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Neurodevelopmental Outcome of Extremely Low Birth Weight Infants With Posthemorrhagic Hydrocephalus Requiring Shunt Insertion

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Abstract

OBJECTIVE—We aimed to evaluate neurodevelopmental and growth outcomes among extremely low birth weight infants who had severe intraventricular hemorrhage that required shunt insertion compared with infants without shunt insertion.

METHODS—Infants who were born in 1993–2002 with birth weights of 401 to 1000 g were enrolled in a very low birth weight registry at medical centers that participate in the National Institute of Child Health and Human Development Neonatal Research Network, and returned for follow-up at 18 to 22 months' corrected age were studied. Eighty-two percent of survivors completed follow-up, and 6161 children were classified into 5 groups: group 1, no intraventricular hemorrhage/no shunt (n = 5163); group 2, intraventricular hemorrhage grade 3/no shunt (n = 459); group 3, intraventricular hemorrhage grade 3/shunt (n = 103); group 4, intraventricular hemorrhage grade 4/no shunt (n = 311); and group 5, intraventricular hemorrhage grade 4/shunt (n = 125). Group comparisons were evaluated with χ^2 and Wilcoxon tests, and regression models were used to compare outcomes after adjustment for covariates.

RESULTS—Children with severe intraventricular hemorrhage and shunts had significantly lower scores on the Bayley Scales of Infant Development IIR compared with children with no intraventricular hemorrhage and with children with intraventricular hemorrhage of the same grade and no shunt. Infants with shunts were at increased risk for cerebral palsy and head circumference at the <10th percentile at 18 months' adjusted age. Greatest differences were observed between children with shunts and those with no intraventricular hemorrhage on these outcomes.

CONCLUSIONS—This large cohort study suggests that extremely low birth weight children with severe intraventricular hemorrhage that requires shunt insertion are at greatest risk for adverse neurodevelopmental and growth outcomes at 18 to 22 months compared with children with and without severe intraventricular hemorrhage and with no shunt. Long-term follow-up is needed to determine whether adverse outcomes persist or improve over time.

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Keywords

hydrocephalus; neuromotor outcome; prematurity

During the past 2 decades, there has been remarkable improvement in the survival of extremely low birth weight (ELBW) infants; however, the most immature of these infants remain at increased risk for neonatal complications that potentially affect long-term neurodevelopmental outcome, including intraventricular hemorrhage (IVH). The risk for severe IVH varies inversely with gestational age (GA) with an overall incidence of 7% to 23%.[1–6] Approximately one third of ELBW infants with an IVH develop posthemorrhagic hydrocephalus (PHH), 15% of whom will require shunt insertion.[7–10]

As the limits of viability continue to expand to lower GA groups, it is important for clinicians to identify specific risk factors that modify the risk for adverse neurodevelopmental outcome. The high incidence of neurocognitive impairment in the ELBW population cannot solely be attributed to severe IVH; however, IVH is clearly a predictor of adverse outcome and an indicator of brain injury. Contemporary data regarding the neurodevelopmental outcome of ELBW infants with PHH that requires shunt insertion are lacking, and it is unclear how much the requirement for shunt insertion modifies that risk. Although physicians are unable to predict which infant with a severe IVH will progress to require shunt insertion, specific data outlining the relative risk for affected infants provide evidence-based information to help guide family counseling and medical decision-making. The purpose of this retrospective cohort study was to compare the neurodevelopmental outcome of infants with PHH that required shunt insertion with that of their age-adjusted peers of similar birth weight in a large contemporary cohort of ELBW infants.

METHODS

Surviving infants at the 19 participating neonatal centers of the National Institute of Child Health and Human Development Neonatal Research Network who were born between January 1, 1993, and December 31, 2002, with birth weights of ≤1000 g and who participated in the Generic Database (GDB) and Follow-up Studies were eligible to be included in this study. The institutional review boards of all participating centers approved both studies, and informed consent was obtained from parents or legal guardians for follow-up.

Infants with major malformations or syndromes, including central nervous system defects, congenital heart defects, gastrointestinal defects, and chromosomal abnormalities, were excluded. Maternal and neonatal information collected from birth to death, hospital discharge, or 120 days was recorded in the GDB and included maternal age, receipt of antenatal antibiotics and steroids, rupture of membranes (ROM) >24 hours before birth, mode of delivery, infant birth weight, head circumference (HC), GA, gender, race, receipt of surfactants and postnatal steroids, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), IVH, placement of a shunt for posthemorrhagic hydrocephalus/persistent ventriculomegaly, periventricular leukomalacia (PVL), chronic lung disease or bronchopulmonary dysplasia (CLD/BPD), necrotizing enterocolitis (NEC), and infections.

