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Neonatal Cranial Ultrasound Abnormalities in Low Birth Weight Infants: Relation to Cognitive Outcomes at Six Years of Age

Agnes H. Whitaker, MD*‡; Judith F. Feldman, PhD*; Ronan Van Rossem, PhD*; Irvin Sam Schonfeld, PhD, MPH*§; Jennifer A. Pinto-Martin, PhD‖; Carolyn Torre, RN, MA*; Suzannah R. Blumenthal*; and Nigel S. Paneth, MD, MPH¶

ABSTRACT. *Objective.* **To assess the independent relation of neonatal cranial ultrasound (US) abnormalities in low birth weight (LBW) infants to cognitive outcomes at 6 years of age.**

Design. **Prospective cohort study.**

Sample and Methods. **Six-year follow-up data were obtained on a regional birth cohort of LBW infants (<2 kg) systematically screened as neonates with serial US. US abnormalities were dichotomized into isolated germinal matrix/intraventricular hemorrhage (GM/IVH) and parenchymal lesions/ventricular enlargement (PL/VE). Global cognitive outcomes (mental retardation, borderline intelligence, and normal intelligence) and selected specific cognitive abilities were assessed at 6 years of age with standardized instruments. Multivariate techniques were used to assess the effects of US independent of maternal social disadvantage at birth and other perinatal and neonatal risk factors.**

Results. **The sample as a whole had a significantly elevated rate of mental retardation (MR; 5%), almost all moderate to profound in severity. PL/VE was independently related to MR (odds ratio [OR], 65.8; confidence interval [CI], 19.1 to 22.4) and borderline intelligence (OR, 3.7; CI, 1.3 to 10.8); isolated GM/IVH was more modestly related to MR (OR, 4.6; CI, 1.2 to 18.6) but not related to borderline intelligence. Approximately half of the cases of MR were attributable to PL/VE independent of other factors. Of non-US factors, the number of days receiving mechanical ventilation increased the risk for MR. Maternal social disadvantage increased the risk for borderline intelligence but not MR. Among children of normal intelligence, those with PL/VE, but not isolated GM/IVH, performed more poorly than those without US abnormalities on tests of visual perceptual organization but not on tests of language, memory, or quantitative skills.**

Conclusion. **Prevention of white matter injury would substantially improve cognitive outcomes for LBW infants.** ***Pediatrics* 1996;98:719–729; *low birth weight, ultrasound, white matter injury, mental retardation, cognitive outcomes.***

From the *Division of Child and Adolescent Psychiatry, Columbia University College of Physicians and Surgeons and New York State Psychiatric Institute, New York; ‡Gertrude H. Sergievsky Center, Columbia University College of Physicians and Surgeons; §City College of New York; ‖Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine, Department of Pediatrics, Division of General Pediatrics and Biostatistics and Epidemiology; and ¶Department of Pediatrics and Human Development, College of Human Medicine, Michigan State University, East Lansing, Michigan.

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Reprint requests to (A.H.W.) Unit 78, 722 West 168th St, New York, NY 10032.

ABBREVIATIONS. LBW, low birth weight; VLBW, very low birth weight; MR, mental retardation; US, ultrasound; GM/IVH, germinal matrix/intraventricular hemorrhage; PL/VE, parenchymal lesion/ventricular enlargement; NBHS, Central New Jersey Neonatal Brain Hemorrhage Study; CP, cerebral palsy; SB, Stanford-Binet; TOLD, Test of Language Development; VMI, Developmental Test of Visual Motor Integration; TVPS, Test of Visual Perceptual Skills; NA, no abnormality; FGR, fetal growth ratio; OR, odds ratio; CI, confidence interval; *B*, unstandardized partial regression coefficient.

Concern about cognitive impairments in school-aged children born at low birth weight (LBW; <2.5 kg) has intensified because of the improved survival of very low birth weight (VLBW; <1.5 kg) and extremely low birth weight (<1 kg) infants in the modern era of newborn intensive care.[1,2] These cognitive impairments range in severity from mental retardation (MR) to more subtle deficits that may impede learning.[3,4] Since the 1991 review by Ornstein et al,[5] numerous studies have confirmed that school-aged children of LBW,[6–8] VLBW,[9–11] and extremely low birth weight[12–17] are at excess risk for MR and borderline intelligence[6–12,14–17] and perform more poorly than peers on tests related to language,[7,9,11,13–15] visual perceptual organization,[6,7,11–14,16,17] and memory,[9,11] even when neurologically intact[8,11,13] or of normal intelligence.[11]

Before the advent of brain imaging, postmortem studies implicated perinatal brain injury in the etiology of MR[18,19] and more subtle cognitive deficits[20] in premature LBW infants. After the introduction of neonatal cranial ultrasound (US) in the early 1980s, it became possible to study the relation of perinatal brain injury to suboptimal cognitive outcomes in LBW survivors. The most commonly seen US abnormalities in LBW neonates can be categorized on the basis of neuropathology[21,22] into two groups: (1) isolated germinal matrix/intraventricular hemorrhage (GM/IVH); and (2) parenchymal lesions/ventricular enlargement (PL/VE) with or without GM/IVH. Both injury groups are potentially relevant to cognitive impairment: isolated GM/IVH, because the germinal matrix, a fetal brain structure that involutes by 34 to 36 weeks' gestation,[23] has importance for neuronal and glial proliferation and migration;[24] and PL/VE, because both PL and VE reflect injury to white matter[21] with implications for brain organization[24,25] and myelination.[24,26–29]

In addition to perinatal brain injury, other risk

factors for suboptimal cognitive outcomes by school age may accompany LBW; these include other medical complications and maternal social disadvantage. Most studies that have used multivariate techniques to assess the independent relation of US abnormalities to school-age cognitive outcomes have examined relatively small, hospital-based samples.[30–33] The only report to date on a regional birth cohort examined the relation of one type of US abnormality (PL/VE) to one outcome (MR) in children with a very restricted range of birth weights (<750 g).[17]

By contrast, the present study examines the relation of both groups of US abnormalities (GM/IVH and PL/VE) to a range of cognitive outcomes at school age in a large, regionally defined LBW cohort. The cohort has been well described in terms of other risk factors at birth and neurodevelopmental impairment at 2 years of age.[34] The school-age cognitive outcomes studied include MR and borderline intelligence as well as specific abilities (language, visual perceptual organization, short-term memory, and quantitative reasoning) in children of normal intelligence.

