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Seizures in Extremely Low Birth Weight Infants Are Associated with Adverse Outcome

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Abstract

Objective—To examine risk factors for neonatal clinical seizures and to determine the independent association with death or neurodevelopmental impairment (NDI) in extremely low birth weight (ELBW) infants.

Study design—A total of 6499 ELBW infants (401–1000 g) surviving to 36 weeks postmenstrual age (PMA) were included in this retrospective study. Unadjusted comparisons were performed between infants with (n=414) and without (n=6085) clinical seizures during the initial hospitalization. Multivariate logistic regression modeling examined the independent association of seizures with late death (after 36 weeks PMA) or NDI after controlling for multiple demographic, perinatal, and neonatal variables.

Results—Infants with clinical seizures had a greater proportion of neonatal morbidities associated with poor outcome, including severe intraventricular hemorrhage, sepsis, meningitis, and cystic periventricular leukomalacia (all $P < .01$). Survivors were more likely to have NDI or moderate-

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severe cerebral palsy at 18 to 22 months corrected age (both $P < .01$). After adjusting for multiple confounders, clinical seizures remained significantly associated with late death or NDI (odds ratio 3.15 [95% confidence interval 2.37–4.19]).

Conclusions—ELBW infants with clinical seizures are at increased risk for adverse neurodevelopmental outcome, independent of multiple confounding factors.

Keywords

preterm; neurodevelopmental impairment; electroencephalography

The incidence of clinical seizures in the neonatal population is approximately 2 to 3 per 1000 live births, with higher rates between 9 and 11 per 1000 in preterm and low birth weight infants.[1,2] Neonatal seizures have been associated with adverse neurologic outcomes, including cerebral palsy and post-neonatal epilepsy,[3–6] but whether this is a causal relationship is controversial. Some suggest that seizures themselves cause brain injury and contribute to adverse outcome,[7–9] and others maintain that the underlying cause of seizures, such as asphyxia, hemorrhage, or infection, is the primary contributor to poor outcome.[10]

Studies reporting the long-term sequelae of neonatal seizures have primarily focused on term infants with perinatal asphyxia.[11–13] Despite the higher reported rates of clinical seizures in preterm infants, few have investigated outcomes in this group. Prior analyses have been limited by small sample size, confounding neonatal morbidities, and other factors.[14–16]

We hypothesized that ELBW infants with clinical seizures during the initial hospitalization were at increased risk for adverse outcome. We compared demographic, perinatal and neonatal risk factors between extremely low birth weight (ELBW) infants with and without clinical seizures in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN). We then utilized multivariate regression analyses to determine whether clinical seizures were independently associated with adverse neurologic and neurodevelopmental outcomes.

Methods

Patient Selection and Definitions

This was a retrospective analysis of prospectively collected data from the NICHD NRN registry. Infants born at NICHD NRN sites between January 1, 2000 and December 31, 2005, birth weight (BW) 401 – 1000 grams, and surviving to 36 weeks postmenstrual age (PMA) were included in this study. Each center's institutional review board approved the NRN registry. Infants with major malformations or syndromes, including congenital central nervous system (CNS) defects, congenital heart defects, and chromosomal abnormalities were excluded.

Demographic, maternal and neonatal information was collected from birth until death, hospital discharge, or 120 days using common definitions developed by the investigators.[17] Estimated gestational age (GA) was determined by best obstetric estimate. Antenatal antibiotics were the administration of any antibiotics to the mother during the admission that resulted in delivery. Antenatal steroids (ANS) were defined as the administration of any corticosteroids to accelerate fetal maturity in the present pregnancy. Infants were classified as small for gestational age (SGA) at birth, defined by a birth weight < 10^{th} percentile for sex and GA.[18]

