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Clinical Data Predict Neurodevelopmental Outcome Better than Head Ultrasound in Extremely Low Birth Weight Infants

Eduardo Broitman, MD¹, Namasivayam Ambalavanan, MD¹, Rosemary D. Higgins, MD², Betty R. Vohr, MD³, Abhik Das, PhD⁴, Brinda Bhaskar, MS⁴, Kennan Murray, MPH⁴, Susan R. Hintz, MD⁵, and Waldemar A. Carlo, MD¹ for the National Institute of Child Health, Human Development Neonatal Research Network*

¹ University of Alabama at Birmingham, Birmingham, Alabama ² National Institute of Child Health and Human Development, Bethesda, Maryland ³ Women and Infants' Hospital, Providence, Rhode Island ⁴ RTI International, Research Triangle Park, NC ⁵ Stanford University, Palo Alto, California

Abstract

Objective— To determine the relative contribution of clinical data versus head ultrasound (HUS) in predicting neurodevelopmental impairment (NDI) in extremely low birth weight (ELBW) infants.

Study design— 2103 ELBW infants (<1000g) admitted to a National Institute of Child Health and Human Development Neonatal Research Network center who had a HUS within the first 28 days, a repeat one around 36 weeks' post-menstrual age, and neurodevelopmental assessment at 18–22 months corrected age were selected. Multivariate logistic regression models were developed using clinical and/or HUS variables. The primary outcome was the predictive abilities of the HUS done before 28 days after birth and closer to 36 weeks post-menstrual age, either alone or in combination with “Early” and “Late” clinical variables.

Results— Models using clinical variables alone predicted NDI better than models with only HUS variables at both 28 days and 36 weeks (both $p < 0.001$), and addition of the HUS data did not improve prediction. NDI was absent in 30% and 28% of the infants with grade IV intracranial hemorrhage or periventricular leukomalacia, respectively, but was present in 39% of the infants with a normal head ultrasound.

Conclusions— Clinical models were better than head ultrasound models in predicting neurodevelopment.

Keywords

Logistic models; Predictive value of tests; ROC curve; Infant; premature; Intracerebral hemorrhage; Leukomalacia; periventricular

Corresponding Author: Namasivayam Ambalavanan, MD, University of Alabama at Birmingham, 525 New Hillman Building, 619 South 19th St, Birmingham, AL 35249, Phone: (205) 934-4680; Fax: (205) 934-3100; E-mail: ambal@uab.edu.

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Advances in perinatal care have increased survival of extremely low birth weight (ELBW) infants (< 1000 grams).^{1,2} However, improvements in survival have not led to better neurodevelopmental outcomes.^{3,4} Many ELBW infants who survive develop major physical or behavioral disabilities such as severe neurological impairment, cerebral palsy, deafness, or blindness.⁴⁻⁶ In addition to these neurodevelopmental disabilities, survivors are at high risk for learning difficulties leading to school failure, stressed families, and increased health care costs.⁷⁻¹¹

Clinicians have attempted to predict neurodevelopmental impairment using many perinatal risk factors such as gestational age, race, maternal socioeconomic status, antenatal steroid use, mode of delivery, low Apgar scores, birth weight, severe intracranial hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, nosocomial sepsis, and necrotizing enterocolitis.^{4,12-15} Decisions to limit therapeutic interventions to avoid futile therapy and postponement of death are often based on a prediction of mortality and neurodevelopmental impairment. Identification of abnormal head ultrasound findings such as severe intracranial hemorrhage (grades III or IV) and periventricular leukomalacia are generally considered strong predictors of handicap^{4,14,16} and mortality.^{17,18} However, the variance in neurodevelopmental impairment explained by severe intracranial hemorrhage/periventricular leukomalacia has been generally low in these studies – 8% for a low mental developmental index (<70 or below 2 Standard Deviations of the mean) at 2 years of age¹⁴ and 5–7% for cognitive, language, and achievement performance at 8 years of age.¹⁹ The existing literature on the predictive ability of head ultrasound for neurodevelopmental outcome consists mostly of studies from single centers with small numbers of patients. Identification of severe intracranial hemorrhage (grades III or IV) and periventricular leukomalacia may occur early in the first few hours after birth or later in the clinical course,²⁰ with progression or resolution commonly observed.^{16,21-23}

Despite the uncertainty regarding the prediction of neurodevelopmental outcome, decisions to withdraw or withhold life-saving support are frequently based, at least in large part, on neurosonographic findings.^{17,18,24-26} Therefore, this study was designed to compare clinical variables and head ultrasound data in the prediction of neurodevelopmental impairment at 18–22 months corrected age.

METHODS

Population

This study analyzed data from a retrospective cohort of all ELBW infants (401–1000 g) who were admitted (both inborn and outborn) to any of the 19 participating centers of the National Institute of Child Health and Human Development Neonatal Research Network from January 1, 1998 to June 30, 2001. Infants were included if they had at least two head ultrasounds, one within 28 days after birth and a later ultrasound close to 36 weeks postmenstrual age, as well as follow-up assessment at 18–22 months corrected age. Exclusion criteria were lethal congenital malformations and chromosomal abnormalities. Data were routinely collected by trained research personnel and entered into a database as previously described.⁴ Data collection was approved by the institutional review board at each of the participating institutions.

