ARTICLE

Neurodevelopmental Outcomes of Extremely Low-Gestational-Age Neonates With Low-Grade Periventricular-Intraventricular Hemorrhage

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Importance: Low-grade periventricular-intraventricular hemorrhage is a common neurologic morbidity among extremely low-gestational-age neonates, yet the outcomes associated with this morbidity are not fully understood. In a contemporary multicenter cohort, we evaluated the impact of such hemorrhages on early (18-22 month) neurodevelopmental outcomes of extremely premature infants.

Objective: To compare neurodevelopmental outcomes at 18 to 22 months' corrected age for extremely low-gestational-age infants with low-grade (grade 1 or 2) periventricular-intraventricular hemorrhage with those of infants with either no hemorrhage or severe (grade 3 or 4) hemorrhage demonstrated on cranial ultrasonography.

Design: Longitudinal observational study.

Setting: Sixteen centers of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network.

Participants: A total of 1472 infants born at less than 27 weeks' gestational age between January 1, 2006, and December 31, 2008, with ultrasonography results within the first 28 days of life and surviving to 18 to 22 months with complete follow-up assessments were eligible.

Main Exposure: Low-grade periventricular-intraventricular hemorrhage.

Main Outcome Measures: Outcomes included cerebral palsy; gross motor functional limitation; cognitive and language scores according to the Bayley Scales of Infant Development, 3rd Edition; and composite measures of neurodevelopmental impairment. Regression modeling evaluated the association of hemorrhage severity with adverse outcomes while controlling for potentially confounding variables and center differences.

Results: Low-grade hemorrhage was not associated with significant differences in unadjusted or adjusted risk of any adverse neurodevelopmental outcome compared with infants without hemorrhage. Compared with low-grade hemorrhage, severe hemorrhage was associated with decreased adjusted continuous cognitive (β, −3.91 [95% CI, −6.41 to −1.42]) and language (β, −3.19 [−6.19 to −0.19]) scores as well as increased odds of each adjusted categorical outcome except severe cognitive impairment (odds ratio [OR], 1.46 [0.74 to 2.88]) and mild language impairment (OR, 1.35 [0.88 to 2.06]).

Conclusions and Relevance: At 18 to 22 months, the neurodevelopmental outcomes of extremely low-gestational-age infants with low-grade periventricular-intraventricular hemorrhage are not significantly different from those without hemorrhage. Additional study at school age and beyond would be informative.

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Periventricular-intraventricular hemorrhage (PIVH) is the most common form of intracranial hemorrhage among premature infants[1] and affects approximately one-third of infants born at less than 29 weeks' estimated gestational age (EGA).[2] Grading of PIVH is traditionally based on the Papile classification system,[3] and its use remains pervasive in the literature and clinical setting despite debate regarding appropriate nomenclature.[4,5] The presence of severe PIVH (grade 3 or 4) is understood to correlate strongly with adverse motor and cognitive outcomes. Outcomes of survivors with low-grade PIVH (grade 1 or 2) are less fully understood despite accounting for 50% to 80% of all PIVH cases. Neonatologists continue to face uncertainty when relating the consequences of low-grade PIVH to parents of affected infants.[2,6,7]

For editorial comment see page 487

Developmental biology may suggest that any PIVH for extremely low-gestational-

age (ELGA) (<27 weeks EGA) infants has potential to destroy glial precursor cells.[1] Interruption of oligodendrocyte and astrocyte development may affect myelination and organization of the cerebral cortex. Destruction of these precursors theoretically could result in adverse neurodevelopmental outcomes.

Previous studies addressing low-grade PIVH outcomes have reached differing conclusions. Some studies[8-11] report no differences between low-grade PIVH and no PIVH groups; others[3,12-16] report outcomes ranging from increased risk of mild to severe delays in specific domains or global delays.[17-21] Differences in the results of these studies may be attributable to study design, cohort definition, evaluation methods, and evolution of practice.

The objective of this study was to characterize 18- to 22-month corrected age (CA) outcomes associated with low-grade PIVH among ELGA infants in the Eunice Kennedy Shriver National Institute of Child Health and Human Developmental Neonatal Research Network (NRN). We compared outcomes of these infants with those of ELGA infants (1) without PIVH and (2) with severe PIVH. We hypothesized that infants with low-grade PIVH would be at increased risk for cognitive impairment compared with those without PIVH but at lower risk compared with infants with severe PIVH.