Surfactant treatment was defined as at least one dose of any surfactant. Bronchopulmonary dysplasia (BPD) was defined as requiring supplemental oxygen at 36 weeks PMA. Postnatal steroid treatment was any steroid given for the prevention or treatment of BPD. Indomethacin

treatment was for closure of a patent ductus arteriosus (PDA) diagnosed through clinical means or echocardiogram. Prophylactic indomethacin in the first 24 hours of life was for the prevention of PDA or severe intraventricular hemorrhage (IVH). IVH was defined using Papile criteria19 and utilized interpretation by a staff radiologist at each participating center. Periventricular leukomalacia (PVL) was diagnosed by the presence of cystic echolucencies in the periventricular white matter on cranial ultrasound (US) performed closest to 36 weeks PMA. Ventriculomegaly was defined by the presence of enlarged ventricles on cranial imaging performed closest to 36 weeks PMA. However, timing and frequency of cranial US was not dictated by the NRN and a 36 week cranial US was not required. Necrotizing enterocolitis (NEC) was defined as modified Bells stage IIA or greater.20 Severe retinopathy of prematurity (ROP) was defined as stage 3 or greater with "plus" disease. Early-onset sepsis (within 72 hours of birth) and late-onset sepsis (after 72 hours) were defined by a positive blood culture or antibiotic/antimicrobial therapy for ≥ 5 days for presumed sepsis or when there was intent to treat but the infant died prior to 5 days of therapy. Meningitis was defined by a positive cerebrospinal fluid culture. Late death was defined as death after 36 weeks PMA.

Clinical seizures at any time during the initial hospitalization were recorded based on observation and judgment of the treatment team as documented in the medical record. Seizures characterized as subtle (such as unusual movements of limbs, eyes, or mouth), tonic (focal or generalized), clonic (focal or multifocal), or myoclonic (focal, multifocal, or generalized) were included.[21] An electroencephalogram (EEG) was obtained at the discretion of the medical team; the timing and technique for performing the EEG were not standardized, and obtaining an EEG after clinical seizure activity was not required. If an EEG was performed, it may have been obtained after treatment was initiated. The registry documented if the EEG confirmed clinical seizures, as determined by local interpretation.

Results of the final hearing test and use of anticonvulsant medications at discharge were collected beginning February 14, 2002. A failed hearing screen was defined as one or both ears failing. Discharge on any anticonvulsant medication was recorded.

Neurodevelopmental Assessments

A comprehensive neurodevelopmental assessment was performed on surviving infants at 18 to 22 months corrected age. The follow-up visit included a standardized medical history and special service use interview with the infant's mother or other primary caregiver and an examination, which included a measurement of weight, length, head circumference, and a standardized neuromotor examination. The Bayley Scales of Infant Development-IIR Mental Development Index (MDI) and the Psychomotor Development Index (PDI) were administered.[22] The mean score for MDI or PDI is 100; a score of < 70 on either index indicates significant delay. Children with such severe delay that they were untestable were assigned MDI and PDI scores of 49. Moderate cerebral palsy (CP) was defined as no ambulation or ambulation only with assistive devices but able to sit independently or with support. Severe CP was defined as the inability to ambulate or sit with support. Hearing impairment was defined based on history or observation during the follow-up visit; deafness was defined as the need for hearing aids in both ears. Vision impairment was defined as blind in either eye, though some functional vision could be present. Neurodevelopmental impairment (NDI) was defined as any of the following: moderate-severe CP, MDI or PDI < 70, bilateral blindness, or deafness. Unimpaired was defined as the presence of all of the following: no CP or mild CP, MDI ≥ 85, PDI ≥ 85, and no blindness or deafness. Isolated developmental impairment was defined as an MDI or PDI < 70 without moderate-severe CP, blindness, or deafness.

Additional information collected at the follow-up visit included the primary caregiver's education and medical history of the infant since discharge. An infant was classified as having post-neonatal seizures if the parent reported any seizure activity since discharge from the initial

birth hospitalization, excluding febrile seizures. Anticonvulsant medication was documented if the child required medication in the 3 months prior to the follow-up appointment.

Statistical Analyses

Demographic, perinatal, neonatal, discharge, and follow-up outcomes including late death or NDI were compared between infants with and without clinical seizures during the initial hospitalization. Statistical significance of the difference in proportions was determined using the χ^2 test, and the Student's *t* test was used to determine the difference in mean BW. The association of clinical seizures with late death or NDI was estimated using multiple logistic regression modeling, controlling for confounders, to report the adjusted odds ratio (OR) and 95% confidence interval (CI). In order to examine the differential impact of demographic, perinatal and neonatal contributions on the primary outcome, three models were constructed: 1) Model I included baseline factors, including maternal education, GA, BW, SGA, multiple gestation, mode of delivery, and ANS; 2) Model II included all of the variables from Model I as well as in-hospital morbidities, including 5-minute Apgar score ≤ 4, delivery room cardiopulmonary resuscitation (CPR) or epinephrine, NEC, BPD, surgical PDA, postnatal steroids, and infection (early-onset sepsis [EOS], late-onset sepsis [LOS], meningitis); and 3) Model III included all variables from Model II and further included CNS morbidities, such as severe IVH (grade III or IV) and cystic PVL. All potential confounders were entered as categorical except for BW, which was a treated as a continuous variable. NRN center was entered into the model as a random effect. An exploratory analysis of the association of EEG-confirmed seizures with late death or NDI was also performed, using the same models described above.