Procedures

A comprehensive assessment was performed at 18–22 months corrected age. This assessment consisted of medical history, physical and neurologic examinations, and developmental assessment. The neurologic assessment (including muscle tone, strength, reflexes, angle, and posture) was performed using the Amiel-Tison method.²⁷ Cerebral palsy was defined as a non-progressive central nervous system disorder characterized by abnormal muscle tone in at least

one extremity and abnormal control of movement and posture. The developmental assessment consisted of the Bayley Scales of Infant Development II, 28 which included the mental and psychomotor developmental indices. Hearing impairment was defined as the use of hearing aids. Visual impairment was defined as blind with some functional vision or no useful vision. Neurodevelopmental impairment was defined as the infant having one or more of the following: psychomotor developmental index <70, mental developmental index <70, cerebral palsy, and hearing or visual impairment. Functional status was assessed by the presence or absence of independent walking and independent feeding.

Assessment of Head Ultrasounds

According to the standardized Neonatal Research Network data collection procedures, early head ultrasound (HUS-28) was the most abnormal head ultrasound obtained within the first 28 days after birth, and head ultrasound closer to 36 weeks (HUS-36) was the head ultrasound obtained after day 28 and closest to 36 weeks post-menstrual age. HUS-28 data were classified as: normal, blood/echodensity in germinal matrix/subependymal area (grade I), blood/echodensity in the ventricles (grade II), ventricular size enlarged (grade III), blood/echodensity in the parenchyma (grade IV), cystic area in the parenchyma (if a previous grade IV hemorrhage was documented previously), and/or periventricular leukomalacia (cystic area in the parenchyma was also considered periventricular leukomalacia if no grade IV was documented previously) by trained research nurses based on local radiology reports. HUS-36 data were classified as: normal, ventricular size enlarged, cystic area in the parenchyma (if a grade IV was documented previously), cystic periventricular leukomalacia, porencephalic cyst, and/or shunt. Data on size or location of the lesions were not collected. Central readers were not used. The specific frequency and timing of the head ultrasounds was based on clinical status and local protocols at each Network center.

Variables Analyzed

The variables analyzed were those that have been reported as associated with poor neurodevelopmental outcome by other investigators. Clinical variables were grouped as “Early” if they could be assessed by postnatal day 28. These included maternal education, antenatal steroids, antenatal antibiotics, mode of delivery, outborn, male, race, gestational age, 1 minute Apgar score <3, 5 minute Apgar score <3, 5 minute Apgar score 3–6, intubation at delivery, medications for resuscitation, birth weight (in 100 gram increments), intrauterine infection, breech presentation, surfactant, indomethacin <24 hours, indomethacin for patent ductus arteriosus treatment, early sepsis (culture positive), late onset sepsis (culture positive), proven necrotizing enterocolitis ($\geq$ Bell Stage II), seizures, pneumothorax, conventional ventilation, and high frequency ventilation. Clinical variables were grouped as “All” if they could be assessed before discharge home, death, and at 120 days, and included the “Early” clinical variables as well as supplemental O₂ at 36 weeks postmenstrual age, steroids for bronchopulmonary dysplasia, and threshold retinopathy of prematurity. Head ultrasound variables were grouped as early (HUS-28) or late (HUS-36) depending on ultrasound timing.

Statistical Analyses

The data were randomly divided into a development set of 70% of the population (n=1472) and a validation set of 30% (n=631). Stepwise variable selection was performed on the development set to obtain clinical and/or sonographic variables significantly associated with neurodevelopmental impairment, at $p = 0.1$ for the entry and exit criteria. For the combined head ultrasound/clinical models, the head ultrasound variables were forced to remain in the model. Using the selected clinical and head ultrasound variables, multiple logistic regression analysis was performed to develop a regression equation on the development set. This equation was applied to the validation set to predict neurodevelopmental impairment and its

components. Neurodevelopmental impairment was defined as mental developmental index <70, psychomotor developmental index <70, cerebral palsy, deafness and/or blindness. The process was repeated for HUS-28 and “Early” clinical variables, as well as for HUS-36 and “All” clinical variables alone and in combination. Predictive abilities of the different models were compared using the area under the curve of the receiver operating characteristic curves.

RESULTS

Demographic and Clinical Characteristics

Of 5867 ELBW infants admitted to any of the participating centers, 3096 infants had both HUS-28 and HUS-36 (Figure). HUS-28 was done before 7 days in 50%, 39% between 7 and 14 days, and 12% between 15 and 28 days of age. The median age at HUS-36 was day 57 (25th–75th centile of 37–74 days).

