Cranial Ultrasound and Minor Motor Abnormalities at 2 Years in Extremely Low Gestational Age Infants

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Abstract

Objectives: The objectives of this study were to determine whether abnormalities on neonatal cranial ultrasound (CUS) are associated with minor motor abnormalities at 2 years corrected age (CA), and to assess functional outcomes and resource utilization among children with minor motor abnormalities.

Methods: Infants born <27 weeks in the NICHD Neonatal Research Network between 1/1/2010 and 12/31/2014, who underwent neuroimaging with CUS both <28 days and ≥28 days, and were evaluated at 18–26 months CA, were included. Follow-up included Bayley-3, neuromotor examination, Gross Motor Function Classification System (GMFCS) level, and parent questionnaires about special services and resource needs. Children were classified by most severe motor abnormality at 18–26 months CA: none, minor, or major motor function abnormality. Minor motor abnormalities were defined as any of: (a) Bayley-3 motor composite, fine motor score, or gross motor score 1–2 standard deviations below the test normative mean; (b) mild abnormalities of axial or extremity motor skills on standardized neuromotor exam; or (c) GMFCS level 1.

Results: 809 (35%) of 2,306 children had minor motor function abnormalities only. This did not increase substantially with CUS findings (no IVH: 37%, grade I IVH: 32%, grade II IVH: 38%, grade III/IV IVH: 30%, isolated ventriculomegaly: 33%, cystic periventricular leukomalacia: 24%). The adjusted odds of minor axial and upper extremity function abnormalities and GMFCS level 1 were significantly higher in children with more severe CUS findings. Children with minor...
motor abnormalities had increased resource utilization and evidence of functional impairment compared to those without motor function abnormalities.

**Conclusions:** Minor motor abnormalities at 2 years CA are common and cannot be predicted by neonatal CUS abnormalities alone. Minor motor abnormalities are associated with higher resource utilization and evidence of functional impairment. These findings have important implications for early counseling and follow-up planning for extremely preterm infants.

**Keywords**
Cranial Ultrasound; Extremely low gestational age; Motor Function

**INTRODUCTION**

Since the initial descriptions of staging of intraventricular hemorrhage (IVH) in preterm infants, it has been clearly established that IVH is associated with increased risk for adverse early childhood developmental outcomes. Most reports have focused on the strong associations between high-grade (grades III-IV) IVH and periventricular leukomalacia (PVL) on cranial ultrasound (CUS) and moderate to severe neurodevelopmental impairment.\(^1\)\(^-\)\(^3\) In addition, while individual studies have inconsistent results, a recent meta-analysis demonstrates that even low-grade (grades I-II) IVH is associated with increased odds of moderate to severe neurodevelopmental impairment.\(^4\) However, little is known about whether abnormalities on CUS, and low-grade abnormalities in particular, are associated with minor motor impairments in early childhood.

The incidence of moderate to severe CP in former preterm infants has been decreasing over time.\(^5\)\(^-\)\(^7\) Thus, it is increasingly important to understand and predict more subtle motor abnormalities, and to understand how these abnormalities are related to functional outcomes over time. The objectives of this study were to determine whether abnormalities on neonatal CUS are associated with minor motor abnormalities at 18–26 months corrected age (CA) and to assess functional outcomes and resource utilization among children with minor motor abnormalities.

**METHODS**

**Study Design**

This study is a secondary analysis of the NICHD Neonatal Research Network (NRN) Generic Database and Follow-up Registry. The Generic Database includes infants born in study centers before 29 weeks of gestation or enrolled in a clinical trial. The Follow-up Registry includes the subset of those infants born before 27 weeks of gestation or enrolled in a trial. The registries are approved by each participating center’s institutional review board and written informed consent was obtained from a parent or guardian per local guidelines.

**Study Cohort**

Infants with birth weights 400–1000 grams and GA ≤27 0/7 weeks, who were born at any of 21 participating centers between 1/1/2010 and 12/31/2014 (centers listed in appendix), were included if they had at least one CUS before 28 days of life, at least one CUS at ≥28 days of life, and at least one CUS at 18–26 months CA.
age, and a neurodevelopmental evaluation at 18–26 months CA. Children with only an early (<28 days) CUS were excluded because this evaluation is less predictive of 2-year outcomes than later imaging. Children with incomplete assessments at 18–26 months CA or with congenital and/or acquired abnormalities that may affect neurodevelopment were excluded.

Exposure

Trained research coordinators collected data throughout the inpatient hospitalization, including details of most severe CUS findings before 28 days of life and results of late imaging that was performed after 28 days and closest to 36 weeks postmenstrual age. For the current study, infants were categorized based on the most severe finding on any CUS study using the following definitions and order of severity:

1. Blood/echodensity in germinal matrix/subependymal area: Grade I IVH
2. Blood/echodensity in the ventricle: Grade II IVH
3. Ventricular size enlarged with concurrent or prior blood in the ventricles: Grade III IVH
4. Blood/echodensity in the parenchyma: Grade IV IVH
5. Ventricular size enlarged without concurrent or prior blood in the ventricles: Isolated ventriculomegaly
6. Cystic periventricular leukomalacia (cPVL) or porencephalic cyst

Data regarding cerebellar hemorrhage were not collected throughout the study period and thus could not be included. Infants with asymmetric findings (ex: Grade II/IV IVH) were classified based on the most severe finding. Term corrected age MRI is not performed routinely at most centers that participated in this study. Therefore, MRI results were not included in the current study.