METHODS

Infants born at $26^{6}/_{7}$ weeks' or less EGA within 16 NRN centers between January 1, 2006, and December 31, 2008, with documented cranial ultrasonography (CUS) results within 28 days of life and surviving to 18 to 22 months' CA with complete follow-up assessment were identified. Those with major congenital anomaly, porencephalic cyst on CUS before 28 days of life, meningitis, or hydrocephalus requiring shunt were excluded, since these factors have been independently associated with poor neurodevelopmental outcomes and may exist outside of the causal pathway between PIVH and outcome.[22-25]

Infants were grouped according to the most severe grade of PIVH reported on CUS documents within 28 days of life. Grade 1 or 2 PIVH was categorized as low grade; grade 3 or 4 PIVH was categorized as severe.

This study was a secondary analysis of the NRN's Generic Database and Follow-up Study protocols. According to each center's institutional review board policies, informed consent or waiver of consent was obtained for the Generic Database; informed consent was obtained for the Follow-up Study. Trained research coordinators prospectively gathered maternal, delivery, and neonatal data according to each study's manual of operations and common definitions.[2,26,27]

BASELINE DEMOGRAPHICS AND CHARACTERISTICS

Maternal Characteristics

Maternal hypertension refers to obstetric documentation of any hypertension diagnosis (acute or chronic) during pregnancy. Prolonged rupture of membranes was defined as rupture more than 18 hours before delivery. Chorioamnionitis was determined by clinical obstetric documentation. Antenatal corticosteroid (ANS) exposure was defined as maternal receipt of 1 or more doses of any corticosteroid for the purpose of accelerating fetal lung maturity.

Neonatal Characteristics

The EGA was determined by best obstetric estimate. Cardiopulmonary resuscitation during the delivery period was defined as receipt of chest compressions or epinephrine. Bronchopulmonary dysplasia was defined by physiologic definition at 36 weeks' postmenstrual age.[28] Postnatal corticosteroid (PNS) exposure was defined as any corticosteroids given for prevention or treatment of bronchopulmonary dysplasia. Patent ductus arteriosus (PDA) was diagnosed on the basis of clinical or echocardiographic examination. Patent ductus arteriosus–surgical refers to PDA closure by surgical ligation. Indomethacin sodium or ibuprofen sodium use was classified as PDA-medical for closure of a diagnosed PDA and PDA/PIVH prophylaxis for empirical prevention of either condition. Periventricular leukomalacia was defined as evidence of cystic lesions in the periventricular area on any CUS during the neonatal admission. Sepsis was defined as blood culture showing pathogenic microorganisms any time during the neonatal admission. Necrotizing enterocolitis was defined as Bell Staging Criteria of IIA or greater.[29]

NEURODEVELOPMENTAL ASSESSMENT

Comprehensive neurodevelopmental assessment at 18 to 22 months' CA consisted of a structured medical history and a battery of neurologic, developmental, and behavioral tests, as previously described.[30,31] Neurologic and developmental testing were performed by annually certified examiners trained to reliability. Gross motor function was assessed by the Palisano Gross Motor Function Classification System (GMFCS).[32] Cognitive and language development were assessed using the Bayley Scales of Infant Development, 3rd Edition (Bayley III),[33] with mean (SD) scores of 100 (15).

OUTCOME DEFINITIONS

Cerebral palsy (CP) is a nonprogressive central nervous system disorder. "Any CP" was defined as abnormal tone or reflexes in at least 1 extremity and abnormal control of movement or posture to a degree that interferes with age-appropriate activity. A GMFCS score greater than 2 indicated gross motor functional limitation. Toddlers with a diagnosis of moderate to severe CP were nonambulatory or required an assistive device for ambulation. Severe visual impairment was defined as bilateral acuity worse than 20/200. Deafness was defined as bilateral permanent hearing loss requiring amplification.