Of the 3009 infants without major malformations/syndromes, death before and after discharge occurred in 6.6% of the patients with normal head ultrasound or grade I intracranial hemorrhage, 11% of those with grade II intracranial hemorrhage, and 14% and 18% of those with grade III and IV intracranial hemorrhage, respectively. Cystic periventricular leukomalacia was noted in 5% of patients who died. 2,271 infants survived to follow-up at 18 to 22 month corrected age. Some or all neurodevelopmental impairment data were missing in 168 infants. Thus, a total of 2,103 infants were included in the analysis of neurodevelopmental impairment. A comparison of the infants lost to follow-up to those followed up shows that infants were comparable for birth weight and grade of intracranial hemorrhage, but there was a lower incidence of periventricular leukomalacia in infants lost to follow-up (Table I).

The mean gestational age for the study population was 26 weeks (± 1.8 weeks SD) and the mean birth weight was 773 grams (± 136 g SD). Eighty percent of the infants were exposed to at least one dose of antenatal steroids, 22% were multiple births, 53% were females, and 47% were black/non-Hispanic.

The overall rate of the combined outcome of death or neurodevelopmental impairment was 50%, with 45% (638/1430) infants with a normal HUS-28, 46% (121/266) of those with grade I intracranial hemorrhage, 58% (102/176) with grade II, 63% (163/259) with grade III, and 76% (140/184) with grade IV having neurodevelopmental impairment or death ($p < 0.0001$ for death or neurodevelopmental impairment by grade of intracranial hemorrhage). 77% (127/164) of those with periventricular leukomalacia and 81% (50/62) of those with cystic periventricular leukomalacia also either died or developed neurodevelopmental impairment. Overall, 2.3% (50/2153 infants) died after discharge, and the post-discharge death rate was comparable among those with normal HUS-28 (2.2%), grade 4 intracranial hemorrhage (2.7%) and those with periventricular leukomalacia (2.2%).

Prediction of Neurodevelopmental Impairment

Neurodevelopment impairment increased with worse head ultrasound findings (Table II). However, neurodevelopmental impairment was not present in 30% and 24% of the infants with grade IV intracranial hemorrhage and cystic periventricular leukomalacia, respectively, but was present in 39% of infants with normal head ultrasounds.

The “Early” and “All” clinical models were better predictors of neurodevelopmental impairment (areas under the curve = 0.68 for both), compared with the corresponding HUS-28 (areas under the curve = 0.58) and HUS-36 models (areas under the curve = 0.57) ($p < 0.001$ vs. the clinical models) (Figure 2_[L1]). The HUS-36 model did not improve prediction of neurodevelopmental impairment when compared to the HUS-28 model ($p = 0.4$). The combined

head ultrasound and clinical models were comparable to isolated clinical models for neurodevelopmental impairment prediction for both “Early” (0.68 vs 0.68, $p=0.5$) and “All” models (0.68 vs. 0.68, $p=0.9$).

Predictions of the major neurological outcomes were comparable for the HUS-36 model and HUS-28 model except for non-independent walking for which the HUS-36 model was superior (0.71 vs. 0.65, $p<0.01$). There was an improvement in the predictive ability for mental developmental index <70 (0.72 vs. 0.69, $p<0.05$), cerebral palsy (0.78 vs. 0.72, $p<0.01$), and non-independent walking (0.79 vs. 0.74, $p<0.01$) for the HUS-36/“All” clinical model as compared to the HUS-28/“Early” clinical model.

Multiple logistic regression analyses controlling for clinical variables and timing of head ultrasound revealed that only periventricular leukomalacia and shunt placement in HUS-36 were significantly associated with neurodevelopmental impairment (Table III; available at www.jpeds.com). Head ultrasound and clinical variables findings were significantly associated with various components of neurodevelopmental impairment.

DISCUSSION

This study addresses the ability of clinical models, head ultrasound models, and their combination to predict neurodevelopmental impairment at 18–22 months corrected age. Many ELBW infants with a normal head ultrasound later develop neurodevelopmental impairment, although some infants with abnormal head ultrasounds do not have significant impairment. Clinical models were stronger predictors for neurodevelopmental impairment and its components than head ultrasound models. Isolated head ultrasound findings had a poor predictive ability for neurodevelopmental outcome when compared to clinical data and generally demonstrated no improvement in predictive ability over time. Only when combined with clinical data was a head ultrasound closer to 36 weeks post-menstrual age better than an ultrasound in the first 28 days for the prediction of low mental developmental index, cerebral palsy, and non-independent walking. Overall, these models are not optimal for use in individual neonates due to lack of sufficient accuracy, but the models are suitable for evaluation of the relative importance of the predictors.

