 1506 infants enrolled in the ELGAN Study, a prospective cohort study designed to identify characteristics and exposures that increase the risk of structural and functional neurologic disorders in preterm infants.¹² During the years 2002-2004, women delivering between 23 and 27 6/7 weeks of gestation at one of 14 participating institutions in 11 cities in 5 states were enrolled in the study. The enrollment and consent processes were approved by the individual institutional review boards.

Mothers were approached for consent either upon antenatal admission or shortly after delivery, depending on clinical circumstance and institutional preference. 1249 (83%) mothers consented and approximately 260 women were either missed or did not consent to participate for a total population of 1506 infants. After excluding 143 infants whose NEC or late bacteremia status was unknown, 49 who had an isolated perforation, 3 who did not undergo a protocol head ultrasound scan, and 156 who did not survive to 2 years and thus were not eligible for the 2 year evaluation, we studied a sample of 1155 infants.

Gestational Age

Gestational age (GA) estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasound before the 14th week of gestation (62%). When these were not available, reliance was placed sequentially on a fetal ultrasound at 14 or more weeks of gestation (29%), last menstrual period without fetal ultrasound (7%), and GA recorded in the log of the NICU (1%).

NEC Definition and Staging

NEC was defined by the Modified Bell's staging criteria.¹³ NEC "watch" referred to evaluations for NEC for a brief period (48 to 72 hours), without abdominal radiographs that

demonstrated pneumatosis. Stage 1 included infants who had “suspected” NEC and, despite the absence of pneumatosis on abdominal radiographs, were treated with antibiotics and suspension of enteral feedings for at least one week. Stage IIa represented infants who had pneumatosis, but did not experience clinical deterioration or laboratory derangements. Stage IIb included infants with pneumatosis and metabolic (acidosis) and/or hematologic changes (thrombocytopenia). Stage IIIa included infants with Stage IIb criteria plus respiratory or cardiovascular deterioration (e.g., increased need for respiratory support, new vasopressor requirement, oliguria, disseminated intravascular coagulation). Finally, Stage IIIb identified those infants who required surgical intervention, an exploratory laparotomy or placement of a Penrose drain. For analysis, we classify NEC as medical (Stages IIa, IIb, and IIIa) or surgical (Stage IIIb).

Early and Late Bacteremia

Because results from bacterial cultures were collected weekly on days 7, 14, 21, and 28, we do not know the precise day on which a positive blood culture result was obtained, although we do know the week. This led us to define early bacteremia as a positive blood culture in the first postnatal week and late bacteremia as a positive blood culture in weeks 2, 3 or 4. All positive cultures were considered in the analyses regardless of species.

Neurodevelopmental Diagnoses and Correlates at 2 years corrected age

Cerebral Palsy—When infants were 24 months corrected age, a certified examiner who was unaware of the neuroimaging findings in the NICU completed a comprehensive, standardized neurological exam.¹⁴ The findings from this examination were used to diagnose cerebral palsy and classify children as to cerebral palsy type (quadriplegia, hemiparesis, and diparesis).¹⁵

Gross Motor Functional Classification System—The neurological examiners rated each child using the Gross Motor Function Classification System.¹⁶ All children with a Gross Motor Functional Classification System of 2 or higher had been given a diagnosis of severe cerebral palsy.

Bayley Scales of Infant Development-Second Edition (BSID-II)—The BSID II was administered by certified examiners who were unaware of the infant’s medical history, including neuroimaging results. Infants were scheduled for assessment at 24 months post-term equivalent, with 77% evaluated between 23.5 and 27.9 months of age. A score of < 70, more than two standard deviations below the mean, represents significant mental (Mental Development Index; MDI) or psychomotor delay (Psychomotor Development Index; PDI).

Head Growth—The head circumference (HC) was measured as the largest possible occipital-frontal circumference and rounded to the closest 0.1 centimeter. The HC Z-score represents the number of standard deviations the infant’s HC is above or below the median HC of infants at the same GA in a referent sample.¹⁷

Statistical Analyses

The generalized form of the major null hypothesis evaluated is that neither NEC, nor documented late bacteremia, is associated with the risk of developmental dysfunctions (cerebral palsy diagnoses, GMFCS score, and low MDI and PDI scores) and small head circumference. We selected variables as confounders if they had been identified in the literature, or if in our data they were associated with both the exposure (late bacteremia or NEC) and with one of the developmental outcomes with probabilities $\leq .25$.¹⁸

Findings from Table I prompted us to model the contribution of late bacteremia and NEC (Bell stage IIa and higher) to the occurrence of developmental dysfunctions and microcephaly in

two different ways. One model has variables for late bacteremia only, medical NEC only, and the combination of late bacteremia and medical NEC (Table II). Another model is identical, but replaces medical NEC with surgical NEC (Table III). Both of these models excluded children who had other forms of NEC (*i.e.*, children with surgical NEC were excluded from the first model, and children with medical NEC were excluded from the second model).