Statistical analyses were performed at RTI International using the SAS statistical software version 9.1 (SAS Institute, Cary, NC). Statistical significance was established at $P < .01$.

Results

During the study period, 9726 ELBW infants were born in participating NRN centers: 172 infants were excluded due to major malformations, 5 were excluded due to unknown seizure status, and 3050 died prior to 36 weeks PMA. Of the 6499 infants included in this study, 414 (6.4%) had clinical seizures, and the rate of seizures ranged from 0 to 15% among NRN centers. Ninety percent of infants (n=5866) completed follow-up or died after 36 weeks PMA. Of the 414 infants with clinical seizures, 92 (22%) had seizures confirmed by EEG.

Maternal and perinatal characteristics

Infants with clinical seizures were more likely to be of lower GA and BW, to have required intubation or CPR in the delivery room, and to have a 5-minute Apgar ≤ 4 (Table I). The proportion of those born SGA or delivered by cesarean section was lower in the seizure group.

Short term outcomes

The unadjusted rates of in-hospital morbidities were higher in infants with clinical seizures (Table II). Those with clinical seizures were more likely to have had a PDA, BPD, received postnatal steroids, or experienced late-onset sepsis. They were also more likely to have required surgery for PDA, NEC, or ROP. Infants with clinical seizures were more likely to receive indomethacin treatment for a PDA, but those without clinical seizures received prophylactic indomethacin with greater frequency. Infants with clinical seizures had significantly more severe IVH, cystic PVL, and meningitis compared with infants without seizures. Later CNS morbidities were seen more frequently in infants with clinical seizures, including ventriculomegaly, severe ROP, and the need for shunt placement for post hemorrhagic

hydrocephalus (PHH). Infants with clinical seizures were also more likely to fail the discharge hearing test and to be discharged home on anticonvulsant therapy.

Late outcomes

The outcomes of late death or NDI, late death or moderate-to-severe CP, and late death or MDI < 70 were more common among infants with a history of clinical seizures (Table III). Among survivors, those with a history of clinical seizures were more likely to have hearing or visual impairment or to have moderate-severe CP. NDI, MDI < 70, and PDI < 70, and isolated developmental impairment were also more common among survivors in the seizure group. Infants with a history of clinical seizures during the initial hospitalization were more likely to have seizures in the post-neonatal period and require ongoing anticonvulsant therapy. Infants without a history of clinical seizures were more likely to be unimpaired at 18 to 22 months corrected age.

The estimated odds ratios of clinical seizures with the primary outcome of late death or NDI are shown in Table IV. The unadjusted odds of late death or NDI were six-fold greater in infants with clinical seizures. After including CNS morbidities (Model III), neonatal clinical seizures remained significantly associated with late death or NDI ($P < 0.0001$). When the analysis was limited to infants with EEG-confirmed seizures, the result was similar (OR 2.95 [CI 1.62–5.39]). Additionally, some of the infants' baseline and morbidity characteristics included in the models were found to have statistically significant effects. Across all models, male sex, lower BW, multiple birth, and non-white race were significantly associated with an increased risk of late death or NDI (data not shown). In models II and III, BPD, PDA, NEC, meningitis, and LOS were positively related to late death or NDI.

Discussion

Few studies have addressed the potential association of seizures with the outcomes of preterm infants. This study compared the demographic, perinatal, and neonatal factors as well as neurodevelopmental outcomes of inborn ELBW infants surviving to 36 weeks PMA with and without clinical seizures in the NICHD NRN sites. Importantly, our multivariate model adjusted for the potential confounding effects of several morbidities to which seizures and adverse outcomes are commonly attributed, including infection, meningitis, severe IVH, and PVL. After these adjustments, a significant association remained between clinical seizures and late death or NDI among ELBW infants.