Periventricular leukomalacia was an important risk factor for neurodevelopmental impairment and its components but only if considered after the first 28 days. Echodensities diagnosed early in life may partially or completely resolve and consequently may not predict neurodevelopmental impairment.^{22,29,30} Independent of the time of the exam, enlarged ventricles was the only head ultrasound finding that predicted poor neurodevelopmental outcome. It is possible that enlarged ventricles may be a marker of abnormal white matter development.^{23,31}

Infants with normal head ultrasound and grades I and II intracranial hemorrhage had an incidence of neurodevelopmental impairment ranging from 39% to 51%. When corrected for other variables by regression analysis, a normal head ultrasound was not associated with normal outcome, which is consistent with the recent work by Laptok et al,³² who demonstrated that nearly 30% of ELBW infants with a normal head ultrasound had either cerebral palsy or a low MDI. It is likely that neurodevelopmental impairment will not always be preceded by abnormal ultrasound findings. Detection of subtle white matter damage may be better with magnetic resonance imaging.^{33,34}

Severe intracranial hemorrhage and periventricular leukomalacia are believed to be strong predictors of poor neurodevelopmental outcome.^{4,14–19} Abnormal ultrasonographic findings are considered often in decisions to withdraw or withhold therapy. Clinicians may consider the cranial ultrasound to provide additional prognostic data to the “pre-test probability” estimated

based upon multiple clinical variables (birth weight, antenatal variables, need for resuscitation, severity of illness). The current study shows that head ultrasounds do not reliably predict neurodevelopmental impairment in survivors. When controlled for clinical variables and timing of the exam, only periventricular leukomalacia diagnosed closer to 36 weeks and shunt placement were significantly associated with subsequent neurodevelopmental impairment. The high prevalence of neurodevelopmental impairment in infants with normal head ultrasound or minor grades of intracranial hemorrhage, and the frequent absence of severe neurodevelopmental impairment despite grade IV intracranial hemorrhage and/or periventricular leukomalacia indicate that the association between head ultrasound findings and neurodevelopmental outcome is not as strong as previously believed.^{14,19}

A limitation of this study is that the analysis was constrained to already existing data; however, the database was comprehensive and collected by trained personnel. Although head ultrasound interpretations are subject to interobserver variability^{35,36} and central readers were not used, the effect of inter-reader variability was minimized by using a predefined classification. Our study may also more closely approximate routine clinical practice as central readers are not used for clinical decision making. Another limitation is that the timing of the head ultrasound (both early and late) were variable, and this variability in timing may influence the observations. Again, however, this may more closely approximate routine clinical practice in which timing is variable. Only infants who survived to follow-up were evaluated. Therefore, differential bias is possible as infants in whom support was withdrawn as a result of severe intracranial hemorrhage would not have been included. Differential bias is also possible in this study as examiners during follow-up were not masked to the infants' clinical course, head ultrasound findings, or clinical findings on prior evaluations.

Important strengths of the current study include the analysis of a large multicenter cohort of ELBW infants with a standardized and comprehensive evaluation of neurodevelopment at 18–22 months corrected age. Furthermore, the analyses performed on head ultrasound findings were controlled not only for clinical variables but also for the time of the exam.

Clinical variables were stronger predictors than head ultrasound findings as the addition of head ultrasound data did not improve the predictive abilities of models with only clinical variables. The poor predictive ability for head ultrasound may be partly explained by the use of a classification that considers increasing grades of IVH as a progression of a single disease with cumulative effect.³⁷ Ventriculomegaly is considered a consequence of intraventricular hemorrhage although it may represent atrophy secondary to white matter damage from other causes.³¹ In addition to the anatomical site and extension of the hemorrhage,^{38,39} a classification that considers the degree of white matter damage,²² its location,⁴⁰ and whether these findings are persistent or transient⁴¹ may improve the prediction of neurologic outcome. Additional limitations of the current methods of ultrasound analysis include the lack of standardization in determination of ventricular size and of reporting of cerebellar lesions. It is possible that a classification of head ultrasound that takes into account the site, extension, and persistence of the hemorrhage as well as the degree of white matter damage may correlate better with longer-term outcome.

Clinicians often overestimate the incidence of major disability or death in these extremely sick babies, and this may lead to restriction of life support therapies.^{42,43} The current study documents that head ultrasound findings are poor predictors of outcome and indicates that decisions on withdrawal or withholding support in preterm infants should not be made based solely on head ultrasound findings. A large study with more accurate imaging techniques and/or classifications is required to identify specific characteristics that may improve the predictive ability of imaging studies for neurodevelopmental outcomes.