Outcomes

The NRN neurodevelopmental assessment at 18–26 months CA includes the Bayley Scales of Infant Development-3rd Edition (Bayley-3), a neurologic examination, Gross Motor Function Classification System (GMFCS) classification, and parent report of special services and resource utilization. Bayley examiners and personnel performing the neuromotor examination undergo rigorous yearly recertification in order to ensure standardized and reliable outcome reporting. Children born before 7/1/12 were evaluated at 18–22 months CA; those born on or after 7/1/12 were evaluated at 22–26 months CA.

The primary outcome measure was the prevalence of minor motor abnormalities at 18–26 months CA, based on highest severity of CUS findings. Minor motor abnormalities were defined as any of the following: (a) Bayley-3 motor composite, fine motor score, or gross motor score 1–2 standard deviations (SD) below the test normative means; (b) mild abnormalities of axial or extremity motor skills on standardized neuromotor exam; or (c) GMFCS level 1 (detailed definitions are provided in Supplemental Table 1). At 2 years, children with GMFCS level 1 walk independently but do not have a normal and fluent gait. More severe neurologic examination findings (for example: GMFCS 2–5) and lower scores
on the Bayley were defined as major motor abnormalities. Children without the findings listed above were classified as having no motor abnormalities. For subsequent analyses, children were classified by the highest severity of motor function abnormality. When children were evaluated at 18–22 months CA, examiners were permitted to code GMFCS “possible Level 1” if children walked 10 steps independently but not fluently. This category was removed when the assessment was moved to 22–26 months CA. In the current study, children with “possible level 1” were categorized as normal.

Secondary outcomes were: (1) parent-reported rates of medical resource utilization; (2) special therapies; and (3) abnormal oral feeding. Medical resource utilization was defined as re-hospitalizations (dichotomized as number of hospitalizations >75th vs. <75th percentile in the study cohort), use of medical equipment in the home, receipt of medication to treat seizures or spasticity, and living in a chronic care facility or requiring medical day care. Special therapies were defined as currently receiving, recently received, or recommended to receive occupational, physical, or speech therapy. Children were classified as having an abnormal diet if parents reported feeding them thickened liquids or pureed foods at 18–26 months CA. Detailed questions about oral motor skills were introduced in 2011, and thus were available for a subset of the children (n=1754, 76% of the cohort). Children were categorized with abnormal oral motor skills if: (a) the child fed by mouth but was unable to do so independently; (b) the child required some food via a feeding tube or parenteral nutrition; or (c) the parents endorsed abnormal feeding behaviors such as refusing oral feeding, difficulty swallowing, or aspiration.

Analyses

We compared demographic characteristics and motor function abnormalities of children with each category of abnormal CUS finding to children without abnormalities on CUS. Frequencies, percentages, and chi-square tests were computed for categorical variables and means, standard deviations, and t-tests for continuous variables. The Cochran Armitage test and linear contrasts were used to assess for changes in risk factors or outcomes across categories of CUS findings and across categories of motor abnormalities.

Logistic regression analyses were conducted to compute adjusted odds ratios (ORs) and 95% confidence intervals, based on CUS findings, controlling for GA, sex, small for gestational age (SGA) status, receipt of antenatal steroids, 5-minute Apgar ≤5, race, bronchopulmonary dysplasia (BPD, defined as oxygen use at 36 weeks postmenstrual age), patent ductus arteriosus (PDA, defined as documentation of PDA regardless of subsequent treatment), sepsis (culture positive early or late onset sepsis with documentation of treatment), necrotizing enterocolitis (NEC) requiring surgery, severe retinopathy of prematurity (ROP, defined as ≥stage 3 or requiring treatment), postnatal steroids, and CA at assessment, including center as a random effect. Resource utilization in children with no, minor, or major motor abnormalities was compared using the same regression models. Two-sided p-values <0.05 indicated statistical significance, and adjustments for multiple comparisons were not performed. Analyses were performed with SAS version 9.4 (Cary, NC).
RESULTS

A total of 3,157 infants <27 weeks GA were born in NRN centers during the study period and survived to discharge. Of these, 2,890 had CUS both < and ≥28 days of life; 52 of these children died after discharge, 265 were lost to follow-up, 118 were missing outcomes data, and 149 were assessed outside of the 18–26 month CA window, resulting in a final sample of 2,306 children (73% of survivors) with complete data for the current study. Mean age at follow-up in this cohort was 20 +/- 2 months CA. In general, baseline characteristics of the included children (n=2,306) were not different from those of children who survived to discharge but were excluded from the analyses (n=851). However, included children were less likely to receive antenatal steroids (89% vs. 93%, p=0.004) and more likely to have PDA (57% vs. 51%, p=0.007) and sepsis (33% vs. 29%, p=0.049).

The numbers and characteristics of children with each type of CUS abnormality are shown in Table 1. In unadjusted analyses, many baseline characteristics and all medical morbidities varied significantly by abnormality on CUS.