RDS was defined as the presence of all 4 of the following: (1) required oxygen at 6 hours of life continuing to age 24 hours, (2) demonstrated clinical features of respiratory distress within age 24 hours, (3) had need for respiratory support to age 24 hours, and (4) had an abnormal chest radiograph within age 24 hours. CLD/BPD was defined as the need for supplemental oxygen at 36 weeks postmenstrual age. Cranial sonograms were reviewed by the staff radiologist at each participating center. IVH was defined on the basis of Papile criteria.[11] PVL

was diagnosed on the basis of finding of cystic echolucencies in the periventricular white matter. Because of changes in data collection during the study period, PVL was diagnosed on the basis of sonogram findings at ≥2 weeks for infants who were born before August 1998 and within 28 days or at 36 weeks' PCA for infants who were born after August 1998.

NEC was defined as modified Bells stage IIA or greater.[12] Early onset sepsis (within 72 hours of birth) and late-onset sepsis (after 72 hours) were defined by a positive blood culture and antibiotic therapy for ≥5 days. Cultures that were positive for organisms that generally are considered contaminants (eg, *Corynebacterium, Propionibacterium*, diphtheroids, *Alcaligenes*) were not counted as indicative of sepsis. In addition, infants who received a diagnosis of late-onset sepsis but were not treated with antibiotics for ≥5 days and survived were not considered to have sepsis. Meningitis was defined by a positive cerebrospinal fluid (CSF) culture and antibiotic therapy for ≥5 days. Clinical infection was defined as late-onset cultures negative but infant had clinical symptoms suggestive of infection and received antibiotic treatment for ≥5 days.

Growth charts developed by Alexander et al13 were used to classify infants as small for GA at birth, defined by a birth weight at the <10th percentile for gender and GA. Infants were classified as being in the <10th percentile for HC at birth by using intrauterine growth data reported by Thomas et al.[14] (Data that were used to create the curves in this article were received from Reese Clark, Pediatrix Medical Group, Fort Lauderdale, FL.) These data were further used to classify infants as being at the <10th percentile on weight and HC at 36 weeks postmenstrual age. When the infant's weight or HC was not available at 36 weeks, the closest measurement between 34 and 38 weeks' PCA was used.

Infants were assessed at a comprehensive follow-up visit at 18 to 22 months' corrected age. The follow-up visit included an interview with the infant's mother or other primary caregiver and an examination, which included measurement of weight, length, and HC and assessment of cognitive and neuromotor development by using a standardized neurosensory assessment and the Bayley Scales of Infant Development IIR[15] (both administered by certified examiners). Bayley scores were recorded for the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). The mean score is 100; a score of <70 (>2 SD below the mean) indicates significant delay. Children who were judged to have such severe developmental delay that they were untestable were assigned MDI and PDI scores of 49. Additional information collected at the follow-up visit included caregiver's education, medical history reported by the caregiver, including surgical procedures performed after initial hospital discharge and results of child's vision and hearing examinations, and presence of cerebral palsy (CP) or abnormal findings on the neurologic examination. Visual impairment was defined as the need for corrective lenses or blindness in 1 or both eyes. Hearing impairment was defined by hearing aid use in 1 or both ears. A composite outcome, neurodevelopmental impairment (NDI), was defined as ≥1 of the following: MDI of <70, PDI of <70, CP, blind in both eyes, or hearing aids in both ears. Centers for Disease Control and Prevention growth charts were used to determine whether children were below the 10th percentile for gender and age in weight, length, and HC at follow-up and to calculate *z* scores corresponding to each of these measures.[16]

IVH information recorded in the GDB and information about shunt placement obtained from the GDB and parent interview at follow-up were used to classify children into 5 analysis groups: group 1, no IVH/no shunt; group 2, IVH grade 3/no shunt; group 3, IVH grade 3/shunt; group 4, IVH grade 4/no shunt; group 5, IVH grade 4/shunt. Infants who received a shunt but did not have an IVH diagnosed were excluded from the analysis.