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References

1. Horbar JD, Badger GJ, Carpenter JH, Fanaroff AA, Kilpatrick S, LaCorte M, et al. Trends in mortality and morbidity for very low birth weight infants, 1991–1999. *Pediatrics* 2002;110:143–51. [PubMed: 12093960]
2. Arias E, MacDorman MF, Strobino DM, Guyer B. Annual summary of vital statistics—2002. *Pediatrics* 2003;112:1215–30. [PubMed: 14654589]
3. Lorenz JM, Wooliever DE, Jetton JR. A quantitative review of mortality and development disability in ELBW. *Arch Pediatr Adolesc Med* 1998;152:425–35. [PubMed: 9605024]
4. Vohr BR, Wright LL, Dusick AM, Mele L, Verter J, Steichen JJ, et al. Neurodevelopment and functional outcomes of extremely low birth weight infants in the national institute of child health and human development neonatal research network, 1993–1994. *Pediatrics* 2000;105:1216–26. [PubMed: 10835060]
5. Wood N, Marlow N, Costeloe K. Neurologic disability after extremely preterm birth. *N Engl J Med* 2000;343:378–84. [PubMed: 10933736]
6. Doyle LW, Casalaz D. Victorian Infant Collaborative Study Group. Outcome at 14 years of extremely low birth weight infants: a regional study. *Arch Dis Child Fetal Neonatal Ed* 2001;85:F159–64. [PubMed: 11668155]
7. Singer LT, Salvator A, Guo S, Collin M, Lilien L, Baley J. Maternal psychological distress and parenting stress after the birth of a very low birth weight infant. *JAMA* 1999;281:799–805. [PubMed: 10071000]
8. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA* 2002;288:728–37. [PubMed: 12169077]
9. Petrou S, Sach T, Davidson L. The long-term costs of preterm birth and low birth weight: results of a systematic review. *Child Care Health Dev* 2001;27:97–115. [PubMed: 11251610]
10. Stevenson RC, Pharoah PO, Stevenson CJ, McCabe CJ, Cooke RW. Cost of care for a geographically determined population of low birth weight infants to age 8–9 years. II Children with disability. *Arch Dis Child Fetal Neonatal Ed* 1996;74:F118–21. [PubMed: 8777658]
11. Saigal S, den Ouden L, Wolke D, Hoult L, Paneth N, Streiner DL, et al. School-age outcomes in children who were extremely low birth weight from four international population-based cohorts. *Pediatrics* 2003;112:943–50. [PubMed: 14523190]
12. Zernikow B, Holtmannspoecker K, Michel E, Pielemeier W, Hornschuh F, Westermann A, et al. Artificial neural network for risk assessment in preterm neonates. *Arch Dis Child Fetal Neonatal Ed* 1998;79:F129–34. [PubMed: 9828740]
13. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA* 2004;292:2357–65. [PubMed: 15547163]
14. Ambalavanan N, Nelson KG, Alexander G, Johnson SE, Biasini F, Carlo W. Prediction of neurologic morbidity in extremely low birth weight infants. *J Perinatol* 2000;20:496–503. [PubMed: 11190589]
15. Hack M, Wilson-Costello D, Friedman H, Taylor GH, Schluchter M, Fanaroff AA. Neurodevelopment and predictors of outcomes of children with weight less than 1000 g. *Arch Pediatr Adolesc Med* 2000;154:725–31. [PubMed: 10891026]
16. Pierrat V, Duquennoy C, van Haastert IC, Ernst M, Guille N, de Vries LS. Ultrasound diagnosis and neurodevelopmental outcome of localized and extensive cystic periventricular leukomalacia. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F151–6. [PubMed: 11320039]

17. McMenamin JB, Shackelford GD, Volpe JJ. Outcome of neonatal intraventricular hemorrhage with periventricular echodense lesions. *Ann Neurol* 1984;15:285–90. [PubMed: 6721450]
18. Volpe, JJ. Neurology of the newborn. 4. 2001. Intracranial hemorrhage: germinal matrix-intraventricular hemorrhage of the premature infant; p. 428-93.
19. Vohr BR, Allan WC, Westerveld M, Schneider KC, Katz KH, Makuch RW, et al. School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 2003;111:340–6.
20. Perlman JM, Rollins N. Surveillance protocol for the detection of intracranial abnormalities in premature neonates. *Arch Pediatr Adolesc Med* 2000;154:822–6. [PubMed: 10922280]
21. Goetz MC, Gretebeck RJ, Oh KS, Shaffer D, Hermansen MC. Incidence, timing, and follow-up of periventricular leukomalacia. *Am J Perinatol* 1995;12:325–7. [PubMed: 8540933]
22. Lai FF, Tsou KY. Transient periventricular echodensities and developmental outcome in preterm infants. *Pediatr Neurol* 1999;21:797–801. [PubMed: 10593669]
23. Kuban K, Sanocka U, Levinton A, Allred EN, Pagano M, Dammann O, et al. White matter disorders of prematurity: association with intraventricular hemorrhage and ventriculomegaly. *J Pediatr* 1999;134:539–46. [PubMed: 10228286]
24. Cook LA, Watchko JF. Decision making for the critically ill neonate near the end of life. *J Perinatol* 1996;16:133–6. [PubMed: 8732563]
25. Wall SN, Partridge JC. Death in the intensive care nursery: physician practice of withdrawing and withholding life support. *Pediatrics* 1997;99:64–70. [PubMed: 8989340]
26. Cuttini M, Nadai M, Kaminski M, Hansen G, de Leeuw R, Lenoir S, et al. End-of-life decisions in neonatal intensive care: physicians' self-reported practices in seven European countries. EURONIC Study Group. *Lancet* 2000;355:2112–8. [PubMed: 10902625]
27. Amiel-Tison, C. Neuromotor status. In: Taesch, HW.; Yogman, MW., editors. *Follow-up Management of the High-Risk Infant*. Boston, MA: Little, Brown Company; 1987. p. 115-26.
28. Bayley, N. Bayley Scales of Infant Development-II. San Antonio, TX: The Psychological Corporation; 1993.
29. Ringelberg J, van de Bor M. Outcome of transient periventricular echodensities in preterm infants. *Neuropediatrics* 1993;24:269–73. [PubMed: 8309516]
30. Fawer CL, Diebold P, Calame A. Periventricular leukomalacia and neurodevelopmental outcome in preterm infants. *Arch Dis Child* 1987;62:30–6. [PubMed: 2434037]
31. Leviton A, Gilles F. Ventriculomegaly, delayed myelination, white matter hypoplasia, and “periventricular” leukomalacia: how are they related? *Pediatr Neurol* 1996;15:127–36. [PubMed: 8888047]
32. Laptook AR, O’ Shea TM, Shankaran S, Bhaskar B. the NICHD Neonatal Network. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:1–8. [PubMed: 15629973]
33. Maalouf EF, Duggan PJ, Counsell SJ, Rutherford MA, Cowan F, Azzopardi D, et al. Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm infants. *Pediatrics* 2001;107:719–27. [PubMed: 11335750]
34. Barnes PD, Keller K, Constantinou JC, Fleisher BE, Hintz SR, Ariagno RL. Neonatal brain magnetic resonance imaging before discharge is better than serial cranial ultrasound in predicting cerebral palsy in very low birth weight preterm infants. *Pediatrics* 2004;114:992–8. [PubMed: 15466096]
35. Pinto J, Paneth N, Kazam E, Kairam R, Wallenstein S, Rose W, et al. Interobserver variability in neonatal cranial ultrasonography. *Paediatr Perinat Epidemiol* 1988;2:43–58. [PubMed: 3070483]
36. O’Shea TM, Volberg F, Dillard RG. Reliability of interpretation of cranial ultrasound examinations of very low-birthweight neonates. *Dev Med Child Neurol* 1993;35:97–101. [PubMed: 8444332]
37. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birthweights less than 1500g. *J Pediatr* 1978;92:529–534. [PubMed: 305471]
38. Paneth N. Classifying brain damage in preterm infants. *J Pediatr* 1999;134:527–9. [PubMed: 10228280]