"Neurodevelopmental impairment (NDI) <70" is a composite outcome of one or more of the following: moderate to severe CP, severe visual impairment, deafness, or cognitive score less than 70 (−2 SD). We defined "NDI (<85)" by using the same composite components as for NDI (<70) but with a cognitive score cutoff of less than 85 (−1 SD). The primary outcome for this study was the continuous Bayley III cognitive score. Secondary outcomes included cognitive score less than 70, cognitive score less than 85, continuous language score, language score less than 70, language score less than 85, any CP, GMFCS score greater than 2, severe visual impairment, deafness, NDI (<70), and NDI (<85).

SAMPLE SIZE ESTIMATE

Sample size estimates were calculated for 2-sided *t* tests of pairwise comparisons of the continuous cognitive score. To detect a 5-point difference in group means with 80% power and $\alpha = .05$, each group would need at least 143 participants. Further assuming a 30% incidence in PIVH, 70% of PIVH cases being low

grade, 10% meeting exclusion criteria, 75% survival, 15% loss to follow-up, and 6% incomplete follow-up testing, an estimated 2900 infants would be required (a follow-up birth cohort of approximately 3 years).

STATISTICAL ANALYSIS

Unadjusted comparisons of maternal demographics, neonatal characteristics, and neurodevelopmental outcomes between the no PIVH, low-grade PIVH, and severe PIVH groups were made using χ^2 or Fisher exact tests for categorical data and 2-sided *t* tests for continuous data. Multivariate mixed-effects regression modeling was performed to adjust for potential confounders of the relationship between PIVH severity and outcomes of interest. Model covariates included PIVH severity (3 levels), EGA, sex, race/ethnicity, maternal educational level less than high school, chorioamnionitis, sepsis, ANS use, PNS use, high-frequency ventilation, and PDA. To preserve the largest possible sample, missing values for predictor variables were imputed as not having the exposure. Less than 2% of predictor data were imputed. The NRN Center was included in all models as a random effect to control for center differences in clinical management and variability in local CUS readings. The a priori model was applied en bloc without further paring procedures, since the model was not intended to be predictive. A correlation matrix to assess potential multicollinearity indicated no significant correlations between any covariates, including with PIVH.

RESULTS

A total of 2514 infants aged less than 27 weeks' EGA with CUS data were identified during the birth cohort (**Figure 1**). Of these, 87.4% of eligible survivors completed follow-up. The final cohort consisted of 1472 ELGA infants with follow-up at 18 to 22 months' CA. Nearly one-third (30.6%) of these infants had PIVH: 140 with grade 1, 130 with grade 2, and 181 with grade 3 or 4.

BASELINE CHARACTERISTICS

Demographics as well as maternal and neonatal course characteristics are reported in **Table 1**. There were no significant differences in birth weight, race/ethnicity, maternal age, educational level, or marital status between groups. There was no significant difference in mean EGA between infants with low-grade vs no PIVH. However, those with severe PIVH had lower mean EGA than did infants with low-grade or no PIVH. Any PIVH infants were more likely to be male but less likely to be exposed to maternal hypertension or cesarean delivery than were those with no PIVH. Any PIVH infants were also more likely to have periventricular leukomalacia or high-frequency ventilation exposure; these likelihoods increased with PIVH severity. There were no significant differences in rates of bronchopulmonary dysplasia, PDA interventions, PDA/PIVH prophylaxis, sepsis, necrotizing enterocolitis, and ANS or PNS exposure among infants with low-grade or no PIVH.

Infants with severe PIVH were more likely to have chorioamnionitis but less likely to have exposure to ANS or prolonged rupture of membranes compared with those in the low-grade or no PIVH group. Infants with severe PIVH also were less likely to have received PDA/PIVH prophylaxis compared with infants without PIVH. The severe PIVH group was also more likely to have other neonatal morbidities.