The contributions of these variables are presented as odds ratios and 95% confidence intervals. All models are adjusted for public insurance (determined at the time of enrollment), maternal or fetal initiator of delivery, gestational age (23-24, 25-26, 27 weeks), birth weight Z-score < -1 and thrombosis of fetal stem vessels (including a missingness indicator). To account for the possibility that infants born at a particular hospital are more like each other than like infants born at other hospitals, a hospital cluster term (random effect) was included in all models. Empty cells prohibited our creating models of hemiparetic cerebral palsy risk.

RESULTS

Of the 1155 eligible children, 59 (5%) had medical NEC, 42 (4%) had surgical NEC, 70 (6%) had culture-proven early bacteremia, and 279 (24%) had culture-proven late bacteremia. The incidence of early bacteremia was not different in infants with and without NEC. In contrast, the incidence of late bacteremia was higher in infants with NEC than in those without NEC (34 vs 23%).

Table I documents the percent of infants in each diagnostic stratum (column headings) who were given the neurodevelopmental diagnosis listed (row headings). Children who had both late bacteremia and surgical NEC were almost eight times more likely to develop diparetic cerebral palsy than children who had neither (23 vs 3%). Among newborns who had late bacteremia, those who had medical NEC were twice as likely to develop diparetic cerebral palsy as newborns who did not have NEC (6 vs 3%). Compared with newborns who had neither late bacteremia nor NEC, those who had both (regardless of whether the NEC was medical or surgical) were twice as likely to have an MDI <70. The risk of a PDI <70 was less prominently increased among newborns who had the combination of NEC and late bacteremia (50 vs 27%). A head circumference more than two standard deviations below the median occurred four times more frequently among children who had both late bacteremia and surgical NEC (38%), and twice as frequently among children who had both late bacteremia and medical NEC (17%) than among children who had neither late bacteremia nor NEC (8%).

The central tendency and dispersion of MDI and PDI scores are presented in box and whiskers displays (Figure). The distribution of MDI values among children with medical NEC unaccompanied by late bacteremia does not differ from the distribution among children with neither bacteremia nor any NEC. The distribution tends to be modestly shifted to the left (lower MDI values) among children with bacteremia alone. The distribution is prominently shifted to the left among children who had surgical NEC (with or without bacteremia), and those with both medical NEC and bacteremia. In contrast, the differences among groups are much less prominent for PDI.

In multivariable models that adjusted for potential confounders, medical NEC, regardless of whether or not accompanied by late bacteremia, was not statistically significantly associated with any of the outcomes of interest (Table II). The combination of medical NEC and late bacteremia was associated with a doubling of the risk a low MDI and a low PDI, but because only 20 children had this combination, statistical significance was not achieved. Late bacteremia alone, however, was associated with an increased risk of an MDI <70.

In similar models with surgical NEC replacing medical NEC, three odds ratios associated with surgical NEC achieved statistical significance (Table III). Compared with children without any

surgical NEC or late bacteremia, those who had both late bacteremia and surgical NEC were at increased risk for diparetic CP and microcephaly, and the children who had surgical NEC unaccompanied by late bacteremia were at increased risk for a PDI <70.

DISCUSSION

In this large prospective cohort of extremely preterm infants, infants who developed medical NEC were not at statistically significantly increased risk of any of the developmental disorders we assessed or of microcephaly. On the other hand, children who had surgical NEC without accompanying late bacteremia were at an increased risk of a PDI <70. Children who developed surgical NEC and had culture-proven late bacteremia were at prominently increased risk of diparetic cerebral palsy and microcephaly. Children who had late bacteremia unaccompanied by surgical NEC were at increased risk of an MDI <70.

Despite the large size of our sample, only 59 children had medical NEC and 42 had surgical NEC. Consequently, the confidence intervals for the odds ratios are wide. In addition, the precise timing of the NEC diagnosis relative to the late bacteremia diagnosis is unknown. Strengths of our study include the large multi-center cohort, prospective collection of data about NEC and bacteremia, and outcome assessments by examiners who were unaware of neonatal exposures.