METHODS

Birth Cohort

Children in this study belong to the birth cohort enrolled in the Central New Jersey Neonatal Brain Hemorrhage Study (NBHS).[22,35] That study prospectively enrolled 1105 consecutive infants with birth weights of 501 to 2000 g who were born in or admitted to three New Jersey hospitals between September 1, 1984, and June 30, 1987. The neonatal intensive care units of these three hospitals provided neonatal care for 83% of all infants born at less than 2000 g and about 90% of all born at less than 1500 g in three New Jersey counties during this period. Based on the 1980 and 1990 census reports, this three-county region had a per capita income ($13 344 in 1980 and $18 517 in 1990) that was higher than that of the United States as a whole ($10 797 and $16 535, respectively), but similar to that of the state of New Jersey ($13 129 and $18 714, respectively). The proportion of African-Americans and other minorities (Hispanics, Asians, and Native Americans) in the region was also lower (8.4% in the 1980 census and 12.8% in 1990) than that reported for the nation (14.9% and 19.7%, respectively) and the state (15.5% and 20.7%).[22,35]

Neonatal Procedures

As part of a protocol described in detail elsewhere,[35] serial cranial US was performed at 4 and 24 hours and 7 days of life; 98% of the cohort had at least one of the three films, and 47% were additionally scanned at the fifth hospital week and/or before discharge. In 92% of the infants, two radiologists, informed only of the infants' birth weights, read the scans independently; when they disagreed on the presence or time of onset of an abnormality, a third reader rendered a decision. This report uses the consensus reading whenever available; otherwise, the initial reading by one radiologist is used. A maternal interview and systematic chart abstraction provided other important prenatal, perinatal, and neonatal descriptors.[35]

Procedures at 2 Years

At 2 years of age (corrected for prematurity), 86% of the surviving children were reassessed by examination (80%) or maternal questionnaire (6%) for major neurodevelopmental impairment, including cerebral palsy (CP).[34]

Sample at 6 Years

By 6 years of age, 207 children had died, leaving 898 (81%) children from the birth cohort eligible for follow-up. Of the 898 surviving children, 685 (76%) participated in the study at 6 years of age, 45 (5%) families refused, 143 (16%) could not be located, and 25 (3%) had been adopted. The 213 nonparticipants did not differ from the participants in birth characteristics, including US status. However, mothers of nonparticipants were more likely to be socially disadvantaged, as reflected on a composite index described below ($P < .001$). Of the 685 participants, 597 (87%) were assessed at home visits, 85 (12%) by phone, and 3 (0.4%) by mail. Phone or mail assessments were conducted only when the child resided more than 1 day's travel from the field office or the family strongly preferred that option. Children assessed by phone or mail did not differ from those seen at home visits in birth characteristics or maternal social disadvantage. Because of the more limited information available from phone or mail interviews, the sample for the present report is confined to the 597 children assessed at home visits (66% of the 898 survivors). This sample was predominantly white (74% white, 22% African-American, and 5% other) and mainly middle class (with 19% of the families receiving public assistance).

Procedures at 6 Years

A pediatric nurse practitioner and a psychologist, both blind to US status, conducted the home visits. The assessment battery covered important child outcomes as well as parental health, family functioning, and the home environment. Child cognitive outcomes (general intellectual functioning, language, and visual perceptual organization) were measured with standardized instruments administered to the child by the psychologist (see Table 1). The overall adaptive functioning of the child was measured with a standardized maternal interview conducted by the nurse, who also collected information on the child's activity limitations (Activity Limitations Questionnaire[36]) and health status (Health Problems Questionnaire[36] and Service Utilization and Risk Factors modules[37]). Informed consent by parents or legal guardians was obtained for all children before participation in the 6-year follow-up. All procedures were approved by the New York State Psychiatric Institute Institutional Review Board.

Measures and Definitions of Cognitive Outcomes

Global cognitive outcomes (mental retardation, borderline intelligence, and normal intelligence) are defined as shown in Table 1. As required by the American Psychiatric Association[38] and the American Association on Mental Retardation,[39] impairment in both intelligence and adaptive functioning was necessary to meet criteria for MR. Children who were too impaired to be administered the Stanford-Binet (SB)[40] (n = 21) were assigned a composite score of 35, one point lower than the lowest obtainable score; this strategy is similar to that used in the Scottish Low Birthweight Study[7] and others.[17] All the untestable children scored less than 78 on the composite score of the Vineland Adaptive Behavior Scale,[41] and all but two had Vineland Adaptive Behavior Scale scores of less than 55, confirming that they were impaired rather than uncooperative.[42]

More specific cognitive outcomes were assessed using the measures shown in Table 1. Language was assessed by the Verbal Reasoning Area of the SB and by the Test of Language Development (TOLD).[43] One to three subtests of the TOLD (Picture and Oral Vocabulary and Sentence Imitation) were not administered to 138 children because of time constraints. For these children, scores from comparable subtests of the SB (transformed to accommodate the differing SDs of the two tests) were substituted when computing the three major quotients. Short-term memory and quantitative reasoning were assessed with the areas of the SB covering these domains, bearing in mind that the subtests of the SB have not been as extensively validated as the overall composite score.[44] Visual perceptual organization was assessed with the Abstract Visual Reasoning Area of the SB, which consists of tests of pattern recognition and copying of designs; the Developmental Test of Visual Motor Integration (VMI),[45] which also tests the ability to copy designs; and the Test of Visual Perceptual Skills (TVPS)[46] (see Table 1). The TVPS assesses the ability to recognize abstract forms when they are presented alone or embedded in other figures and/or transformed in scale or orientation; responses require no manual dexterity. Impairment on any of the above tests was defined as a score more than 2 SDs below the mean for that test; such impairments are considered important factors in the poorer academic performance of preterm LBW children relative to peers.[3,4]