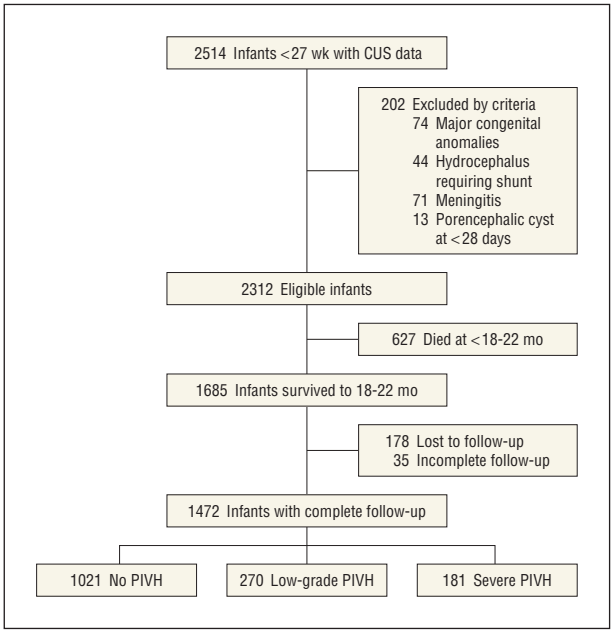

Figure 1. Study enrollment flow. CUS indicates cranial ultrasonography; PIVH, periventricular-intraventricular hemorrhage.

UNADJUSTED NEURODEVELOPMENTAL OUTCOMES

Low-grade PIVH was not associated with increases in poor neurodevelopmental outcomes compared with no PIVH (**Table 2**). Severe PIVH was associated with increased rates of poor outcomes when compared with low-grade PIVH for each nonsensory outcome except mild language impairment.

ADJUSTED NEURODEVELOPMENTAL OUTCOMES

Compared with no PIVH, low-grade PIVH was not independently associated with any adverse outcomes at 18 to 22 months' CA after adjusting for model covariates (**Table 3** and **Figure 2**). Compared with low-grade PIVH, severe PIVH was associated with significant decreases in continuous cognitive and language scores as well as increased odds of each categorical outcome with the exception of severe cognitive impairment and mild language impairment. Modeling was impossible for severe vision impairment or deafness because of the small number of affected infants.

Independent predictors of the outcomes of interest, after adjustment for all other specified model covariates, are summarized in the eTable (http://www.jamapeds.com). No covariate was an independent predictor of every poor outcome after adjustment for all other covariates. Low-grade PIVH and chorioamnionitis did not independently predict any outcome. Patent ductus arteriosus approached significance as a predictor only of mild language delay ($P = .06$). Male sex was a predictor of all outcomes except isolated poor motor outcomes. When ANS was a predictor, receipt

Table 1. Population Demographics

Characteristic	%			*P* Value		
	No PIVH (n = 1021)	Low-Grade PIVH (n = 270)	Severe PIVH (n = 181)	No vs Low-Grade	No vs Severe	Low-Grade vs Severe
Infant characteristics						
Gestational age, mean (SD), wk	25.1 (0.9)	25.0 (1)	24.7 (1)	.08	<.001	.001
Birth weight, mean (SD), g	769 (154)	769 (151)	749 (154)	.93	.11	.16
Male sex	47	61	57	<.001	.01	.39
Race, black	39	39	35	.99	.43	.50
Maternal characteristics						
Age, mean (SD), y	28 (6)	27 (7)	27 (6)	.38	.27	.76
Educational level ≥high school	83	81	81	.57	.65	.98
Married	47	47	44	.93	.39	.43
Hypertension	23	16	14	.02	.01	.58
Prolonged ROM	28	28	19	.84	.01	.03
Chorioamnionitis	17	21	29	.12	<.001	.04
Cesarean delivery	68	58	57	.002	.004	.85
Antenatal corticosteroids[a]						
Any	91	89	78	.26	<.001	.004
Full	61	57	44	.22	<.001	.01
Neonatal course						
5-min Apgar score <6	21	26	31	.11	.005	.24
CPR	9	8	14	.70	.01	.02
Surfactant	88	90	92	.20	.11	.63
High-frequency ventilator	37	46	61	.01	<.001	.002
Pneumothorax	4	5	7	.66	.08	.29
Postnatal corticosteroids	14	14	22	.92	.01	.04
BPD, physiologic	47	53	60	.12	.001	.09
PDA						
Medical	38	41	49	.85	.98	.88
Surgical	17	20	29	.50	.01	.14
PIVH prophylaxis	44	38	35	.10	.03	.47
PVL	2	5	14	.005	<.001	<.001
Sepsis	39	44	49	.10	.02	.38
NEC	10	10	8	.95	.45	.49

Abbreviations: BPD, bronchopulmonary dysplasia; CPR, cardiopulmonary resuscitation; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PIVH, periventricular-intraventricular hemorrhage; PVL, periventricular leukomalacia; ROM, rupture of membranes.