39. de Vries LS, Van Haastert ILC, Rademaker KJ, Koopman C, Groenedaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. *J Pediatr* 2004;144:815–20. [PubMed: 15192633]
40. Holling EE, Leviton A. Characteristics of cranial ultrasound white-matter echolucencies that predict disability: a review. *Dev Med Child Neurol* 1999;41:136–9. [PubMed: 10075101]
41. Dammann O, Leviton A. Duration of transient hyperechoic images of white matter in very-low-birthweight infants: a proposed classification. *Dev Med Child Neurol* 1997;39:2–5. [PubMed: 9003722]
42. Meadow W, Frain L, Ren Y, Lee G, Soneji S, Lantos J. Serial assessment of mortality in the neonatal intensive care unit by algorithm and intuition: certainty, uncertainty, and informed consent. *Pediatrics* 2002;109:878–86. [PubMed: 11986450]
43. Morse SB, Haywood JL, Goldenberg RL, Bronstein J, Nelson KG, Carlo WA. Estimation of neonatal outcome and perinatal therapy use. *Pediatrics* 2000;105:1046–50. [PubMed: 10790461]

Appendix

List of Participating NICHD Neonatal Research Network Centers during the period of the study

	Center	Principal Investigator (PI)	Follow up Principal Investigator (FPI)	Network Coordinator (NC)	Follow-up Coordinator
1	Brown University	William Oh, MD	Betty Vohr, MD	Angelita Hensman, RNC	Lucy Noel, RNC
2	Case Western Reserve University	Avroy A. Fanaroff, MB BCH	Dee Wilson, MD	Nancy Newman, RN	Bonnie Siner, RN
3	Duke University	Ronald N Goldberg, MD	Ricki Goldstein, MD	Kathy Auten, RN, BS	Melody Lohmeyer, RN
4	Emory University	Barbara J. Stoll, MD	Barbara J. Stoll, MD	Ellen Hale, RNC, BS	Ellen Hale, RNC, BS
5	Harvard University	Ann R. Stark, MD	Ann R. Stark, MD	Kerri Fournier, RN	
6	Indiana University	James A. Lemons, MD	Anna Dusick, MD	DeeDee Appel, RN	Leslie Richards, RN
7	Stanford University	David K. Stevenson, MD	Susan Hintz, MD	Bethany Ball, RN, BS	Bethany Ball, RN, BS
8	University of Alabama	Waldemar A. Carlo, MD	Kathy Nelson, MD	Monica Collins, RN	Vivien Phillips, RN
9	University of California, San Diego	Neil N. Finer, MD	Yvonne Vaucher, MD	Chris Henderson, RN	Martha Fuller, RN
10	University of Cincinnati	Edward F. Donovan, MD	Jean Steichen, MD	Cathy Grisby, RN	Tari Gratton, RN
11	University of Miami	Shahnaz Duara, MD	Charles Bauer, MD	Ruth Everett, RN	Mary Allison, RN
12	University of New Mexico	Lu-Ann Papile, MD	Lu-Ann Papile, MD	Conra Backstrom, RN	
13	University of Rochester	Dale L. Phelps, MD	Gary Myers, MD	Linda Reubens, RN	Diane Hust, RN
14	University of Texas, Houston	Jon E. Tyson, MD, MPH	Brenda Morris, MD	Georgia McDavid, RN	Shannon Rossi
15	Wake Forest University	T. Michael O'Shea, MD	Robert Dillard, MD	Nancy Peters, RN	Barbara Jackson, RN
16	Wayne State University	Seetha Shankaran, MD	Yvette Johnson, MD	Gerry Muran, BSN	Debbie Kennedy, RN
17	Yale University	Richard A. Ehrenkranz, MD	Linda Mayes, MD	Pat Gettner, RN	Elaine Romano, MSN
18	NICHD	Linda L. Wright, MD, Rosemary D. Higgins, MD		Beth B. McClure, MS	
19	Research Triangle Institute	W. Kenneth Poole, PhD	W. Kenneth Poole, PhD	Betty Hastings, Carolyn Petrie, MS	Beth B. McClure, MS