Seizures in neonates arise as a consequence of neural injury, resulting from hypoxia, ischemia, or metabolic disturbances such as hypoglycemia or hypocalcemia.[23] Possible sequelae of seizure activity in the developing CNS include altered neuronal circuitry, decreased neurogenesis, impaired learning, and brain injury.[24–26] There are also potential detrimental effects of anticonvulsant therapy to the developing CNS.[27] A National Institutes of Health workshop on the treatment of neonatal seizures emphasized the need for well-designed clinical trials with long-term follow-up as an endpoint, rather than seizure control.[28]

Previous studies have explored the association between clinical seizures and adverse outcomes among preterm survivors. NRN investigators have reported higher unadjusted rates of clinical seizures of ELBW infants who survived to 18 to 22 months corrected age with NDI, CP, and MDI < 70.[14, 29] Neubauer et al examined 135 ELBW survivors at school age and found a 9% rate of clinical seizures in their cohort, of whom 33% had severe IVH.[15] Although adjustments were performed for some obstetric and neonatal morbidities, the small sample size precluded a statistically significant association between seizures and an abnormal outcome. Because these studies examined only surviving infants, there was possible underreporting of adverse outcomes such as death.

Pisani et al examined the 24–30 month outcome of 51 preterm (≤ 36 weeks GA) infants with video EEG-confirmed seizures and reported an unfavorable outcome in 80% of the cohort.[16] Similarly, Ronen et al found a 42% rate of death and a 46% rate of disability among survivors in 26 preterm infants with seizures over a 10-year follow-up period.30 The strengths of these two studies lie in the selection of infants following a diagnosis of seizures. However, the lack of a control group did not permit analysis of the independent association between seizures and adverse outcome.

A recent analysis by Glass et al examined the association between clinical seizures and neurodevelopmental outcomes in a cohort of term newborns at risk for hypoxic-ischemic injury.[31] All infants had magnetic resonance imaging (MRI) performed and neurodevelopmental evaluation at 4 years of age. Infants with seizures were more likely to have an abnormal neurologic examination, and increasing severity of seizures was associated with a decline in the full-scale intelligence quotient. After adjusting for the degree of brain injury on MRI, seizures were independently associated with adverse outcome, suggesting that neurologic injury may result from seizures, particularly within neuronal structures, such as the hippocampus, that may not be fully visualized on conventional MRI.

Overall, infants with clinical seizures in our study had a greater illness severity compared with the control group, perhaps as a result of their lower GA and BW. Higher rates of severe IVH, cystic PVL, and infection were seen in the seizure group, and these CNS events have been associated with an increased rate of seizures[32] and adverse outcomes[14] in other studies. Indeed, the frequent overlap between seizures and many comorbidities has limited the ability to determine the independent contribution of seizures to the outcomes of ELBW infants. A significant advantage of our study is the large sample size of ELBW infants, including more than 400 infants with clinical seizures. We were able to investigate the association of clinical seizures with adverse outcome after adjusting for multiple comorbidities. By limiting our eligibility criteria to infants who survived until 36 weeks, we attempted to eliminate over-reporting of early death, which could have preceded a diagnosis of seizures. Even with a criterion of survival to 36 weeks PMA, late death was observed more frequently in the clinical seizure group compared with control.

A shortcoming of this study was the limited information regarding the circumstances and timing of clinical seizures during the hospital course. No data were available regarding the association of seizures with clinical events, and neither the extent of seizure burden nor anticonvulsant therapy were documented. It was also not possible to determine the number of infants with clinical seizures whose EEG did not confirm electrographic seizure activity. The diagnosis of severe IVH or PVL was determined only by cranial ultrasound; hence, the full extent of brain injury in this cohort may be underestimated. Lastly, fewer than 25% of the infants with clinical seizures had EEG-confirmed events. It is unclear if this reflects the efficacy of anticonvulsant medication or the decision-making of the medical team in obtaining an EEG.