[a] "Any" indicates 1 or more dose of corticosteroids before delivery. "Full" indicates 2 doses of betamethasone separated by 12-24 hours or 4 doses of dexamethasone separated by 6 hours and delivery 24 hours or more from initial dose.

Table 2. Unadjusted Neurodevelopmental Outcomes by Periventricular-Intraventricular Hemorrhage Grade

Outcome	%			*P* Value		
	No PIVH (n = 1021)	Low-Grade PIVH (n = 270)	Severe PIVH (n = 181)	No vs Low-Grade	No vs Severe	Low-Grade vs Severe
Any CP	8	9	28	.92	<.001	<.001
Moderate-severe CP	4	2	10	.14	<.001	<.001
GMFCS score >2	5	3	14	.36	<.001	<.001
Severe visual impairment	1	1	1	.62	.51	.81
Deafness	3	3	2	.89	.68	.80
Cognitive score, mean (SD)	90 (14)	89 (14)	84 (15)	.11	<.001	<.001
<70	7	7	15	.84	<.001	<.001
<85	25	29	44	.24	<.001	.01
Language score, mean (SD)	86 (17)	83 (15)	80 (18)	.06	<.001	.02
<70	16	16	29	.66	<.001	<.001
<85	45	53	59	.06	.001	.12
NDI						
<70	10	10	22	.75	<.001	<.001
<85	27	30	46	.35	<.001	<.001

Abbreviations: CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; NDI, neurodevelopmental impairment; PIVH, periventricular-intraventricular hemorrhage.

Table 3. Adjusted Neurodevelopmental Outcomes by PIVH Grade

Outcome	OR or β (95% CI)		
	Low-Grade vs No PIVH	Severe vs No PIVH	Severe vs Low-Grade PIVH
Any CP[a]	1.00 (0.61 to 1.64)	3.43 (2.24 to 5.27)	3.44 (1.96 to 5.98)
GMFCS score >2[a]	0.66 (0.32 to 1.39)	2.51 (1.43 to 4.44)	3.79 (1.67 to 8.61)
Cognitive score[b]	−0.54 (−2.34 to 1.25)	−4.46 (−6.62 to −2.30)	−3.91 (−6.41 to −1.42)
<70[a]	0.94 (0.54 to 1.61)	1.37 (0.79 to 2.37)	1.46 (0.74 to 2.88)
<85[a]	1.03 (0.75 to 1.43)	1.82 (1.26 to 2.64)	1.76 (1.14 to 2.72)
Language score[b]	−0.31 (−2.45 to 1.83)	−3.50 (−6.10 to −0.90)	−3.19 (−6.19 to −0.19)
<70[a]	0.76 (0.52 to 1.13)	1.57 (1.04 to 2.37)	2.05 (1.24 to 3.39)
<85[a]	1.08 (0.80 to 1.45)	1.45 (1.00 to 2.10)	1.35 (0.88 to 2.06)
Neurodevelopmental impairment			
<70[a]	0.82 (0.51 to 1.31)	1.68 (1.06 to 2.65)	2.04 (1.15 to 3.64)
<85[a]	1.00 (0.73 to 1.37)	1.78 (1.24 to 2.57)	1.79 (1.16 to 2.75)

Abbreviations: CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; OR, odds ratio; PIVH, periventricular-intraventricular hemorrhage.
[a] For categorical outcomes, the adjusted OR (95% CI) from logistic regression models is presented.
[b] For continuous outcomes, the regression coefficient for PIVH grade (β, 95% CI)) from linear regression models reflects the adjusted difference in score with exposure.

was a protective effect against the outcome. Severe PIVH, lower EGA, PNS, high-frequency ventilation, and sepsis were predictors of poor outcome. Maternal educational level less than high school was a predictor of poor cognitive outcomes, mild language impairment, and decreased continuous language score. When race was a predictor, black infants were at increased risk of poor outcome. Hispanic infants were at increased risk for language impairment.

In post hoc analysis, PNS and high-frequency ventilation were eliminated from the model together and separately because of the possibility that these covariates could be considered elements in the causal pathway between PIVH and outcome. There were no significant changes in any of the reported outcomes with any of these model iterations.