Among infants without abnormal findings on neonatal CUS, 49% had at least one minor motor abnormality, with or without concurrent major abnormalities, at 2 years CA (Table 2). Unadjusted risk of having any minor motor abnormality increased significantly with severity of CUS findings (p<0.001). GMFCS level 1, minor upper and lower extremity function abnormalities, and minor axial tone abnormalities were more common among infants with more severe neonatal CUS findings.

When adjusted for variables known to impact neurodevelopment, the odds of minor motor abnormalities on the Bayley-3 were not significantly increased over the range of abnormal CUS findings (Table 3). Minor abnormalities of gait or lower extremity function were only associated with cPVL or porencephalic cysts. However, the adjusted odds of minor axial tone abnormalities, upper extremity function abnormalities, and GMFCS level 1 were significantly higher in children with more severe CUS findings. As expected, adjusted odds for major motor function abnormalities were significantly increased in children with severe CUS findings.

We then categorized children based on most severe motor abnormality at 18–26 months CA. Overall, 1025 (44.5%) children had no motor function abnormalities, 809 (35.1%) had minor motor function abnormalities alone, and 472 (20.5%) had major motor function abnormalities (with or without concurrent minor abnormalities) at 2 years CA. The prevalence of major motor abnormalities increased with increasing severity of CUS findings. On the other hand, the overall prevalence of minor motor abnormality in the absence of major motor abnormality did not increase substantially with CUS findings (no abnormalities: 37%, grade I IVH: 32%, grade II IVH: 38%, grade III/IV IVH: 30%, ventriculomegaly: 33%, cPVL: 24%). When compared to children with normal motor function, children in the minor motor abnormality group were younger and smaller at birth, and were more likely to have had a 5-minute Apgar score ≤5; diagnosis of BPD, PDA, surgical NEC, and ROP requiring treatment; and postnatal steroid exposure (Supplemental Table 2).
Lastly, we evaluated resource utilization and functional outcomes based on highest degree of motor function abnormality. Resource utilization and evidence of functional impact of motor disability at 18–26 months CA were highest among children with major motor abnormalities (Table 4). However, adjusted odds of requiring home equipment, occupational or physical therapy, or anticonvulsant/anti-spasticity medications were higher in children with minor motor abnormalities, compared to those with normal exams. Odds of living in a chronic care facility were 2.41 (95% CI 1.12 5.20) times higher in those with minor motor abnormalities, although this outcome was relatively rare across all categories. Parents were more likely to report abnormal feeding skills or behaviors, and were more likely to be still feeding pureed foods or thickened liquids to children with minor motor abnormalities at 2 years CA.

DISCUSSION

This large multicenter study evaluated predictors of minor motor abnormalities at 18–26 months CA in former extremely preterm infants and whether such deficits are associated with functional problems and resource utilization. This work demonstrates that when children born <27 weeks GA are categorized based on the highest degree of motor function abnormality at 18–26 months CA, more than a quarter have minor motor function abnormalities. Even though CUS findings do not predict minor motor outcomes as well as they predict major motor outcomes, adjusted odds of minor abnormalities in axial tone and upper extremity function and GMFCS level 1 were highly associated with CUS findings. On the other hand, Bayley motor scores 1–2 standard deviations below the test normative mean and minor abnormalities of gait/lower extremity function were not closely associated with CUS findings in this study. This inconsistency in our findings may be related to insufficient sensitivity of these assessments for detecting subtle delays or differences in quality of motor skills. Minor motor function abnormalities were associated with significantly increased medical resource utilization.

The accuracy of CUS in predicting outcomes varies based on the population, the outcome of interest, the frequency with which the study is repeated, and the timing of the studies. Ultrasound is generally a specific but not sensitive test for prediction of outcomes when the most severe findings are considered the “positive test” of interest. Severe brain injury identified on any CUS is one of three neonatal variables – together with BPD and ROP – that have independent and additive effects on prediction of neurodevelopmental impairment up to 5 years in very preterm infants. Unfortunately, CUS has insufficient sensitivity, as evidenced by the current study in which 14% of children without abnormalities on CUS had major motor function abnormalities and 49% had minor motor function abnormalities. Reports of normal CUS among infants who later developed impairments have led some to advocate for the wider use of MRI. However, MRI is also of limited utility for predicting with certainty the neurodevelopmental outcomes of preterm infants. Recent research highlights the continuing value of ultrasound, particularly when performed at term-equivalent age and combined with perinatal risk factors. In addition, the “Choosing Wisely Top Five” for newborn medicine list recommends avoidance of term-equivalent MRI in preterm infants because it does not improve prediction of outcomes. The relationships between both traditional MRI and novel techniques such as resting-state and diffusion tensor imaging may provide additional insights into the mechanisms underlying motor development in preterm infants.

J Dev Behav Pediatr. Author manuscript; available in PMC 2021 May 01.
imaging and minor motor findings are unknown and remain an important area of future research.