TABLE 1. Cognitive Outcomes and Predictors: Measures and Definitions*

Outcome/Predictor	Measure/Definition
Global cognitive outcomes	
Continuous measures	
General intellectual functioning	SB fourth edition[40] composite score
Overall adaptive functioning	VABS[41] composite score
Categories of global cognitive outcomes	
Normal intelligence	SB composite ≥ 84
Borderline intelligence	68 ≤ SB composite < 84
MR	SB composite < 68 and VABS composite < 78
Mild MR	52 ≤ SB composite < 68 and VABS composite < 78
Moderate to profound MR	SB composite < 52 and VABS composite < 78
Specific cognitive outcomes	
Language	
Overall	TOLD[43] spoken language quotient
Receptive	TOLD listening quotient
Expressive	TOLD speaking quotient
Verbal Reasoning	SB verbal reasoning area score
Short-term memory	SB short-term memory area score
Quantitative reasoning	SB quantitative reasoning area score
Visual perceptual organization	
Abstract visual reasoning	SB abstract visual reasoning area score
Visual motor integration	Developmental Test of Visual Motor Integration[45] standard score
Visual perceptual skills	Test of Visual Perceptual Skills[46] perceptual quotient
Major predictors	
Ultrasound abnormalities	
Germinal matrix hemorrhage	A focal echodensity, on at least one scan, in the thalamocaudate groove, sometimes extending to the head of the caudate nucleus, just lateral to the frontal horns of the lateral ventricles
Intraventricular hemorrhage	An echodense focus or foci, on at least one scan, within the lateral, third, or fourth ventricles separate from, and at least as echodense as, the choroid plexus; also diagnosed when irregularity of the choroid plexus margin indicated adherent intraventricular blood
Parenchymal lesions	Focal or confluent echodense and/or echolucent areas, on at least one scan, in the parenchyma, replacing the normal pattern of alternating or interlaced gracile echogenic or echopoor lines
Ventricular enlargement	At least moderate enlargement of at least one lateral ventricle, as read by the radiologist on the final scan obtained

* SB indicates Stanford-Binet scale; VABS, Vineland Adaptive Behavior Scale, MR, mental retardation; and TOLD, Test of Language Development.

Definitions of Perinatal Predictors

US Status

US abnormalities were defined as shown in Table 1. GM hemorrhage and IVH frequently co-occur, and both represent stages in the evolution of brain hemorrhage in the subependymal area.[22,47] PLs and VE are both likely to represent injury to white matter,[21,22] regardless of cause. US groups are defined here as: (1) isolated GM and/or IVH (GM/IVH) (2) PL and/or VE (PL/VE) with or without GM/IVH, and (3) no abnormality (NA). These groupings are more consistent with pathologic findings[21] than is the widely used Papile classification.[48] Assignment to a given US group was based on the most abnormal scan in the entire series for a given infant. Of the 597 children in the present sample, there were 468 with NA, 83 with isolated GM/IVH, and 46 with PL/VE. Of those in the last group, 20 children had PL without VE (12 with and 8 without GM/IVH), 15 had both PL and VE (13 with and 2 without GM/IVH), and 11 had VE without PL (all with GM/IVH); no child had VE alone.

Non-US Predictors from the Prenatal, Perinatal, and Neonatal Periods

Maternal social disadvantage was defined by a composite index modeled after that used by Hack et al.[11,17] The following five maternal characteristics at the time of the infant's birth were coded as 1 (present) or 0 (absent) and added to yield an index: (1) not a high school graduate; (2) nonwhite race; (3) any income from public assistance; (4) younger than 19 years; and (5) not married. This index had an acceptable level of reliability (Cronbach's α = 0.69); when data were missing for one or more components, the mean of the remaining components was substituted for the missing one(s) in calculating the sum. Perinatal data included sex, plurality, mode of delivery, Apgar scores at 1 and 5 minutes, birth weight, gestational age, and fetal growth ratio (FGR). FGR was defined as the birth weight relative to the 50th percentile point of the weight-for-gestational age distributions (specific for sex and multiple versus singleton birth) compiled by Williams et al.[49] Infants with birth weights below the 10th percentile on these normative distributions were considered small for gestational age. Neonatal complications of prematurity included the lowest diastolic blood pressure between the 4th and 24th hours of life, the fraction of inspired oxygen at the end of 24 hours, and the presence or absence of respiratory distress syndrome, patent ductus arteriosus, and septicemia. Measures of neonatal chronic illness included days receiving supplemental oxygen, days receiving mechanical ventilation, oxygen dependence at 36 weeks postconceptional age, and days in the hospital.

Statistical Analysis

Bivariate associations between global cognitive outcomes and the predictor variables, as well as between US status and the other predictor variables, were assessed using analysis of variance and χ^2 tests. All significance levels are two tailed, with a minimum of α = 5%. The attributable risk of the different US groups for MR and borderline intelligence was calculated according to the method of Fleiss.[50]

For multivariate prediction of global cognitive outcomes (MR, borderline intelligence, and normal intelligence), multinomial logistic regression was used. US status was entered first into the equation, and the remaining predictor sets (maternal social disadvantage, perinatal data, neonatal complications of prematurity, and neonatal chronic illness) were entered in chronologic order. The FGR, rather than birth weight, was entered as part of the perinatal set. Because of collinearity among variables, the fraction of inspired oxygen was selected to represent the neonatal complications set in the multivariate analyses, and days receiving mechanical ventilation, the neonatal chronic illness set. Each selected

variable related strongly to outcome and loaded highly on the first principal component of its set.