COMMENT

This analysis of a large, multicenter contemporary cohort of ELGA infants surviving to 18 to 22 months' CA demonstrates that neurodevelopmental outcomes of infants with grade 1 or 2 PIVH are not significantly different from those without PIVH, even after adjustment for potential confounders. The inclusion of comparisons between severe PIVH and no PIVH provide internal validity to our results.

The results of our study are in contrast to those of a cluster of studies reporting on outcomes of low-grade hemorrhage for extremely preterm infants born in the 1990s. Two regional cohorts[14,16,34] found no significant differences in cognitive or educational outcomes for infants with low-grade hemorrhage. However, both studies[14,16] suggested an increased risk of CP associated with even grade 2 PIVH. In a single-center retrospective birth cohort, Patra et al[19] found dramatic increases in the rates of NDI, major neurologic abnormality, and cognitive/language impairment at 20 months' CA, each with adjusted odds ratios approximately two-fold when comparing infants with low-grade PIVH with infants without PIVH. The results of the study by Patra et al are intriguing because they reflect higher risk for major disability

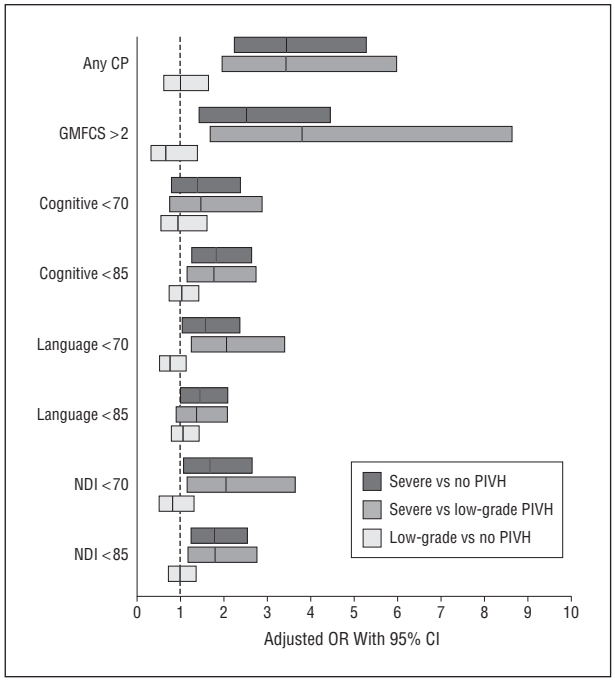

Figure 2. Comparison of adjusted odds ratios (ORs) for neurodevelopmental outcomes. Odds ratios with 95% CI are represented by the horizontal bars. Vertical line is a reference line equal to an OR of 1. Confidence intervals crossing the reference line are not significant ($P > .05$). CP indicates cerebral palsy; GMFCS, Gross Motor Function Classification System; NDI, neurodevelopmental impairment; and PIVH, periventricular-intraventricular hemorrhage.

than generally reported in relationship to low-grade hemorrhages. Differences in the results of the current and prior studies may be related to issues of study design.

Previous studies[3,8-21,34] reporting on low-grade PIVH have used various cohort definitions, including narrow and broad ranges of either birth weight (from <1000 g to <2000 g) or gestational age (from <27 weeks to <32 weeks). Results for broadly defined cohorts may be biased toward the null hypothesis because the incidence of PIVH in older and larger preterm infants is lower and the impact of PIVH may be less than the incidence and

impact for extremely premature infants. Our study defines ELGA using a cutoff of less than 27 weeks' EGA, since this is the population at greatest risk for PIVH.[2,35]

Multicenter studies benefit from rapid accumulation of large sample sizes and increased power. The time required to establish a cohort is a matter of not only efficiency but also of minimizing variability in cohort demographics, clinical exposures, treatments, and evaluation methods. As a result, multicenter studies typically have greater ability to generalize results to the population beyond the study cohort. However, center-to-center differences in multicenter studies may influence outcomes, as demonstrated by Vohr et al.[30] To control for clustering of infants by center and potential center differences in our study, "center" was included as a random effect in mixed-effects regression modeling. Although the homogeneity of the populations across centers is not explicitly stated in the Etude Epidémiologique sur les Petits Ages Gestationnels (EPIPAGE)[14,34] or Sherlock et al[16] studies, neither controlled for center differences within their multicenter studies.