Importantly, nearly all research about the prognostic accuracy of cranial imaging has focused on the accuracy of imaging – and particularly high-grade abnormalities – for prediction of severe adverse cognitive or motor outcomes or death. Lower grade (grades I-II) IVH is more common than higher grade findings (grades III-IV IVH or PVL). Though individual reports about the impact of lower grade ultrasound findings on outcomes are conflicting, a 2015 meta-analysis of 21 studies reported that surviving preterm infants with mild CUS findings had 1.39 times higher adjusted odds of moderate or severe neurodevelopmental impairment than preterm infants without CUS abnormalities. Mild CUS findings were not associated with an increase in cerebral palsy alone. Less is known about the impact of various degrees of ultrasound abnormalities and other perinatal factors on minor motor abnormalities in early childhood. Yet, subtle neurologic findings in the early years may be critical antecedents to later functional deficits.

Rates of CP have decreased in recent years, and there is a trend toward less severe phenotypes among former preterm infants with CP. Thus, it is increasingly important to understand other types of motor disorders that also occur in high-risk children. Minor neurologic dysfunction (MND) and/or Developmental Coordination Disorder (DCD) occur in at least a third of very preterm-born children who do not have CP. These disorders are associated with cognitive disability, poor visuomotor coordination, lower academic achievement, and behavioral, social, and psychiatric problems. These motor problems cannot be diagnosed until preschool age or older. Little is known about the incidence of minor neurologic abnormalities before preschool age, prediction of these findings, or the relationships between early motor abnormalities and later deficits. Using different cutoffs than the current study, one Swedish study has reported that extremely preterm infants have 3.7 higher odds of mild deficits on the motor domain of the Bayley-3 than term controls. The current study builds on this by evaluating not only minor differences on the Bayley-3 but also abnormalities in the neurologic examination at 2 years CA that may allow for a more complete assessment of motor abilities. While some of the subtle motor deficits identified in our study are associated with increasing severity of CUS findings, others are not as closely associated and are commonly found even in children who had unremarkable neonatal imaging.

The current study suggests that any abnormal CUS finding is associated with increased odds for upper extremity function abnormalities. Though standardized tools for classification of upper extremity function in childhood have been developed, most commonly used CP definitions rely on classification of lower extremity abilities (e.g. GMFCS). However, minor dysfunction of the upper extremities might have important implications for performance of common activities of daily living, such as feeding and school performance, at all ages. The current study reports abnormal feeding skills and need for speech therapy in nearly half of children with minor motor abnormalities.

Children with major deficits nearly all require significant medical, social, and educational resources. However, children with mild CP or non-CP motor challenges may also require

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high rates of community supports and services.\textsuperscript{27,28} Large populations of children with modest needs can ultimately create more of an economic burden than small populations of children with significant needs.\textsuperscript{29} This study demonstrates that minor motor abnormalities at 2 years CA are associated with significantly increased rates of medical resource utilization. In addition to incurring cost, these outcomes represent potential burden and stress for families. Notably, in this cohort, physical/occupational therapy, speech therapy, and use of thickened feedings at 2 years CA were common (27–43\%) even among children without motor abnormalities. Along with others, we suggest that future research should include functional outcomes such as feeding abilities, rather than maintaining a narrow focus on traditional definitions of developmental disabilities.\textsuperscript{30}

This study has several limitations. Only 73\% of the eligible sample had complete data for analysis. The group of children included and the group of children not included differed only in rates of antenatal steroid exposure, PDA, and sepsis, all of which are associated with risk for IVH and likelihood of increased surveillance with CUS. The results of this study depend on a single neurologic examination performed at 18–26 months CA. The neurologic examination may evolve during this time period; therefore, the analyses were adjusted for age at assessment. Though the exam can be subjective, the NRN neurologic examiners undergo a rigorous annual recertification.\textsuperscript{10} Similarly, interpretation of routine clinically- indicated CUS may not be equivalent to “research quality” assessments. Sensitivity of local diagnosis of low-grade IVH is lower than sensitivity for higher-grade findings.\textsuperscript{31} Nevertheless, because specificity is >90\%, a local diagnosis of Grade I-II IVH has a low likelihood of being a false positive. Furthermore, use of clinical information in this study yields results that are more easily generalizable to other clinical scenarios. Because we classified children with “possible level 1” GMFCS exams as normal and excluded some infants with low risk for poor outcomes who did not undergo serial CUS we may have underestimated the incidence or impact of minor motor impairment at 2 years CA. We do not have information about grading of cPVL on CUS. We did not report results of MRI studies because these were not obtained in all infants. Furthermore, MRI is not currently considered standard of care for routine evaluation of extremely low gestational age infants, and in particular for infants with minimal findings on CUS.\textsuperscript{19} Therefore, we cannot precisely report rates of white matter abnormalities in our population. However, all infants had near term CUS, on which both ventriculomegaly and cystic lesions could be identified. Most importantly, it is unknown whether minor abnormalities at 2 years CA are associated with longer-term adverse outcomes such as DCD. Therefore, future work to evaluate relationships between these abnormalities and motor and developmental outcomes at school age will be essential. On the other hand, our study provides contemporary data about a large and generalizable patient population with high rates of comprehensive and rigorous follow-up.