In examining associations with specific cognitive outcomes (eg, language), the sample was restricted to children with at least normal intelligence, as defined in Table 1. The bivariate associations of US status with specific cognitive outcomes were assessed with one-way analyses of variance. To assess the effects of US status independent of non-US factors on the specific cognitive outcomes, all predictors listed above were entered simultaneously in a series of ordinary least squares regressions.

In all regressions, missing data were handled by substituting an arbitrary constant for the missing value and adding a dummy missing value indicator to the equation. This strategy preserved sample size and maintained interpretability of the coefficients associated with each predictor.[51] Data were missing for only two predictors, the 5-minute Apgar score (17 cases) and fraction of inspired oxygen (193 cases in which oxygen was not used); both missing value indicators were unrelated to outcome.

RESULTS

Global Cognitive Outcomes: Mental Retardation and Borderline Intelligence—Prevalence and Relation to US Status

For the sample as whole, the mean scores on general intellectual functioning (99.7 ± 18.1) and adaptive functioning (94.5 ± 16.7) were within the normal range. However, as shown in Table 2, the sample included significantly more children with MR than expected based on the population distribution of the SB composite (5.0% vs 2.5%; $P < .001$) and significantly fewer children with borderline intelligence (6.4% vs 13.4%, $P < .001$).

The rates of MR and borderline intelligence differed significantly across US groups (Table 2). Compared with the NA group, the PL/VE group was at markedly excess risk for MR (odds ratio [OR], 69.0), with an unadjusted attributable risk of 60%, and modestly increased risk for borderline intelligence (OR, 5.9), with an unadjusted attributable risk of 10%. Compared with the NA group, the GM/IVH group was at modestly excess risk for MR (OR, 5.0), with an unadjusted attributable risk of 3%, but at no excess risk for borderline intelligence.

Bivariate Relation of non-US Predictors to US Status

Table 3 shows that several non-US risk factors differed by US group, with the NA and PL/VE groups generally being at the least and most risk, respectively.

Compared with the NA group, both the PL/VE and GM/IVH groups had significantly lower mean gestational ages and birth weights. (The slightly lower average FGR and significantly higher rate of small-for-gestational age infants in the NA group, compared with the two US abnormality groups, result from using of a birth weight cutoff to define the cohort.[52]) Compared with the NA group, both the US abnormality groups also had significantly lower 1-minute Apgar scores and higher rates of respiratory distress and patent ductus arteriosus and required, on average, higher percentages of inspired oxygen and more days of mechanical ventilation, supplemental oxygen, and hospitalization. The PL/VE group additionally had significantly lower 5-minute Apgar scores and diastolic blood pressures than the NA group.

Bivariate Relation of Non-US Predictors to Global Cognitive Outcomes

Table 4 shows that several non-US risk factors were associated with global cognitive outcomes. Children with MR were born on average about 2.5 weeks earlier and those with borderline intelligence were born about 1.2 weeks earlier than children with normal intelligence. Compared with children with normal intelligence, both children with MR and those with borderline intelligence had significantly lower birth weights and lower Apgar scores; they also had more neonatal complications, as indicated by lower diastolic blood pressure and higher fractions of inspired oxygen, and more neonatal chronic illness, as indicated by more days of mechanical ventilation, supplemental oxygen, and hospitalization. Children with MR, compared with children with normal intelligence, additionally had higher rates of respiratory distress syndrome and patent ductus arteriosus.

Global Cognitive Outcome: Multivariate Analysis

The effects of US status on global cognitive outcomes remained essentially unchanged as successive

TABLE 2. Global Cognitive Functioning by Ultrasound Status*

Global Cognitive Outcomes†	All, n (%) (n = 597)	Ultrasound Group, n (%)			Comparisons, Odds Ratio (95% Confidence Interval)	
		NA (n = 468)	GM/IVH (n = 83)	PL/VE (n = 46)	GM/IVH vs NA	PL/VE vs NA
Normal intelligence‡	529 (88.6)	436 (93.2)	73 (88.0)	20 (43.5)	···§	···§
Borderline intelligence†	38 (6.4)	26 (5.6)	5 (6.0)	7 (15.2)	1.1 (0.4–3.1)	5.9 (2.3–15.2)‡
MR‡	30 (5.0)	6 (1.3)	5 (6.0)	19 (41.3)	5.0 (1.5–16.8)‖	69.0 (24.8–192.1)‡
Mild MR¶	5 (0.8)	2 (0.4)	0 (0.0)	3 (6.5)	···¶	···¶
Moderate to profound MR¶	25 (4.2)	4 (0.9)	5 (6.0)	16 (34.8)	···¶	···¶

* See Table 1 for definitions of outcomes. Significance levels for the χ^2 tests of differences among all three groups are indicated beside the variable label in the first column. Multinomial logistic regressions were used to compare each ultrasound abnormality group to the no abnormality (NA) group on the prevalence of borderline intelligence and mental retardation (MR), with the log odds of borderline intelligence versus normal intelligence and MR versus normal intelligence as dependent variables. The significance level for each comparison, as determined by the t statistic associated with the log odds ratio, is indicated immediately beside the confidence interval. GM/IVH indicates germinal matrix/intraventricular hemorrhage; and PL/VE, parenchymal lesion/ventricular enlargement.

† $P < .050$.

‡ $P < .001$.

§ Reference category.

‖ $P < .010$.

¶ Odds ratios not calculated because of small number of cases for this category.

