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

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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. Using multivariate logistic regression modeling, we 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-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% CI, 2.37-4.19).

Conclusion ELBW infants with clinical seizures are at increased risk for adverse neurodevelopmental outcome, independent of multiple confounding factors. *(J Pediatr 2010;157:720-5)*.

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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 (CP) and post-neonatal epilepsy,[3-6] but whether this is a causal relationship is controversial. Some authors 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 studies have investigated outcomes in this group. Small sample size, confounding neonatal morbidities, and other factors have limited earlier analyses.[14-16]

We hypothesized that extremely low birth weight (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 ELBW infants with clinical seizures and ELBW infants without clinical seizures in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN). We then used multivariate regression analyses to determine whether

aEEG	Amplitude-integrated EEG	MRI	Magnetic resonance imaging
ANS	Antenatal steroids	NDI	Neurodevelopmental impairment
BPD	Bronchopulmonary dysplasia	NEC	Necrotizing enterocolitis
BW	Birth weight	NICHD	National Institute of Child Health and Human Development
CNS	Central nervous system		
CP	Cerebral palsy	NRN	Neonatal Research Network
CPR	Cardiopulmonary resuscitation	OR	Odds ratio
EEG	Electroencephalography	PDA	Patent ductus arteriosus
ELBW	Extremely low birth weight	PDI	Psychomotor Development Index
EOS	Early-onset sepsis	PHH	Post-hemorrhagic hydrocephalus
GA	Gestational age	PMA	Postmenstrual age
IVH	Intraventricular hemorrhage	PVL	Periventricular leukomalacia
LOS	Late-onset sepsis	SGA	Small for gestational age
MDI	Mental Development Index	US	Ultrasound scanning

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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 Jan 1, 2000, and Dec 31, 2005, with a birth weight (BW) 401 to 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 with common definitions developed by the investigators.[17] Estimated gestational age (GA) was determined by using the 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 <10th 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 with Papile criteria[19] and used interpretation by a staff radiologist at each participating center. Periventricular leukomalacia (PVL) was diagnosed with the presence of cystic echolucencies in the periventricular white matter on cranial ultrasound scanning (US) performed closest to 36 weeks PMA. Ventriculomegaly was defined with 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 with "plus" disease. Early-onset sepsis (EOS) (within 72 hours of birth) and late-onset sepsis (LOS) (after 72 hours) were defined with a positive result on blood culture or antibiotic/antimicrobial therapy for >5 days for presumed sepsis or when there was intent to treat but the infant died before 5 days of therapy. Meningitis was defined with a positive result on cerebrospinal fluid culture. Late death was defined as death after 36 weeks PMA.

Clinical seizures at any time during the initial hospitalization were recorded on the basis of 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. When an EEG was performed, it may have been obtained after treatment was initiated. The registry documented when 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 Feb 14, 2002. A failed hearing screening was defined as one or both ears failing. Discharge from the hospital while receiving 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 <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 CP was defined as no ambulation or ambulation only with assistive devices, but ablity to sit independently or with support. Severe CP was defined as the inability to ambulate or sit with support. Hearing impairment was defined on the basis of 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 blindness in either eye, although 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 from the hospital. An infant was classified as having post-neonatal seizures when the parent reported any seizure activity since discharge from the initial birth hospitalization, excluding febrile seizures. Anticonvulsant medication use was documented when the child required medication in the 3 months before the follow-up appointment.