The clinical diagnosis of seizures in neonates can be challenging, owing to the immaturity of the neonatal CNS. Rather than exhibiting classic tonic-clonic manifestations, seizure activity in neonates is often subtle and difficult to distinguish from normal newborn behavior, with preterm infants being even more likely to demonstrate subtle clinical manifestations of seizures.23 The broad range in the rate of clinical seizures among NRN centers in our study reflects this diagnostic challenge. The perception of clinical seizures can be highly qualitative, and infants perceived as being more ill may be more likely to be diagnosed with seizures. Murray et al reported that only one-third of electrographic seizures in term born infants were associated with clinical symptoms and that two-thirds of these clinical manifestations were unrecognized or misinterpreted by neonatology staff.[33] Further, Shah et al recently demonstrated electrographic seizures using routine amplitude-integrated EEG (aEEG) in 11

of 51 preterm infants < 30 weeks GA (21%), though only 2 infants (18%) demonstrated a clinical correlate.[34] Therefore, rates of clinical seizures, including the present study, likely underestimate the true incidence of seizure activity in the preterm population.

Despite the possible pitfalls in the classification of clinical seizures, this study demonstrates that clinical seizure activity and movements perceived as clinical seizures in ELBW infants surviving to 36 weeks PMA are associated with a greater odds of late death or NDI, independent of demographic, perinatal, and neonatal morbidities typically considered to be significant contributors to adverse outcome. Further, these data suggest that the neonatal clinical seizures may be considered a marker for poor outcome. More aggressive surveillance for electrographic seizure activity in preterm infants through more routine use of continuous aEEG monitoring or conventional EEG, particularly in those with known cerebral injury, will provide more accurate data regarding the true prevalence of seizures. Future studies aimed at determining the independent risk of seizures with adverse outcomes should document the timing of seizures in relation to other neonatal morbidities, the use of anticonvulsant therapies, and confirmation of electrographic seizure control using continuous aEEG or frequent EEG recordings. We speculate that aggressive detection and treatment of seizures has the potential to improve outcomes in ELBW infants, however a prospective study is required to confirm this hypothesis.

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List of abbreviations

ANS	antenatal steroids
BPD	bronchopulmonary dysplasia
BW	birth weight
CI	confidence interval
CNS	central nervous system
CP	cerebral palsy
CPR	cardiopulmonary resuscitation
EEG	electroencephalography
aEEG	amplitude-integrated EEG
ELBW	extremely low birth weight
EOS	early-onset sepsis
GA	gestational age
IVH	intraventricular hemorrhage
LOS	late-onset sepsis
MDI	Mental Development Index

MRI	magnetic resonance imaging
NDI	neurodevelopmental impairment
NEC	necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
NRN	Neonatal Research Network
OR	odds ratio
PDA	patent ductus arteriosus
PDI	Psychomotor Development Index
PHH	post hemorrhagic hydrocephalus
PMA	postmenstrual age
PVL	periventricular leukomalacia
SGA	small for gestational age
US	ultrasound

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Table I

Maternal and perinatal characteristics

Characteristic*	Group (*n*, %)	
	Seizures (N=414)	No Seizures (N=6085)
Maternal		
Maternal education < high school	124 (35)	1610 (29)
Antenatal steroids	348 (84)	5238 (86)
Antepartum antibiotics#	307 (75)	4088 (67)
Rupture of membranes > 24 hours	100 (25)	1407 (23)
Antepartum hemorrhage	74 (18)	1024 (17)
Multiple births	104 (25)	1394 (23)
Cesarean delivery#	248 (60)	4109 (68)
Perinatal		
Male#	250 (60)	2859 (47)
Gestational age, weeks#		
≤ 23	48 (12)	260 (4)
24–25	209 (50)	2063 (34)
26–27	121 (29)	2324 (38)
28–29	28 (7)	1021 (17)
≥ 30	8 (2)	416 (7)
Birth weight, grams (mean ± SD) †	725 ± 140	789 ± 138
Small for gestational age#	51 (12)	1133 (19)
Race#		
White	184 (45)	3215 (53)
Black	224 (54)	2602 (43)
Other	5 (1)	264 (4)
5-minute Apgar ≤ 4#	99 (24)	684 (11)
Intubation in delivery room#	334 (81)	4402 (72)
CPR or epinephrine in delivery room#	54 (13)	514 (8)

*Missing data (total number of subjects): maternal education (559), antenatal steroids (10), antepartum antibiotics (13), ROM > 24 hours (84), antepartum hemorrhage (4), cesarean delivery (6), gestational age (1), SGA (1), race (5), 5-minute Apgar (11), delivery room intubation (1), CPR/ drugs in delivery room (4)