TABLE 3. Prenatal, Perinatal, and Neonatal Risk Factors by Ultrasound Status*

Risk Factor	All (n = 597)	Ultrasound Groups		
		NA (n = 468)	GM/IVH (n = 83)	PL/VE (n = 46)
Maternal social disadvantage, no. of characteristics present	1.0 ± 1.1	1.0 ± 1.1	1.0 ± 1.0	1.1 ± 1.3
Perinatal data				
Male sex	302 (50.6)	237 (50.6)	40 (48.2)	25 (54.3)
Multiple birth	169 (28.3)	135 (28.8)	23 (27.7)	11 (23.9)
Cesarean section	344 (57.6)	270 (57.7)	49 (59.0)	25 (54.3)
Apgar score (1 min)†	7 (5–8)	7 (5–8)	6 (3–7)†	5 (3–6)†
Apgar score (5 min)‡	8 (7–9)	8 (7–9)	8 (7–9)	7 (6–8)‡
Birth weight, g†	1480.7 ± 359.1	1529.5 ± 342.9	1339.2 ± 367.0†	1239 ± 337.2†
Gestational age, wk†	31.6 ± 3.2	32.1 ± 3.0	30.1 ± 3.0†	29.4 ± 2.7†
Fetal growth ratio†	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.2†	1.0 ± 0.2§
Small for gestational age†	222 (37.2)	196 (41.9)	19 (22.9)§	7 (15.2)†
Neonatal complications of prematurity				
Lowest diastolic blood pressure, mm Hg†	25.2 ± 6.2	25.6 ± 6.0	25.0 ± 6.0	21.9 ± 6.8†
Inspired oxygen at end of 1st 24 h, %†	38.0 ± 16.4	36.3 ± 13.9	41.8 ± 22.3§	48.7 ± 21.8†
Respiratory distress syndrome†	382 (64.0)	272 (58.1)	66 (79.5)†	44 (95.7)†
Patent ductus arteriosis†	99 (16.6)	64 (13.7)	20 (24.1)‖	15 (32.6)§
Septicemia	35 (5.9)	26 (5.6)	6 (7.2)	3 (6.5)
Measures of chronic illness				
Mechanical ventilation, d†	6.4 ± 14.5	4.8 ± 12.9	9.0 ± 15.6‖	18.2 ± 20.2†
Supplemental oxygen, d†	11.0 ± 22.9	8.6 ± 20.9	17.0 ± 26.7§	25.3 ± 28.3†
Oxygen dependence at 36 wk	31 (5.2)	21 (4.5)	6 (7.2)	4 (8.7)
Hospital stay, d†	42.2 ± 31.8	37.0 ± 29.0	54.4 ± 30.4†	72.6 ± 38.8†

* All data are expressed as mean ± SD or number (with percentages in parentheses), except for Apgar scores, which are given as a median (with interquartile range in parentheses). Significance levels for tests of differences among all three groups (F and χ^2) are indicated beside each risk factor; significance levels for comparisons between each of the ultrasound abnormality groups and the NA group (t tests and Wald z) are in the GM/IVH and PL/VE columns. Fetal growth ratio is defined as birth weight divided by 50th percentile point of Williams[42] weight-for-gestational age distributions (see text). Abbreviations are defined in Table 2.
† $P < .001$.
‡ $P < .010$.
§ $P < .005$.
‖ $P < .050$.

sets of predictors were added to the multinomial logistic regression. Table 5 shows the results for the final equation with all predictors entered. This equation predicts well the categories of global cognitive outcome at age six; $\chi^2(22) = 155.7$ ($P < .001$) with a pseudo-R^2 of 30%.[53]

US status explained 16% of the variance in the three categories of global cognitive outcome, as indicated by the pseudo R^2 for the first step of the regression. Each subsequent predictor set, with the exception of maternal social disadvantage, added significantly to the explanation of variance in outcome. Perinatal data explained a further 5%; neonatal complications, 2%; and neonatal chronic illness, 7%.

MR

US status remained an important predictor of MR. PL/VE was highly related to MR (OR, 65.8; confidence interval [CI], 19.1 to 227.4; $P < .001$). The children with isolated GM/IVH were also at a significantly higher risk for MR (OR, 4.6; CI, 1.2–18.6; $P < .050$). The number of days receiving mechanical ventilation also significantly increased the risk for MR; for every day receiving ventilation the OR for MR increased by 7%.

Borderline Intelligence

Children with PL/VE but not those with isolated GM/IVH were at higher risk for borderline intelligence (OR, 3.7; CI, 1.3–10.8). Of the non-US predictors, maternal social disadvantage at birth, fraction of inspired oxygen, and days receiving mechanical ventilation also significantly increased the likelihood of borderline intelligence.

Adjusted Attributable Risk for MR and Borderline Intelligence

The adjusted attributable risk of PL/VE for MR was 51%. That is, the prevention of PL/VE in the LBW population would have reduced the prevalence of MR by about half. The attributable risks of PL/VE for borderline intelligence (5%) and of GM/IVH for MR (5%) remained essentially at their initial levels after controlling for all other predictors.

Cognitive Outcomes in Children of Normal Intelligence

The majority of children (529 [89%] of 597) were of normal intelligence (SB composite at or above 84). Some of these children (83 [16%] of 529) nonetheless exhibited impairment on tests of visual perceptual organization or language. In particular, 3% were impaired on the VMI, 2% were impaired on the TVPS, and 8% were impaired on the spoken language quotient of the TOLD. Language impairment was primarily expressive (12% impaired); only 3% were impaired in receptive language. Consistent with the SB composite criterion for normal intelligence, impairments were not present in any of the SB areas.