Maternal, neonatal, and clinical characteristics and each of the neurodevelopmental and growth outcomes were compared for children in the analysis groups. Primary comparisons were

between children with and without shunts among those with grade 3 IVH (group 3 versus group 2) and among those with grade 4 IVH (group 5 versus group 4). Each group of children with shunts was also compared with the no IVH/no shunt group (group 3 versus group 1 and group 5 versus group 1). Statistical significance for unadjusted comparisons was determined by using χ^2 tests for categorical variables and Wilcoxon tests for continuous variables. Adjusted comparisons on outcomes were made by using Poisson regression models with robust variance estimators to report adjusted relative risks (RRs) and associated 95% confidence intervals (CIs).17 Along with effects for study center and analysis group, maternal and neonatal risk factors that have been associated with neurodevelopmental outcomes1,18,19 were entered into the models, including GA, birth weight, gender, race, ROM at >24 hours before birth, mode of delivery (cesarean section or not), multiple gestation, mother's age, antenatal antibiotic use, antenatal steroid use, postnatal steroid use, surfactant use, RDS, CLD/BPD, PDA, PVL, infection group (uninfected, clinical infection only, sepsis alone, NEC with or without sepsis, meningitis with or without sepsis and/or NEC), and caregiver's education (high school degree or not). Mother's age was entered as a continuous variable, whereas all other variables were categorical. Because 7% of the infants who were born before 1998 did not have sonograms performed to evaluate for PVL, PVL was entered as a 3-level variable in all models (yes, no, missing). Covariates that were not statistically significant in any of the models fit to the neurodevelopmental outcomes were removed from the final neurodevelopmental models. Similarly, covariates that were not significant in any of the models fit to the growth outcomes were removed from those models. Thus, final neurodevelopmental outcome models included all of the covariates listed minus mother's age, ROM at >24 hours before birth, and antenatal antibiotic use. Final models fit to growth outcomes included all covariates listed minus ROM at >24 hours, RDS, and CLD/BPD. The reported adjusted RRs and associated χ^2 tests are from these final models. Among the subset of children with shunts, a stepwise logistic regression model was used to look for associations between the maternal and neonatal variables listed and NDI at 18 to 22 months. Variables that entered this model with an entry and stay criteria of P of <.1 were included in a Poisson regression model to estimate adjusted RRs and 95% CIs for each significant variable. All analyses were completed by using SAS 9.1 software.[20]

RESULTS

A total of 15 454 ELBW (defined as 401–1000 g) infants were born between January 1, 1993, and December 31, 2002, and were cared for at the 19 Neonatal Research Network centers. Of these, 726 with major malformations or syndromes were excluded, and 5242 infants died in the hospital or before the follow-up visit. Among the remaining 9486 children eligible for follow-up, 7776 (82%) completed the follow-up visit at 18 to 22 months' adjusted age. Children with no IVH information (n = 56) and those who received a shunt but did not have an IVH (n = 27) were excluded from analysis. Among the 7693 children studied, 2530 (33%) had an IVH during their initial hospitalization, and the IVH was severe (grade 3 or 4) for 13% (998 of 7693). Three percent of infants (246 of 7693) had a shunt placed for PHH. These 246 infants represent 10% of the 2530 ELBW infants who had an IVH during the study period. The likelihood of shunt insertion increased with increasing severity of IVH (grade 1: 13 [1%] of 1003; grade 2: 5 [1%] of 529; grade 3: 103 [18%] of 562; grade 4: 125 [29%] of 436; Table 1). Because of changes in data collection during the study period, timing of shunt insertion was available only for 102 children with shunts. The average age of shunt insertion among this subset of patients was 77 days (median: 76 days, 25th–75th percentiles: 44–94 days).

Infants who had severe IVH and those without an IVH were studied in depth and classified as follows: group 1: no IVH/no shunt (n = 5163); group 2: IVH grade 3/no shunt (n = 459); group 3: IVH grade 3/shunt (n = 103); group 4: IVH grade 4/no shunt (n = 311); and group 5: IVH grade 4/shunt (n = 125). Maternal and neonatal characteristics were similar for children with and without shunts among those with grade 3 IVH, and most were similar among those with