Our findings lead to several inferences. In one set, NEC pathophysiology is not in the causal chain. Rather, NEC conveys information about other risk factors. For example, NEC (as an indicator of bowel immaturity) might provide information about brain immaturity/vulnerability beyond that identified by gestational age, or it might be a marker for overall severity of illness during the NICU stay, or it might convey information about exposure to associated risk factors such as anesthesia during abdominal surgery.¹⁹ Conversely, NEC might be associated with the absence of factors that are associated with improved neurodevelopmental outcome, such as human milk.^{20, 21}

In a second set of inferences, NEC pathophysiology is in the causal chain. This set is especially plausible because our findings support the view that NEC can be classified by severity with no NEC as the referent, and increasing with medical NEC, surgical NEC without accompanying late bacteremia, and culminating with surgical NEC accompanied by late bacteremia.

The more severe the NEC, the greater the likelihood of intestinal wall inflammation²² and the greater the likelihood of intestinal barrier dysfunction.^{23, 24} Intestinal barrier dysfunction manifests as the translocation of inflammatory mediators into the systemic circulation. For example, platelet activating factor plasma levels are significantly higher in NEC patients than in controls and correlate with NEC severity.²⁵ Likewise, plasma levels of interleukin-6, a monocyte-derived cytokine, correlated with disease severity in infants with NEC²⁶; and, in another study, were highest among infants with severe NEC and in infants who had both sepsis and NEC, and less elevated among infants with either sepsis or NEC alone.²⁷

As one of the largest defense barriers of the infant, the neonatal gut regulates immune function and the inflammatory response. Disruption or injury to this barrier, as can occur in severe NEC, leads to an increased risk for bacterial translocation, leading to bacteremia, and increased production of pro-inflammatory mediators, which can initiate as well as propagate a systemic inflammatory response.²⁸ Unmitigated systemic inflammation contributes to neuronal injury and to the pathogenesis of other co-morbidities such as retinopathy of prematurity²⁹ and chronic lung disease.³⁰ The observation of adverse neurodevelopment with increased severity of disease (surgical versus medical NEC) or with the prolonged presence of diseased bowel (management with a penrose drain)³¹ supports the hypothesis that the injured gut contributes to a systemic inflammatory response, which, in turn, can affect the developing brain.

In previously published studies of premature infants, NEC predicted poor neurodevelopmental outcomes^{1, 3, 5-9, 11, 32} as well as cystic periventricular leukomalacia on head ultrasound¹ and white matter injury on magnetic resonance imaging.³³ Our findings may support some of these earlier studies. Furthermore, the relationship between NEC and poor neurodevelopmental outcomes is strongest among the more ill infants, as demonstrated by an advanced stage of NEC or need for surgical intervention.^{1, 7, 9, 32} Our findings are also consistent with these previous reports that children with NEC who required surgery were at greater risk for adverse neurodevelopment than infants with NEC who did not require surgery.

In a large study of extremely low birth weight infants, those who were infected were more likely to have cerebral palsy, low MDI and PDI scores, and microcephaly than children who did not have a neonatal infection.¹⁰ In our large sample of ELGANs, we found that in the absence of NEC, late bacteremia was associated with an increased risk of low MDI scores. Potential explanations for the outcome differences between these two studies are that the former study was a birth weight defined cohort of < 1000 grams, and our study was defined by a gestational age of < 28 weeks' gestation; and, the former study included the diagnoses of early-onset sepsis, suspected sepsis (culture negative) and NEC in their infected groups.

A unique contribution of our study to the NEC-sepsis literature is our distinction between early and late-onset sepsis, proven and clinically suspected sepsis, and NEC with or without late onset bacteremia. Each of these designations helped us evaluate the influence of NEC alone and NEC plus late bacteremia on later neurodevelopment.

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Abbreviations

BSID-II Bayley Scales of Infant Development-Second Edition

ELGAN	extremely low gestational age newborn
GA	gestational age
GMFCS	Gross Motor Functional Classification System
HC	head circumference
MDI	Mental Development Index
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
PDI	Psychomotor Development Index

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Figure 1.

In these box and whisker displays of the distribution of MDI and PDI, the median is indicated by the vertical line close to the middle of each box and the 25th and 75th centiles by the sides of each box. The dispersion of the MDI and PDI scores is indicated by the length of the horizontal lines that emanate from the box, as well as by the large dots, which identify outliers. There is a box for each combination of NEC and late bacteremia.

Table 1

The percent of all infants with or without late bacteremia who also had the NEC stage that heads each column who were given the neurodevelopmental diagnosis listed on the left (Column percents)

Neurodevelopmental correlate/diagnosis		Late bacteremia						Overall %	Row N
		Yes		No					
		NEC Stage grouping*							
		Surg	Med	No	Surg	Med	No		
Cerebral palsy diagnosis	Quadripareisis	0	6	7	8	3	6	6	59
	Diparesis	23	6	3	4	6	3	4	36
	Hemiparesis	0	0	2	4	6	1	2	18
GMFCS	2+	0	6	7	4	3	5	5	51
Bayley scales	MDI < 70	50	47	36	40	24	22	26	256
	PDI < 70	50	47	37	48	21	27	30	298
Head circumference Z-score	<-2	38	17	14	12	9	8	10	97
	≥ -2, <-1	23	28	24	24	15	16	18	183
Column N		14	20	245	28	39	809		1155

Overall % reveals the percent of infants with the neurodevelopmental diagnosis listed on the left regardless of the diagnostic stratum (column headings). **Row N** indicates the actual number of infants who were given the neurodevelopmental diagnosis listed on the left regardless of the diagnostic stratum. **Column N** indicates the actual number of infants placed within each of the six diagnostic strata (column headings).