TABLE 4. Prenatal, Perinatal, and Neonatal Risk Factors by Global Cognitive Outcomes*

Risk Factor	Global Cognitive Outcomes		
	Normal Intelligence (n = 529)	Borderline Intelligence (n = 38)	Mental Retardation (n = 30)
Maternal social disadvantage (no. of characteristics present)	1.0 ± 1.1	1.3 ± 1.3	1.2 ± 1.2
Perinatal data			
Male sex	266 (50.3)	20 (52.6)	16 (53.3)
Multiple birth	149 (28.2)	9 (23.7)	11 (36.7)
Cesarean section	308 (58.2)	18 (47.4)	18 (60.0)
Apgar score (1 min)†	7 (5–8)	6 (3–8)‡	5 (3–6)†
Apgar score (5 min)‡	8 (7–9)	8 (6–8)‡	7 (6–8)‡
Birth weight, g†	1512 ± 340.6	1287.4 ± 395.0†	1160.2 ± 406.5†
Gestational age, wk†	31.8 ± 3.0	30.6 ± 3.8‡	29.3 ± 3.8†
Fetal growth ratio	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2
Small for gestational age	201 (38.0)	14 (36.8)	7 (23.3)
Neonatal complications of prematurity			
Lowest diastolic blood pressure, mm Hg†	25.6 ± 6.0	22.7 ± 7.2§	22.1 ± 5.0§
Inspired oxygen at end of 1st 24 h, %†	38.8 ± 19.0	51.3 ± 25.9§	55.0 ± 26.7†
Respiratory distress syndrome‡	328 (62.0)	29 (76.3)	25 (83.3)‡
Patent ductus arteriosis§	79 (14.9)	9 (23.7)	11 (36.7)§
Septicemia	29 (5.5)	3 (7.9)	3 (10.0)
Measures of chronic illness			
Mechanical ventilation, d†	4.2 ± 9.8	19.0 ± 28.6†	29.5 ± 25.8†
Supplemental oxygen, d†	8.1 ± 17.6	27.1 ± 40.6†	41.9 ± 39.3†
Oxygen dependence at 36 wk†	20 (3.8)	4 (10.5)	7 (23.3)†
Hospital stay, d†	38.0 ± 26.4	63.3 ± 49.0†	88.5 ± 44.3†

* All data are expressed as mean ± SD or number (with percentages in parentheses), except for the Apgar scores, which are given as a median (with an interquartile range in parentheses). Significance levels for tests of differences among all three groups (F and χ^2) are indicated beside the name of each risk factor; significance levels for comparisons between each of the nonnormal intelligence groups and the normal intelligence group (t tests and Wald z) are given in the Borderline Intelligence and Mental Retardation columns. Fetal growth ratio is defined as birth weight divided by 50th percentile point of Williams[42] weight-for-gestational age distributions (see text).
† $P < .001$.
‡ $P < .050$.
§ $P < .005$.

TABLE 5. Multinomial Logistic Regressions for Global Cognitive Outcomes*

Risk Factor	Odds Ratio (95% Confidence Interval)	
	MR vs Normal Intelligence	Borderline vs Normal Intelligence
Ultrasound status		
GM/IVH	4.64 (1.16–18.56)†	0.72 (0.23–2.33)
PL/VE	65.83 (19.06–227.36)‡	3.72 (1.28–10.81)†
Maternal social disadvantage (no. of characteristics present)	1.42 (0.95–2.12)	1.46 (1.09–1.97)†
Perinatal data		
Male sex	1.26 (0.48–3.25)	1.13 (0.55–2.32)
Apgar score at 5 min	0.92 (0.69–1.24)	1.04 (0.80–1.34)
Gestational age, wk	1.08 (0.84–1.39)	1.02 (0.85–1.22)
Fetal growth ratio	0.13 (0.01–2.75)	0.30 (0.03–2.81)
Neonatal complication of prematurity		
Fraction of inspired oxygen	1.01 (0.98–1.03)	1.02 (1.01–1.04)†
Measure of chronic illness		
Mechanical ventilation, d	1.07 (0.22–5.29)‡	1.05 (1.03–1.08)§
Constant	0.00 (0.00–55.27)	0.01 (0.00–20.19)

* For the continuous variables in the model the odds ratio corresponds to one unit change in the risk factor. The significance of the effects was determined by their associated t statistic. Abbreviations are defined in Table 2.
† $P < .050$.
‡ $P < .001$.
§ $P < .005$.

Bivariate Relations With US Status

Because the rates of impairment for these more specific cognitive abilities were generally low among the children with normal intelligence, their association with US status was assessed using continuous scores (see Table 6). The US groups differed significantly on all three scores reflecting visual perceptual organization, with the PL/VE group scoring 7 to 13 points lower than those of the NA group ($P < .050$). Language abilities, short-term memory, and quantitative skills did not differ significantly across US groups.

Multivariate Relations With US and Other Perinatal Predictors

With all remaining predictors controlled in a simultaneous ordinary least squares regression, PL/VE still had a significant effect on the three assessments of visual perceptual organization. As indicated by the unstandardized partial regression co-

TABLE 6. Specific Cognitive Outcomes in Children With Normal Intelligence in Relation to Ultrasound Status*

Outcome	Ultrasound Groups		
	NA	GM/IVH	PL/VE
Language			
Overall (TOLD SLQ)	n = 429 95.6 ± 16.1	n = 73 94.6 ± 18.4	n = 17 91.9 ± 17.8
Receptive (TOLD LIQ)	n = 428 97.2 ± 13.7	n = 73 95.5 ± 15.2	n = 19 93.4 ± 14.4
Expressive (TOLD SPQ)	n = 432 94.7 ± 17.1	n = 73 94.5 ± 19.6	n = 17 91.8 ± 19.3
Verbal reasoning (SB area score)	n = 436 104.3 ± 10.9	n = 73 102.9 ± 10.5	n = 20 98.9 ± 10.8†
Short-term memory (SB area score)	101.4 ± 11.4	99.2 ± 11.0	102.0 ± 12.7
Quantitative reasoning (SB area score)	108.8 ± 10.0	107.2 ± 9.1	104.5 ± 10.9
Visual perceptual organization			
Abstract visual reasoning (SB area score)†	102.1 ± 13.0 n = 431	101.2 ± 10.4 n = 73	94.0 ± 10.0‡ n = 20
Visual-motor integration (VMI standard score)†	93.1 ± 10.7 n = 421	92.2 ± 10.7 n = 71	86.2 ± 13.2§ n = 18
Visual perceptual skills (TVPS perceptual quotient)†	106.9 ± 19.7	105.7 ± 20.6	93.8 ± 21.6‡