HUS Analysis Sample Flow Chart

Figure.

Flow chart showing numbers of infants available for analysis in the study.

Table 1

Comparison of infants lost to follow-up to those followed up. The lost to follow-up includes the infants that had follow-up but data on NDI was missing.

	Lost to Follow-up	Followed up	p-Value
N	647	2103	
Birth Weight	777 $\pm$ 137	773 $\pm$ 136	0.53
Gestational Age	26.0 $\pm$ 2.0	25.8 $\pm$ 1.8	0.04
Male	310 (48.0%)	988 (47.0%)	0.69
IVH Grade 0	425 (66.4%)	1308 (63.4%)	0.22
IVH Grade 1	71 (11.1%)	244 (11.8%)	
IVH Grade 2	52 (8.1%)	151 (7.3%)	
IVH Grade 3	62 (9.7%)	215 (10.4%)	
IVH Grade 4	30 (4.7%)	145 (7.0%)	
PVL	24 (3.7%)	134 (6.4%)	0.01
Cystic PVL	7 (1.1%)	50 (2.4%)	0.06

Table 2

Percentage of infants with each neurological outcome at 18–22 months corrected age by head ultrasound findings.

Head ultrasound variable	NDI n=929	MDI<70 n=174	PDI<70 n=478	Cerebral palsy n=347	Blindness n=66	Deafness n=42	Non-independent walking n=260	Non-independent feeding n=318
Normal (n=1308)	39.4	31.9	18.8	10.1	1.6	1.5	7.7	12.8
Intracranial hemorrhage								
grade 1 (n=244)	40.6	31.5	18.0	17.2	2.9	1.2	10.7	13.9
grade 2 (n=151)	51.0	36.9	22.3	17.2	4.0	3.3	9.3	13.9
grade 3 (n=215)	55.4	43.3	36.7	31.3	7.0	2.8	25.1	23.4
grade 4 (n=145)	69.7	52.6	55.5	51.4	11.2	4.9	42.4	28.5
Periventricular leukomalacia (n=134)	72.4	60.3	52.8	50.0	10.5	3.7	44.0	29.1
Cystic periventricular leukomalacia (n=50)	76.0	60.4	64.6	64.0	18.0	6.3	50.0	32.0

All infants were counted only once and were assigned the highest grade of intracranial hemorrhage/leukomalacia from either head ultrasound.

Missing values in either the row or column variable were excluded from the analysis.

Table 3

Odds ratios and 95% confidence intervals of clinical and head ultrasound predictors (at $p < 0.05$) on neurodevelopmental outcomes.