#$P < 0.01$ based on χ^2 test

†$P < 0.01$ based on Student's t-test

Table II

Short-term outcomes

Characteristic*	Group (*n*, %)	
	Seizures (N=414)	No Seizures (N=6085)
In-hospital		
Surfactant administered#	373 (90)	4873 (79)
Prophylactic indomethacin#	127 (31)	2305 (38)
Treatment indomethacin#	216 (52)	2249 (37)
PDA#	270 (65)	2752 (45)
BPD#	300 (72)	2818 (46)
Postnatal steroids#	170 (41)	1176 (19)
Early-onset sepsis	13 (3)	93 (2)
Late-onset sepsis#	253 (61)	2226 (37)
Surgery (PDA/NEC/ROP) #	198 (48)	1364 (22)
Meningitis#	62 (15)	167 (3)
IVH, grade III or IV#	163 (39)	573 (10)
Cystic PVL#	65 (16)	221 (4)
Ventriculomegaly#,†	168 (43)	652 (14)
Shunt for PHH#	59 (14)	97 (2)
ROP ≥ stage 3#	163 (39)	1185 (19)
At discharge ‡		
Hearing screen failed#	36/271 (13)	291/3973 (7)
Anticonvulsant therapy#	18/272 (7)	8/4006 (<1)

*Missing data (total number of subjects): surfactant (20), prophylactic indomethacin (3), treatment indomethacin (27), PDA (1), BPD (8), postnatal steroids (8), late-onset sepsis (4), meningitis (1), IVH grade III or IV (52), cystic PVL (30), shunt for PHH (7), hearing screen failed (35), anticonvulsant therapy (1).

#$P < 0.01$ using χ^2 test.

†Ultrasound at 36 weeks not routinely performed by all centers. Seizure group has missing data for 20 subjects; control group has missing data for 1370 subjects.

‡Hearing screen and discharge medications were not queried before 2/14/2002; data represent subjects enrolled into database after this date and data are represented as *n*/N (%).

Table III

Outcomes at 18 to 22 months corrected age

Characteristic*	Group (n, %)	
	Seizures (N=383)	No Seizures (N=5483)
Late death#	86 (22)	250 (5)
Late death or NDI#	293 (79)	1913 (38)
Late death or moderate-severe CP#	180 (48)	487 (9)
Late death or MDI < 70#	263 (73)	1626 (32)
Among survivors	(N=297)	(N=5233)
NDI#	207 (72)	1663 (35)
Moderate-severe CP#	94 (32)	237 (5)
PDI < 70#	154 (55)	884 (19)
MDI < 70#	177 (64)	1375 (29)
Unimpaired#	37 (14)	1612 (35)
Isolated developmental impairment#	89 (32)	1133 (24)
Head Circumference <10%ile#	161 (55)	1702 (33)
Hearing impaired#	32 (11)	212 (4)
Vision impaired#	119 (43)	634 (14)
Post-neonatal seizures#	47 (16)	189 (4)
Anticonvulsant therapy#	23 (8)	37 (<1)

* Missing data (total number of subjects): late death or NDI (484); late death or moderate-severe CP (77); late death or MDI < 70 (478); NDI (460); moderate-severe CP (53); PDI < 70 (499); MDI < 70 (454); unimpaired (575); isolated developmental impairment (496); head circumference (55); hearing impaired (59); vision impaired (529); post-neonatal seizures (61); anticonvulsant therapy (59)

# $P < 0.01$ using χ^2 test

Table IV

Logistic regression estimates for primary outcome of late death or NDI

Model	OR estimate (95% CI)
Unadjusted	6.56 (5.04, 8.54)
Model I (baseline variables)*	4.81 (3.66, 6.33)
Model II (Model I + non-CNS morbidities)#	3.70 (2.79, 4.91)
Model III (Model II + CNS morbidities)†	3.15 (2.37, 4.19)

*Baseline model variables: center, gender, multiple gestation, cesarean section, race, GA, BW, ANS, maternal education

#Non-CNS morbidity variables: delivery room CPR/epinephrine, 5-minute Apgar score ≤ 4, NEC, BPD, infection (EOS, LOS, meningitis), surgical PDA, postnatal steroids, BPD

†CNS morbidity variables: grade III/IV IVH, cystic PVL