* All data are expressed as means ± SD. Significance levels for tests of differences among the three ultrasound status groups (*F*) are indicated beside the name of each outcome; significance levels for tests of differences between each of the ultrasound abnormality groups and the NA group (*t*) are given in the columns for GM/IVH and PL/VE. SLQ indicates speaking quotient; LIQ, listening quotient; VMI, Developmental Test of Visual Motor Integration; and TVPS, Test of Visual Perceptual Skills. Other abbreviations are defined in Tables 1 and 2.
† $P < .050$.
‡ $P < .010$.
§ $P < .005$.

efficients (*B*s), the adjusted mean for the PL/VE group was lower than that of the NA group by 6.73 points on the abstract visual reasoning area score of the SB scale, 6.33 points on the VMI, and 10.23 points on the TVPS (all $P < .050$). The adjusted means for the GM/IVH group did not differ from those of the NA group on any of these variables.

With the effects of all other predictors controlled, two of the non-US risk factors, namely maternal social disadvantage and the FGR, had fairly consistent effects on specific cognitive outcomes. With each additional component of maternal social disadvantage, adjusted scores on all cognitive outcomes, with the exception of the VMI, dropped, on average, by about two to four points (*B*s ranged from −1.76 to −3.97; all $P < .001$); the VMI was unrelated to social disadvantage. Higher FGRs were also significantly associated with better performance on several tests; for each 10th of a unit increase in the FGR (eg, from 0.8 to 0.9 of the expected weight for age), adjusted scores rose, on average, by 1.1 points on the overall spoken language quotient of the TOLD ($P < .050$), by 0.9 points on the receptive language quotient of the TOLD ($P < .050$), by 0.8, 1.1, and 1.2 points, respectively, on the quantitative reasoning ($P < .005$), short-term memory ($P < .001$), and abstract visual reasoning ($P < .010$) area scores of the SB scale, and by 1.7 points on the TVPS ($P < .005$). Both gender and the 5-minute Apgar score were significantly related to VMI performance but to no other outcomes. Boys' adjusted scores on the VMI were on average around three points lower than those of girls ($B = -2.82$; $P < .005$), whereas there was about one point of gain on the VMI for each one point of gain on the Apgar score ($P < .050$).

A further series of regressions explored whether the effect of PL/VE on perceptual performance would be affected by statistically controlling for obvious neurologic complications. In these analyses, terms representing the presence of a ventriculoperitoneal shunt, a history of seizures, and a diagnosis of disabling CP at 2 years of age were added to the regression equation, both individually and as a set. For the abstract visual reasoning subtest of the SB scale, the effect of PL/VE remained significant when controlling for each neurologic condition individually ($P < .010$ for seizures; and $P < .050$ for shunts and disabling CP) but not when all three were controlled. For both the VMI and the TVPS, however, the effect of PL/VE remained significant even after controlling for all three neurologic conditions ($P < .050$).

DISCUSSION

The present study is a 6-year follow-up of infants enrolled in the NBHS,[22,35] a large, regionally defined LBW birth cohort, screened in the neonatal period with serial cranial US according to a prospective, timed protocol. The principal findings were as follows: The sample had twice the expected rate of MR, almost all moderate to profound in severity. PL/VE was related independently of all other predictors to both MR and borderline intelligence; 51% percent of the cases of MR were attributable to PL/VE. Isolated GM/IVH was more modestly related to MR but was not related to borderline intelligence. Of non-US factors, only days receiving mechanical ventilation increased the risk for MR. Maternal social disadvantage at birth increased the risk for borderline intelligence but not for MR. Among children of normal intelligence, those with PL/VE, but not isolated GM/IVH, performed more poorly than those with no US abnormalities on tests of visual perceptual organization.

The distribution of global cognitive outcomes at 6

years of age in the NBHS cohort differs from that of the Scottish Low Birthweight Study, another regional cohort of similar birth weights born during the same period and followed to school age.[7] The prevalence of MR in the NBHS cohort is similar to that of the Scottish cohort (5% in both). However, the prevalence of borderline intelligence is lower (6% vs 24%) and the prevalence of normal intelligence is higher (89% vs 70%) than in the Scottish cohort. Given that other studies have shown a positive relation of socioeconomic status to intelligence in VLBW children,[3,14,54,55] the lower rate of borderline intelligence in this sample may reflect the relative affluence of the region studied, as well as selective attrition of children born to mothers at social disadvantage.

PL/VE on neonatal US was a strong predictor of MR at 6 years of age, whereas GM/IVH was only modestly associated with MR. These findings are consistent, with some exceptions,[30,56] with those of hospital-based studies that found a strong relation of parenchymal lesions and/or ventricular enlargement to developmental delay during the first 2 years of life,[57–65] and the preschool years,[66] as well as to MR by school age[31] in infants of low birth weight. A recent study by Hack et al[17] also found a strong relation between PL/VE and MR at school age in a regional cohort of children whose birth weights were less than 750 g. The present study examined a broader range of birth weights and global cognitive outcomes and found that PL/VE was also associated with borderline intelligence at school age, although the adjusted attributable risk (10%) was far lower than that for MR (51%).