Historical and clinical practice contexts must also be considered when comparing studies across time. For example, the role of corticosteroids in neonatology has changed during the past 20 to 30 years. Antenatal corticosteroids are now considered standard of care for mothers in the setting of imminent preterm delivery, but widespread use started only after the release of a 1994 National Institutes of Health Consensus statement.[36] Postnatal corticosteroids were used frequently in the 1980s to 1990s to facilitate extubation from mechanical ventilation. However, since the late 1990s, PNSs have been used more sparingly because of concerning links to increased rates of CP. The 8-year (1992-2000) cohort in the study by Patra et al[19] encompassed the era of these important changes, and their lack of consideration for corticosteroid use raises the possibility that differences in outcomes may have been related to corticosteroids.

Changes in evaluation methods may further complicate comparisons of outcomes over time. The second edition of the Bayley Scales of Infant Development (Bayley II),[37] used for infants born between 1993 and 2005, reports a Mental Developmental Index (MDI)—an inseparable composite measure of cognitive and language domains. However, the Bayley III[33] separates these scores into 2 reportable domains. Direct comparison of Bayley III scores and Bayley II MDI is problematic, although conversion methods are being sought.[38] The NRN began uniformly using the Bayley III for infants born on or after January 1, 2006; thus, the entire cohort in the present study was assessed using the Bayley III. Comparison of our study with a study using an entirely Bayley II–evaluated cohort should not focus on the numeric score attained by each group but rather the overall trend of how the low-grade group performs relative to the control group.

The limitations of our study involve the interrater reliability of CUS detection of PIVH, particularly at the lowest grades, and the power of tests of categorical outcomes and tests between levels of low-grade PIVH. In addition, excluding early porencephalic cyst and hydrocephalus requiring shunt may underestimate severe PIVH impairment for the sake of providing the clearest possible picture of low-grade PIVH.

Technique and interpretation of CUS are highly operator dependent, such that systematic differences between radiologists may exist. Hintz et al[39] reported 40% agreement for low-grade PIVH between 2 NRN centralized readers; the agreement for grade 1 or grade 2 hemorrhage specifically was only 26% and 20%, respectively. The sensitivity of local readings compared with centralized readers for low-grade PIVH was 48% to 68%.

Our study was powered on a primary outcome of continuous cognitive score. Although the comparison of low-grade PIVH with either no PIVH or severe PIVH is highly powered, we were unable to reach the goal sample size of 143 infants per group for comparisons between grade 1 vs grade 2 PIVH despite a 3-year cohort of infants. In underpowered analyses of grade 1 vs grade 2 PIVH, there were no significant differences in neurodevelopmental outcomes. To achieve adequate power for categorical outcomes, larger cohorts, typically 5- to 7-year birth cohorts, would be necessary. Also, although it would be clinically useful to distinguish results of grade 1 vs grade 2 PIVH, the poor interrater reliability, as previously mentioned, renders such discrete differences difficult to gauge.

We have shown that neurodevelopmental outcomes at 18 to 22 months are not negatively affected by low-grade PIVH; however, it cannot be assumed that the same could be said at later ages. The overall stability in diagnoses between toddler ages and early school age is typically poor.[40-42] Significant motor delay is more likely to remain stable, but cognitive diagnoses are not stable and the direction of change varies among reports.

In addition, cognitive test scores represent only one piece of the puzzle in assessing late outcomes. Nearly two-thirds of extremely low-birth-weight children require special education and are more likely than full-term peers to have subject-specific learning problems.[43] High-prevalence/low-severity disabilities, such as attention-deficit/hyperactivity disorders, specific neuropsychological deficits, and behavioral problems, may gradually emerge and contribute to the trend of worsening outcomes over time for these children. It is not clear what contribution low-grade PIVH may have to these more subtle disabilities.

Cranial ultrasonography has been used routinely as a screening and diagnostic method since the late 1970s. Magnetic resonance imaging continues to emerge as an important research tool in understanding brain development and pathophysiology; however, CUS continues to have a strong clinical presence because of its portability, speed, and lower cost. As such, further investigating the predictive abilities of this modality, particularly over time because more subtle disabilities may emerge, will be useful for counseling parents on the potential outcomes of their ELGA infants.

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