grade 4 IVH (Table 2). A greater proportion of children with grade 4 IVH and shunts were born at ≥25 weeks' GA and by cesarean section delivery compared with those with grade 4 IVH and no shunts. Compared with those with no IVH, children with shunts were more likely to be born at an earlier GA and less likely to be small for GA. Among children with grade 3 IVH, as well as among those with grade 4 IVH, a higher proportion of those with shunts compared with those without had CLD/BPD, PVL, and meningitis during the initial hospitalization, and a lower proportion had HC at the <10th percentile at 36 weeks postmenstrual age (Table 3). In addition, among those with grade 4 IVH, children with shunts were more likely to have had RDS and to have received surfactants than those without shunts. Both groups of children with shunts were more likely than children with no IVH to have had RDS, CLD/BPD, PDA, PVL, and meningitis and were more likely to have received surfactants and postnatal steroids. The overall length of initial hospital stay differed among the 5 groups ($P < .001$) with the longest duration among infants who had shunts(median days: no IVH/no shunt, 87; IVH 3/no shunt, 100; IVH 3/shunt, 114; IVH 4/no shunt, 104; IVH 4/shunt, 110).

Among infants with shunts and PHH, 62 (25%) had at least 1 episode of meningitis. The most common pathogen was coagulase-negative *Staphylococcus*, which was identified in 54% of cases. The majority of remaining cases were secondary to Gram-negative organisms (17.7%), *Candida* (9.7%) and *S aureus* (6.5%).

Follow-up Outcomes

Overall, 40% of the 6161 children in the analysis groups had some type of NDI at 18 to 22 months' corrected age. CP was diagnosed in 14%; 31% had an MDI score of <70; and 22% had a PDI score of <70. Among those evaluated, 11 % of children had impaired vision and 2% had hearing impairment. Impaired growth as indicated by weight, length, or HC at the <10th percentile at the 18- to 22-month follow-up visit was present for 62%, including 26% who had HC at the <10th percentile.

In unadjusted comparisons, the children with shunts were more likely to have lower MDI and PDI scores, CP, and NDI than those in the other groups at the 18- to 22-month assessment (Table 4). Among those with grade 4 IVH, a higher proportion of children who required shunt insertion had vision impairment compared with those without shunts; however, the percentage of children with hearing impairment was not significantly different in children with and without shunts among those with grade 4 IVH or among those with grade 3 IVH. Children with grade 3 IVH and shunts scored on average 8 points lower on MDI and 13 points lower on PDI than did those with grade 3 IVH and no shunt. Similarly, children with grade 4 IVH and shunts scored on average 12 points lower on MDI and 19 points lower on PDI than those with grade 4 IVH and no shunt. Furthermore, infants with the most severe forms of neurosensory impairment were unable to complete the standardized assessment and therefore received a score of 49 on the Bayley Scales of Infant Development IIR. Within each IVH grade, more children with than without shunts were classified as "untestable" (grade 3: 32% vs 17% on MDI, 39% vs 18% on PDI; grade 4: 48% vs 20% on MDI, 65% vs 26% on PDI). Of note, 31 children with severe IVH and shunts had MDI scores >85 (grade 3 IVH: 17 [17%] of 99; grade 4 IVH: 14 [12%] of 115), and 28 had PDI scores >85 (grade 3 IVH: 19 [19%] of 100; grade 4 IVH: 9 [8%] of 114).

Among children with grade 3 IVH, no statistically significant differences were found between those with and without shunts on weight and length at 18 to 22 months, but a higher proportion of those with shunts had HC at the <10th percentile (Table 5). Among children with grade 4 IVH, those with shunts were more likely than those without shunts to be below the 10th percentile on weight and length and HC, and their average *z* scores were lower on all 3 measures. Compared with children with no IVH, both groups of children with shunts were more likely to be below the 10th percentile on length and HC; however, the proportion of

children below the 10th percentile on weight was similar in all groups except for the IVH 4/ shunt.

After adjustment for study center and maternal and neonatal variables, including PVL, statistically significant differences remained between children with and without shunts among those with grade 3 IVH on PDI of <70, CP, NDI, and HC (Table 6). A statistically significant difference was no longer found for MDI at <70. Among those with grade 4 IVH, those with shunts were at greater risk than those without shunts for all neurodevelopmental outcomes except hearing impairment and for all growth outcomes. Compared with children with no IVH, children in both groups with severe grades 3 and 4 IVH and shunts were at greater risk for all neurodevelopmental outcomes except hearing impairment and were at greater risk for impaired growth.