The strong relation of PL/VE and more modest relation of GM/IVH to MR at 6 years of age parallels the relation of PL/VE and GM/IVH to disabling CP at 2 years of age in the same cohort.[34] Indeed, GM/IVH and PL/VE were not associated with MR at 6 years of age in the absence of disabling CP at 2 years of age, a finding similar to that of others.[67] Given the strong relation of white matter injury to disabling CP,[68] it is possible that the modest relation of GM/IVH to both MR and disabling CP was due to white matter injury that was undetected by US, either because the study protocol focused on the first week and PL/VE may occur up to the 5th week after birth,[69] if not later, or because US has been shown to insensitive to smaller brain lesions.[21,22,70]

Of the specific cognitive abilities assessed in children of normal intelligence, only those reflecting visual perceptual organization were significantly associated with US abnormalities. Again, it was the children with PL/VE rather than those with GM/IVH who performed more poorly than the unaffected children, even with control for neurologic problems. Although some prior studies, using small samples, found no relation of these abilities (the VMI, in particular) to US status (eg, Vohr et al,[30] Ford et al,[71] and Lowe and Papile[72]), the present results are consistent with those of Roth et al,[31] who found an effect on the VMI of differing US groups, with the lowest scores being in the group with ventricular dilation. Poor visual-motor integration has been one of the most common findings for premature infants generally.[5] The present results suggest that such deficits in premature infants may be due principally to PL/VE.

The anatomic links between PL/VE and suboptimal cognitive outcomes in LBW infants are not entirely clear. Postmortem evidence that PL/VE reflects white matter injury[21] implicates white matter injury as a direct cause of suboptimal cognitive outcomes and/or as a marker for parallel lesions elsewhere in the brain that cause such outcomes.[22] These alternatives cannot be explored in other than a speculative way here. PL/VE might disrupt processes essential to normal brain organization (ie, establishment and differentiation of subplate neurons; alignment, orientation, and layering of cortical plate neurons; dendritic and axonal ramifications; synaptogenesis; cell death and selective elimination of neuronal processes and of synapses; and glial proliferation and differentiation)[25] via injury to neurons in the transient subplate zone[73,74] or to late-migrating astrocytes that are essential to the organization of the superficial cortical layers.[24,75] PL might interfere with myelination and brain growth by impeding the migration of oligodendroglial precursors from the germinal matrix to the cerebral white matter, where they undergo differentiation and myelination.[2,24,68,76] White matter necrosis may lead to diminished total brain white matter, resulting in VE without cranial enlargement and, in severe cases, microcephaly.[68]

VE secondary to PL, as described above, or to GM/IVH[23] may also affect brain organization by causing axonal stretching and disruption with subsequent loss and gliosis, as well as diminished cerebral blood flow. In the newborn cat, experimental vetriculomegaly causes alterations in neurotransmitter levels[77] and synaptogenesis[78] throughout the cerebral cortex. These effects show a rostrocaudal gradient of severity, with the occipital cortex most affected.[77,78] The greater vulnerability of the parietal and occipital cortices has been attributed to their close proximity to the ventricle wall. The motor cortex, located rostrally, is separated from the ventricle by more white matter, which may resist the outward spread of pressure and/or edema; as a result, the ventricular system enlarges more readily toward the occipital pole.[78] These experimentally induced effects on the cerebral cortex as a whole and, more specifically, on the parietal and occipital cortices are consistent with the findings here of a relation of PL/VE to poor performance both on tests of general cognitive ability (intelligence) and on tests assessing visual perceptual organization specifically. In an individual child, the particular pattern of cognitive (and motor) impairment caused by PL/VE is likely to depend on the site, extent, and timing of the lesions,[79–83] factors not examined here.

Given the important role of the germinal matrix in neuronal proliferation and migration[24] and the probability that the germinal matrix was still active at birth in most of this cohort, the finding that isolated GM/IVH was not related to borderline intelligence or to any of the specific cognitive outcomes studied was somewhat surprising. Although isolated GM/IVH was not related to developmental delay at 1 year

in a regional subgroup of the birth cohort studied here,[64] Scott et al[84] found a significant downward trend in Bayley Mental Index scores among GM/IVH survivors compared with control infants serially tested to 18 months of age, suggesting that subtle deficits caused by "silent hemorrhage" may emerge in time. Lowe and Papile[72] found that, by school age, VLBW children with GM/IVH scored lower than unaffected VLBW children on a combination of neuropsychological tests. Frisk and Whyte[32] found that GM/IVH (with or without mild hypoxic-ischemic damage) was associated with deficits in sentence comprehension and working memory. It is possible that the measures used in this study were not sufficiently sensitive to detect effects of isolated GM/IVH on specific cognitive abilities at this age. It is also possible that the some effects of isolated GM/IVH on cognitive performance may emerge later in development.

Among non-US factors, days receiving mechanical ventilation was the only risk factor examined that was independently related to MR. Others have found that bronchopulmonary dysplasia, the most common medical complication requiring prolonged ventilation and a factor we have not yet examined, is associated with cognitive impairment by school age.[85–87] This may be related to selective neuronal necrosis.[88,89] It is also noteworthy that maternal social disadvantage at the time of the infant's birth was independently related to borderline intelligence but not to MR at 6 years of age. This finding is consistent with the lack of association typically seen between social disadvantage and moderate to profound MR (present in all but a few cases of MR in this cohort), as contrasted with mild MR or borderline intelligence.[90]

Implications of This Study

This is the first population-based study of LBW infants that has examined the independent relation of neonatal cranial US abnormalities to cognitive abilities at school age. Relative to other risk factors, US abnormalities consistent with white matter injury were the single most important determinants of general intellectual functioning, accounting for half of the cases of MR. In children of normal intelligence, these US indicators of white matter injury were related to poor visual perceptual organization and, thereby, may have significance for later school performance. The prevention of white matter injury would reduce substantially the prevalence of suboptimal cognitive outcomes in LBW infants.

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IMAGE TRUMPS REALITY

[Television has produced] a new Gresham's Law of American public life in which counterfeit happenings tend to drive spontaneous happenings out of circulation.

Daniel Boorstin quoted in the *New York Times.* August 17, 1996.

Submitted by Student