In summary, this study describes the associations between postnatal CUS imaging and minor motor abnormalities at 2 years CA in children born <27 weeks of gestation. Such information will be of value when counseling families about potential implications of neonatal neuroimaging and in planning for the care of preterm-born children post-discharge and throughout childhood. Future research should evaluate not only severe outcomes but also more subtle deficits, which may have important short- and long-term functional consequences.
SUPPLEMENTARY MATERIAL

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) provided grant support for the Neonatal Research Network, including for the Follow-up Study. While NICHD staff did have input into the study design, conduct, analysis, and manuscript drafting, the content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator) and Dr. Carla Barr (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Case Western Reserve University, Rainbow Babies & Children’s Hospital (U10 HD21364) - Michele C. Walsh, MD MS; Avroy A. Fanaroﬀ, MD; Nancy S. Newman, RN; Deanne E. Wilson-Costello, MD; Bonnie S. Siner, RN; Harriet G. Friedman, MA.

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Emory University, Children’s Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown (U10 HD27851, UL1 TR454) - Barbara J. Stoll, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC; Yvonne C. Loggins, RN BSN; Diane I. Bottcher, RN MSN; Colleen Mackie, BS RRT; Sheena L. Carter, PhD; Maureen Mulligan LaRossa, RN; Lynn C. Wineski, RN MS; Gloria V. Smikle, PNP MSN; Angela Leon-Hernandez, MD; Salathiel Kendrick-Allwood, MD.

Eunice Kennedy Shriver National Institute of Child Health and Human Development - Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, UL1 TR6) - Brenda B. Poindexter, MD MS; Gregory M. Sokol, MD; Lu Ann Papile, MD; Heidi Harmon, MD MS; Carolyn Lytle, MD MPH; Heike M. Minnich, PsyD HSPP; Abbey C. Hines, PsyD; Dianne...
E. Herron, RN; Leslie Richard, RN; Susan Gunn, NNP CCRC; Lucy Smiley, CCRC; Leslie Dawn Wilson, BSN CCRC.

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Nationwide Children’s Hospital and the Ohio State University Medical Center (U10 HD68278) - Pablo J. Sánchez, MD; Leif D. Nelín, MD; Sudarshan R. Jadcherla, MD; Patricia Luzader, RN; Margaret Crawford, BS; Jenna Gabrio, BS CCRP; Carolyn M. Petrie Huitema, MS; Kristin M. Zaterka-Baxter, RN BSN.

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Tufts Medical Center, Floating Hospital for Children (U10 HD53119, M01 RR54) - Ivan D. Frantz III, MD; John M. Fiascone, MD; Brenda L. MacKinnon, RNC; Ellen Nylén, RN BSN; Anne Furey, MPH; Elisabeth C. McGowan, MD; Cecelia E Sibley PT MHA; Ana K. Brussa, MS OTR/L.

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University of California - San Diego Medical Center and Sharp Mary Birch Hospital for Women and Newborns (U10 HD40461) - Neil N. Finer, MD; Yvonne E. Vaucher, MD MPH; David Kaegi, MD; Maynard R. Rasmussen, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Martha G. Fuller, RN MSN; Chris Henderson, RCP CRTT; Wade Rich, BS HS RRT; Radmila West PhD.

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University of Rochester Medical Center, Golisano Children’s Hospital, and the University of Buffalo Women’s and Children’s Hospital of Buffalo (U10 HD68263, UL1 TR42) - Dale L. Phelps, MD; Carl T D’Angio, MD; Ronnie Guilet, MD PhD; Gary J. Myers, MD; Satyan Lakshminrusimha, MD; Anne Marie Reynolds, MD; Michelle E. Hartley, MD; Andrew, MD; Holly L.M. Wadkins, MA; Michael G. Saciulowski, BS; Linda J. Reubens, RN CCRP; Rosemary L. Jensen; Joan Merzbach, LMSW; William Zorn, PhD; Osman Farooq, MD; Deanna Maffett, RN; Ashley Williams, MS Ed; Julienne Hunn, BS; Stephanie Guilford, BS; Kelley Yost, PhD; Mary Rowan, RN; Diane M. Prinzing, AAS; Karen Wynne, NNP RN; Melissa Bowman, RN NP; Cait Fallone, MA.
University of Texas Southwestern Medical Center, Parkland Health & Hospital System, and Children’s Medical Center Dallas (U10 HD40689) - Myra H. Wyckoff, MD; Pablo J. Sánchez, MD; Luc P. Brion, MD; Roy J. Heyne, MD; Diana M. Vasil, MSN BSN RNC-NIC; Sally S. Adams, MS RN CPNP; Liz Chen, RN PhD; Alicia Guzman; Elizabeth T. Heyne, MS MA PA-C PsyD; Linda A. Madden, BSN RN CPNP; Nancy A. Miller, RN; Lizette E. Lee, RN; Lara Pavageau, MD; Cathy Twell Boatman, MS CIMI.

University of Utah University Hospital, Intermountain Medical Center, LDS Hospital, and Primary Children’s Medical Center (U10 HD53124, M01 RR64, UL1 TR105) - Roger G. Faix, MD; Bradley A. Yoder, MD; Anna Bodnar, MD; Karen A. Osborne, RN BSN CCRC; Shawna Baker, RN; Karie Bird, RN BSN; Jill Burnett, RNC BSN; Jennifer J. Jensen, RN BSN; Manndi C. Loertscher, BS CCRP; Carrie A. Rau, RN BSN CCRC; Cynthia Spencer, RNC BSN; Mike Steffen, PhD; Kimberlee Weaver-Lewis, RN MS; Sarah Winter, MD; Karen Zanetti, RN.