Outcome	“Early” Predictors	OR (CI 95%)	“All” Predictors	OR (CI 95%)
Neurodevelopmental impairment				
Clinical				
	Male	2.0 (1.6–2.5)	Male	1.9 (1.5–2.4)
	Race ⁺	1.3 (1.0–1.6)	Race	1.3 (1.0–1.7)
	Surfactant	1.7 (1.2–2.3)	Surfactant	1.5 (1.0–2.1)
	High frequency ventilation	1.5 (1.2–2.0)	Chronic lung disease	1.4 (1.1–1.8)
	Seizure	2.2 (1.3–3.7)	Late onset sepsis	1.6 (1.2–2.0)
	Late onset sepsis	1.7 (1.4–2.2)	Retinopathy of prematurity	1.9 (1.4–2.6)
	Birth weight [§]	0.8 (0.7–0.9)	Birth weight	0.8 (0.8–0.9)
Head ultrasound				
	None statistically significant at p<0.05		Periventricular leukomalacia	3.3 (1.7–6.4)
			Shunt	3.6 (1.6–8.2)
Mental Developmental Index <70				
Clinical				
	Male	2.4 (1.9–3.0)	Male	2.3 (1.8–2.9)
	Race	1.5 (1.2–2.0)	Race	1.6 (1.2–2.1)
	Surfactant	1.6 (1.1–2.3)	Surfactant	1.5 (1.0–2.3)
	High frequency ventilation	1.5 (1.1–2.0)	Chronic lung disease	1.4 (1.1–1.9)
	Seizure	2.2 (1.4–3.6)	Late onset sepsis	1.5 (1.2–2.0)
	Late onset sepsis	1.6 (1.2–2.0)	Retinopathy of prematurity	1.6 (1.1–2.2)
	Birth weight	0.8 (0.7–0.9)	Birth weight	0.8 (0.7–0.9)
Head ultrasound				
	Periventricular leukomalacia	2.4 (1.1–5.2)	Periventricular leukomalacia	2.3 (1.3–4.4)
			Shunt	2.2 (1.1–4.7)
Psychomotor Developmental Index <70				
Clinical				
	Male	1.5 (1.1–1.9)	Male	1.4 (1.0–1.8)
	High frequency ventilation	1.7 (1.2–2.2)	Steroids for bronchopulmonary dysplasia	1.5 (1.1–2.1)
	Seizure	2.8 (1.7–4.6)	Seizure	2.3 (1.4–3.9)
	Late onset sepsis	1.8 (1.4–2.4)	Late onset sepsis	1.8 (1.3–2.4)
	Birth weight	0.9 (0.8–1.0)	Retinopathy of prematurity	1.8 (1.3–2.6)
			Birth weight	0.9 (0.8–1.0)
			Gestational age	1.2 (1.0–1.2)
Head ultrasound				
	Parenchymal blood	1.9 (1.1–3.3)	Periventricular leukomalacia	3.2 (1.7–6.0)
	Ventricular enlargement	2.3 (1.4–3.7)	Ventricular enlargement	1.7 (1.0–2.7)
			Shunt	3.0 (1.5–6.4)
Cerebral Palsy				
Clinical				

Outcome	“Early” Predictors	OR (CI 95%)	“All” Predictors	OR (CI 95%)
	Male	1.5 (1.1–2.1)	Male	1.4 (1.0–2.0)
	Pneumothorax	1.8 (1.1–2.9)	Pneumothorax	1.7 (1.1–2.8)
	Seizure	3.4 (2.1–5.5)	Steroids for bronchopulmonary dysplasia	1.5 (1.0–2.1)
	Birth weight	0.9 (0.8–1.0)	Seizure	2.8 (1.7–4.6)
			Indomethacin	1.4 (1.0–1.9)
			Birth weight	0.9 (0.8–1.0)
Head ultrasound				
	Normal	0.5 (0.3–0.8)	Periventricular leukomalacia	5.2 (2.8–9.6)
	Parenchymal blood	2.3 (1.3–3.9)	Ventricular enlargement	1.9 (1.2–3.1)
	Ventricular enlargement	2.0 (1.3–3.2)	Shunt	3.7 (1.8–7.8)
Non-independent feeding				
Clinical				
	Male	1.8 (1.3–2.4)	Male	1.8 (1.3–2.5)
	Pneumothorax	1.8 (1.1–2.9)	Pneumothorax	2.0 (1.2–3.2)
	High frequency ventilation	1.6 (1.2–2.3)	Chronic lung disease	1.5 (1.1–2.1)
	Maternal education*	1.9 (1.2–3.1)	High frequency ventilation	1.7 (1.2–2.4)
	Birth weight	0.8 (0.7–0.9)	Gestational age	1.1 (1.0–1.2)
			Birth weight	0.7 (0.7–0.9)
			Maternal education	1.9 (1.2–3.1)
Head ultrasound				
	Ventricular enlargement	2.3 (1.3–3.9)	Ventricular enlargement	2.2 (1.3–3.8)
Non-independent walking				
Clinical				
	Steroids	0.6 (0.4–0.9)	Steroids	0.6 (0.4–0.9)
	Male	1.4 (1.0–2.1)	Chronic lung disease	1.7 (1.2–2.6)
	Seizure	4.5 (2.7–7.3)	Seizure	3.8 (2.2–6.3)
	High frequency ventilation	1.6 (1.1–2.4)	High frequency ventilation	1.5 (1.0–2.2)
	Late onset sepsis	1.8 (1.3–2.6)	Late onset sepsis	1.8 (1.2–2.6)
	Birth weight	0.9 (0.7–1.0)	Birth weight	0.8 (0.7–1.0)
Head ultrasound				
	Periventricular leukomalacia	2.4 (1.0–5.5)	Periventricular leukomalacia	4.4 (2.4–8.3)
	Parenchymal blood	2.2 (1.2–4.0)	Ventricular enlargement	2.1 (1.2–3.5)
	Ventricular enlargement	3.0 (1.7–5.3)	Shunt	2.4 (1.2–5.0)

⁺ Race compares Black and non-Hispanic versus others

[§] Odds ratios for birth weight are given for every 100 grams increment in birth weight

^{*} Comparison of maternal education up to 12th grade versus college/graduate degree