* Surg is surgical NEC (Stage IIIb); Med is medical NEC (Stage IIa, IIb, IIIa)

Table 2

Odds ratios and 95% confidence intervals from multivariable logistic regression models* of the risk of each individual neurodevelopmental correlate/diagnosis associated with medical NEC unaccompanied by late bacteremia and late bacteremia unaccompanied by medical NEC and the co-occurrence of both medical NEC and late bacteremia. Each outcome is a dichotomy. For quadriplegia and diplegia the referent group is no cerebral palsy. For head circumference Z-score < -2 and head circumference Z-score ≥ -2 , < -1 the referent group is head circumference Z-score > -1 .

Neurodevelopmental correlate/diagnosis	Med NEC and Late Bacteremia (n=20)	Med NEC only (n=39)	Late Bacteremia only (N=245)	Neither (n=809)
Quadriplegic CP	1.6 (0.2, 14)	0.6 (0.1, 4.6)	1.3 (0.7, 2.6)	1.0
Diplegic CP	1.6 (0.2, 14)	1.5 (0.3, 7.5)	0.9 (0.4, 2.3)	1.0
GMFCS 2+	1.4 (0.2, 12)	0.6 (0.1, 4.3)	1.5 (0.8, 2.9)	1.0
Bayley MDI < 70	2.6 (0.9, 7.4)	1.0 (0.4, 2.4)	1.5 (1.1, 2.2)	1.0
Bayley PDI < 70	2.2 (0.8, 6.0)	0.8 (0.3, 1.9)	1.4 (0.95, 2.0)	1.0
HC Z-score < -2	2.0 (0.5, 8.4)	1.0 (0.3, 3.9)	1.5 (0.9, 2.6)	1.0
HC Z-score ≥ -2 , < -1	1.5 (0.5, 4.8)	0.9 (0.3, 2.4)	1.4 (0.9, 2.2)	1.0

* All models are adjusted for public insurance, maternal or fetal initiator for delivery, gestational age (23-24, 25-26, 27 weeks), birth weight Z-score < -1 and thrombosis of the fetal stem vessels of the placenta and include a random effect cluster term for birth hospital.

Table 3

Odds ratios and 95% confidence intervals from multivariable logistic regression models* of the risk of each individual neurodevelopmental correlate/diagnosis associated with surgical NEC unaccompanied by late bacteremia and late bacteremia unaccompanied by surgical NEC and the co-occurrence of both surgical NEC and late bacteremia. Each outcome is a dichotomy. For quadriplegia and diplegia the referent group is no cerebral palsy. For head circumference Z-score < -2 and head circumference Z-score ≥ -2 , < -1 the referent group is head circumference Z-score > -1

Neurodevelopmental correlate/diagnosis	Surg NEC and Late Bacteremia (n=14)	Surg NEC only (n=28)	Late Bacteremia only (n=245)	Neither (n=809)
Quadriplegic CP	---	1.1 (0.2, 5.2)	1.4 (0.7, 2.7)	1.0
Diplegic CP	8.4 (1.9, 39)	1.3 (0.1, 11)	0.9 (0.4, 2.4)	1.0
GMFCS 2+	---	0.7 (0.1, 5.9)	1.5 (0.8, 2.9)	1.0
Bayley MDI < 70	2.7 (0.8, 8.9)	2.2 (0.9, 5.2)	1.5 (1.05, 2.2)	1.0
Bayley PDI < 70	2.1 (0.6, 7.1)	2.7 (1.2, 6.4)	1.3 (0.9, 1.9)	1.0
HC Z-score < -2	9.3 (2.2, 40)	1.4 (0.3, 5.9)	1.5 (0.9, 2.6)	1.0
HC Z-score ≥ -2 , < -1	2.6 (0.5, 13)	1.9 (0.7, 5.4)	1.5 (0.98, 2.3)	1.0

* All models are adjusted for public insurance, maternal or fetal initiator for delivery, gestational age (23-24, 25-26, 27 weeks), birth weight Z-score < -1 and thrombosis of the fetal stem vessels of the placenta and include a random effect cluster term for birth hospital.