Wayne State University, Hutzel Women’s Hospital, and Children’s Hospital of Michigan (U10 HD21385) - Seetha Shankaran, MD; Sanjay Chawla, MD; Beena G. Sood, MD MS; Athina Pappas, MD; Girija Natarajan, MD; Rebecca Bara, RN BSN; Mary E. Johnson, RN BSN; Laura Goldston, MA, Stephanie A. Wiggins, MS; Mary K. Christensen, BA RRT; Martha Carlson, MD; John Barks, MD.

Yale University, Yale-New Haven Children’s Hospital, and Bridgeport Hospital (U10 HD27871, UL1-RR024139, U1 TR142) - Richard A. Ehrenkranz, MD; Harris Jacobs, MD; Christine G. Butler, MD; Patricia Cervone, RN; Sheila Greisman, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Elaine Romano, MSN.

Funding Source:
This study was supported by the Eunice Kennedy Shriver NICHD Neonatal Research Network. Grant numbers for all participating sites are included in the Acknowledgements.

REFERENCES

## Table 1.

Patient demographics and neonatal characteristics, by most severe abnormality on cranial ultrasound

<table>
<thead>
<tr>
<th>Highest degree of abnormality on CUS</th>
<th>No abnormalities (N=1502)</th>
<th>Unilateral or bilateral grade I IVH (N=174)</th>
<th>Unilateral or bilateral grade II IVH (N=157)</th>
<th>Unilateral or bilateral grade III/IV IVH (N=212)</th>
<th>Ventriculo-megaly (N=92)</th>
<th>Unilateral or bilateral cystic PVL or porencephalic cyst (N=169)</th>
<th>Test for linear trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>p-value</td>
</tr>
<tr>
<td>Gestational age, weeks (mean ± SD)</td>
<td>25.2 ± 1.1</td>
<td>25.1 ± 1.1</td>
<td>25.0 ± 1.0 *</td>
<td>24.8 ± 1.1 *</td>
<td>24.8 ± 1.2 *</td>
<td>24.7 ± 1.1 *</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight, grams (mean ± SD)</td>
<td>778 ± 166</td>
<td>774 ± 151</td>
<td>765 ± 166</td>
<td>755 ± 167</td>
<td>744 ± 161</td>
<td>756 ± 160</td>
<td>0.025</td>
</tr>
<tr>
<td>SGA</td>
<td>106 (7)</td>
<td>5 (3) *</td>
<td>10 (6) *</td>
<td>7 (3) *</td>
<td>5 (5)</td>
<td>4 (2) *</td>
<td>0.004</td>
</tr>
<tr>
<td>Male</td>
<td>718 (48)</td>
<td>86 (49)</td>
<td>96 (61) *</td>
<td>105 (50)</td>
<td>45 (49)</td>
<td>74 (44)</td>
<td>0.90</td>
</tr>
<tr>
<td>5-minute Apgar ≤ 5</td>
<td>364 (24)</td>
<td>54 (31) *</td>
<td>52 (33) *</td>
<td>88 (42) *</td>
<td>32 (35) *</td>
<td>68 (40) *</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>609 (41)</td>
<td>81 (47)</td>
<td>66 (43)</td>
<td>75 (36)</td>
<td>33 (36)</td>
<td>76 (46)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>778 (53)</td>
<td>76 (44)</td>
<td>76 (49)</td>
<td>117 (56)</td>
<td>56 (62)</td>
<td>83 (50)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>91 (6)</td>
<td>14 (8)</td>
<td>12 (8)</td>
<td>17 (8)</td>
<td>2 (2)</td>
<td>6 (4)</td>
<td></td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>1367 (91)</td>
<td>150 (86) *</td>
<td>135 (87) *</td>
<td>179 (85) *</td>
<td>80 (87)</td>
<td>147 (87)</td>
<td>0.002</td>
</tr>
<tr>
<td>BPD</td>
<td>799 (54)</td>
<td>107 (62) *</td>
<td>86 (55) *</td>
<td>139 (66) *</td>
<td>66 (73) *</td>
<td>114 (68) *</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PDA</td>
<td>788 (53)</td>
<td>111 (64) *</td>
<td>95 (61) *</td>
<td>149 (70) *</td>
<td>56 (61)</td>
<td>109 (65) *</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>460 (31)</td>
<td>62 (36)</td>
<td>56 (36)</td>
<td>78 (37) *</td>
<td>39 (42) *</td>
<td>70 (41) *</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgical NEC</td>
<td>57 (4)</td>
<td>10 (6)</td>
<td>7 (4)</td>
<td>10 (5)</td>
<td>5 (5)</td>
<td>17 (10) *</td>
<td>0.002</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>288 (19)</td>
<td>48 (28) *</td>
<td>41 (26) *</td>
<td>64 (30) *</td>
<td>28 (31) *</td>
<td>52 (31) *</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postnatal steroids</td>
<td>277 (19)</td>
<td>35 (20)</td>
<td>33 (21)</td>
<td>54 (26) *</td>
<td>21 (23)</td>
<td>23 (14)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*p-value <0.05 as compared to infants with no abnormalities (column 1), based on chi-square tests for categorical variables and t-tests for continuous variables.
Table 2.
Unadjusted rates of minor motor abnormalities, by most severe abnormality on cranial ultrasound

<table>
<thead>
<tr>
<th>Highest degree of abnormality on CUS</th>
<th>No abnormalities (N=1,502)</th>
<th>Unilateral or bilateral grade I IVH (N=174)</th>
<th>Unilateral or bilateral grade II IVH (N=157)</th>
<th>Unilateral or bilateral grade III/IV IVH (N=212)</th>
<th>Ventriculomegaly (N=92)</th>
<th>Unilateral or bilateral cystic PVL or porencephalic cyst (N=169)</th>
<th>Test for linear trend</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>Minor motor function abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any minor motor finding</td>
<td>732 (49)</td>
<td>79 (45)</td>
<td>84 (54)</td>
<td>127 (60)*</td>
<td>59 (64)*</td>
<td>113 (67)*</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>GMFCS level 1</td>
<td>62 (4)</td>
<td>6 (3)</td>
<td>10 (6)</td>
<td>26 (12)*</td>
<td>14 (15)*</td>
<td>22 (13)*</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Bayley-3 minor motor delay #</td>
<td>629 (42)</td>
<td>53 (33)*</td>
<td>66 (42)</td>
<td>92 (43)</td>
<td>48 (52)</td>
<td>76 (45)</td>
<td>0.145</td>
<td></td>
</tr>
<tr>
<td>Fine motor scaled score (mean ± SD)</td>
<td>8.9 (2.7)</td>
<td>9.0 (3.0)*</td>
<td>8.3 (3.1)</td>
<td>7.7 (3.1)</td>
<td>8.2 (2.9)*</td>
<td>7.2 (3.4)*</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>Gross motor scaled score (mean ± SD)</td>
<td>7.9 (2.5)</td>
<td>7.6 (2.6)</td>
<td>7.1 (2.7)*</td>
<td>6.4 (3.3)*</td>
<td>6.7 (2.9)*</td>
<td>5.2 (3.4)*</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Axial tone</td>
<td>49 (3)</td>
<td>7 (4)</td>
<td>14 (9)*</td>
<td>21 (10)*</td>
<td>11 (12)*</td>
<td>29 (17)*</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Gait/lower extremity function</td>
<td>172 (11)</td>
<td>30 (17)*</td>
<td>18 (11)</td>
<td>27 (13)</td>
<td>12 (13)</td>
<td>34 (20)*</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Upper extremity function</td>
<td>37 (2)</td>
<td>12 (7)*</td>
<td>10 (6)*</td>
<td>22 (10)*</td>
<td>5 (5)</td>
<td>46 (27)*</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Any major motor function abnormality</td>
<td>204 (14)</td>
<td>30 (17)</td>
<td>30 (19)</td>
<td>76 (36)*</td>
<td>33 (36)*</td>
<td>99 (59)*</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

* p-value <0.05 as compared to infants with no abnormalities (column 1), based on chi-square tests for categorical variables and t-tests for continuous variables.

# Any og motor composite score 71–85, fine motor scaled score 5–7 or gross motor scaled score 5–7.
Table 3.
Adjusted odds ratios for motor outcomes by highest degree of abnormality on cranial ultrasound

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Highest degree of abnormality on CUS</th>
<th>Adj OR (95% CI)</th>
<th>Adj OR (95% CI)</th>
<th>Adj OR (95% CI)</th>
<th>Adj OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unilateral or bilateral grade I IVH (N=174)</td>
<td>1.10 (0.78, 1.55)</td>
<td>0.94 (0.66, 1.36)</td>
<td>0.63 (0.45, 0.88)</td>
<td>0.58 (0.36, 0.94)</td>
</tr>
<tr>
<td></td>
<td>Unilateral or bilateral grade II IVH (N=157)</td>
<td>0.86 (0.61, 1.20)</td>
<td>1.05 (0.73, 1.49)</td>
<td>1.40 (1.02, 1.92)</td>
<td>1.71 (1.07, 2.72)</td>
</tr>
<tr>
<td></td>
<td>Unilateral or bilateral grade III/IV IVH (N=212)</td>
<td>0.81 (0.34, 1.95)</td>
<td>1.68 (0.82, 3.43)</td>
<td>2.59 (1.52, 4.43)</td>
<td>3.61 (1.87, 6.96)</td>
</tr>
<tr>
<td></td>
<td>Ventriculo-megaly (N=92)</td>
<td>0.70 (0.49, 0.99)</td>
<td>0.90 (0.63, 1.29)</td>
<td>0.99 (0.73, 1.36)</td>
<td>1.43 (0.91, 2.23)</td>
</tr>
<tr>
<td></td>
<td>Unilateral or bilateral cystic PVL or porencephalic cyst (N=169)</td>
<td>1.35 (0.38, 5.13)</td>
<td>2.84 (1.43, 5.64)</td>
<td>2.87 (1.58, 5.22)</td>
<td>3.03 (1.43, 6.42)</td>
</tr>
<tr>
<td>Minor motor function abnormalities</td>
<td>Any minor motor finding</td>
<td>1.51 (0.97, 2.36)</td>
<td>0.82 (0.47, 1.44)</td>
<td>0.94 (0.59, 1.50)</td>
<td>0.94 (0.48, 1.86)</td>
</tr>
<tr>
<td></td>
<td>GMFCS level 1</td>
<td>2.71 (1.33, 5.54)</td>
<td>2.58 (1.22, 5.45)</td>
<td>3.78 (2.09, 6.82)</td>
<td>1.69 (0.63, 4.54)</td>
</tr>
<tr>
<td></td>
<td>Bayley-3 minor motor delay #</td>
<td>1.30 (0.82, 2.06)</td>
<td>2.83 (1.99, 4.01)</td>
<td>2.79 (1.71, 4.54)</td>
<td>8.52 (5.84, 12.42)</td>
</tr>
</tbody>
</table>

Note: Reference category is infants with no CUS abnormalities, n=1502. Odds ratios are adjusted for center, GA, male sex, SGA, antenatal steroids, 5-minute Apgar ≤5, race, BPD, PDA, sepsis, surgical NEC, ROP stage 3, postnatal steroids, and adjusted age at assessment.

# Motor composite score 71–85, fine motor scaled score 5–7 or gross motor scaled score 5–7.
Table 4.

Resource utilization by highest degree of motor function abnormality

<table>
<thead>
<tr>
<th>Resource</th>
<th>None N (%)</th>
<th>Minor N (%)</th>
<th>Major N (%)</th>
<th>Minor vs. None</th>
<th>Major vs. None</th>
<th>Major vs. Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children (n=2,306)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any home equipment</td>
<td>138 (13)</td>
<td>170 (21)</td>
<td>297 (63)</td>
<td>1.53 (1.17, 1.99)</td>
<td>8.81 (6.64, 11.68)</td>
<td>5.76 (4.39, 7.57)</td>
</tr>
<tr>
<td>Use of anticonvulsants or anti-spasticity medication</td>
<td>4 (0)</td>
<td>12 (1)</td>
<td>55 (12)</td>
<td>3.86 (1.21, 12.32)</td>
<td>35.08 (12.23, 100.66)</td>
<td>9.09 (4.54, 18.17)</td>
</tr>
<tr>
<td>Resides in chronic care facility or requires medical day care</td>
<td>11 (1)</td>
<td>23 (3)</td>
<td>58 (12)</td>
<td>2.41 (1.12, 5.20)</td>
<td>10.12 (4.93, 20.77)</td>
<td>4.20 (2.45, 7.19)</td>
</tr>
<tr>
<td>Requires OT/PT</td>
<td>438 (43)</td>
<td>461 (57)</td>
<td>413 (88)</td>
<td>1.73 (1.41, 2.13)</td>
<td>8.30 (5.96, 11.54)</td>
<td>4.79 (3.44, 6.69)</td>
</tr>
<tr>
<td>Requires speech therapy</td>
<td>277 (27)</td>
<td>268 (33)</td>
<td>261 (55)</td>
<td>1.22 (0.97, 1.52)</td>
<td>2.73 (2.11, 3.53)</td>
<td>2.24 (1.73, 2.91)</td>
</tr>
<tr>
<td>Rehospitalizations (2 or more) *</td>
<td>154 (15)</td>
<td>159 (20)</td>
<td>213 (45)</td>
<td>1.17 (0.90, 1.52)</td>
<td>3.77 (2.87, 4.97)</td>
<td>3.23 (2.46, 4.24)</td>
</tr>
<tr>
<td>Thickened liquids and/or soft solids</td>
<td>413 (40)</td>
<td>357 (44)</td>
<td>245 (52)</td>
<td>1.37 (1.09, 1.72)</td>
<td>1.76 (1.33, 2.32)</td>
<td>1.29 (0.98, 1.70)</td>
</tr>
<tr>
<td>Children seen in 2011 or later (n=1,754)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal oral feeding skills</td>
<td>48 (6)</td>
<td>110 (18)</td>
<td>161 (45)</td>
<td>3.14 (2.13, 4.63)</td>
<td>11.65 (7.74, 17.54)</td>
<td>3.71 (2.65, 5.20)</td>
</tr>
<tr>
<td>Abnormal feeding behaviors</td>
<td>127 (16)</td>
<td>137 (22)</td>
<td>165 (47)</td>
<td>1.55 (1.15, 2.08)</td>
<td>4.22 (3.04, 5.87)</td>
<td>2.73 (1.99, 3.75)</td>
</tr>
</tbody>
</table>

*Rehospitalizations were dichotomized as ≥ versus < the 75th percentile of number of hospitalizations in the study cohort, or ≥2 versus <2 hospitalizations between initial discharge and 22–26 months CA.

Note: Odds ratios are adjusted for center, GA, male sex, SGA, antenatal steroids, 5-minute Apgar ≤5, race, BPD, PDA, sepsis, surgical NEC, ROP stage 3, postnatal steroids, and adjusted age at assessment.