Although the majority of children with grade 3 or 4 IVH and shunts had some indication of NDI at the 18- to 22-month assessment, 14% (32 of 228) had no evidence of NDI on the basis of our study definition (22 [22%] of those with grade 3 IVH and shunts; 10 [8%] of those with grade 4 IVH and shunts). Among these 32 children, median MDI and PDI scores both were 87; 17 children had MDI of >85, and 21 children had PDI of >85. Fourteen of these 32 children without NDI had evidence of growth delay with weight, length, or HC at the <10th percentile. Thus, 18 (8%) of the 228 children with severe IVH and shunts had no NDI or growth delay as defined for this analysis at 18 to 22 months' corrected age.

To understand better differences between children with shunts and with and without NDI, we explored associations between maternal and neonatal variables and presence of NDI. In this subgroup of 228 children with severe IVH and shunts, more boys than girls had NDI (90% vs 81%; adjusted RR: 1.13; 95% CI: 1.02–1.27; $P = .03$). Children who had evidence of PVL during the initial hospitalization were more likely to have NDI at 18 months (92% vs 83%; adjusted RR: 1.12; 95% CI: 1.02–1.24; $P = .02$) as were those with RDS (89% vs 72%; adjusted RR: 1.25; 95% CI: 1.02–1.52; $P = .03$). It is interesting that among these infants with severe IVH and shunts, the incidence of meningitis was similar for those with or without evidence of NDI (28% vs 25%; P = ns). Children with or without NDI were also similar with respect to birth weight, GA, caregiver's education, and child's medical insurance (private versus other). Statistically significant associations were not found between the other variables studied and presence of NDI in this group of children. Of note, children with shunts and without NDI tended to be bigger at 18 to 22 months as measured by z scores for weight, HC, and length compared with children with shunts and NDI (no NDI versus NDI [median], weight: −0.82 vs −2.12; length: −0.47 vs −1.53; HC: −0.19 vs −1.61; $P < .001$ for each).

DISCUSSION

Although the high incidence of neurocognitive impairment in the ELBW population cannot solely be attributed to severe IVH, it remains a major complication of prematurity that influences long-term developmental and functional outcomes. In our cohort, 13% of ELBW infants had grade 3 or 4 IVH, 3% of whom had a shunt inserted. Among this population of already high-risk infants, shunt insertion represents an additional risk factor associated with adverse long-term neurodevelopmental outcome. Furthermore, infants with PHH that requires shunt insertion represent a disproportionate percentage of children who have moderate to severe neurocognitive impairment in early childhood.

Most published data on the neurodevelopmental outcome of ELBW infants who require shunt insertion are small series of infants who were born in the 1980s.[21–24] Sasidharan et al[21] compared the outcome of 36 infants with severe IVH and found that 62% of the group without shunts had a developmental quotient >85 compared with only 33% of the infants who required

a shunt. In a single-center study of 19 infants who were born between 1980 and 1986, Hislop et al[22] reported that 79% either died or had evidence of significant NDI. In a retrospective analysis of 95 infants with PHH, de Vries et al[10] attempted to evaluate the relationship between timing of shunt insertion and outcome. Patients were classified as "early intervention" when some type of procedure was performed to remove CSF before the ventricular index was at the >97th percentile as compared with the "late intervention" group, who did not have an intervention before the ventricular index was at the >97th percentile. The overall moderate/severe disability rate was 22%; however, there was no statistically significant difference in outcome between patients with early intervention versus late intervention. Similarly, the Ventriculomegaly Trial Group found no difference in outcome at 12 or 30 months between patients who were randomly assigned to early CSF tapping versus conservative treatment.[25,26] Ultimately, 60% of patients in both groups required a ventriculoperitoneal shunt. Children in this trial also had a high disability rate. Overall, in this population, 48% had scores <70 on the Griffith Developmental Scales, 90% with neuromotor impairment and 14% with hearing loss.

Obstetric, neonatal, and neurosurgical care has improved since these early reports; therefore, we felt that it was important to evaluate the neurodevelopmental outcome of a contemporary cohort of infants who required shunt insertion. In this study, a large cohort of ELBW infants who were born between 1993 and 2002 were evaluated to determine the impact of PHH that required shunt insertion on neurodevelopmental outcome at 18 to 22 months' corrected age. Our findings are consistent with previous reports of increased risk for adverse neurodevelopmental and functional outcome in patients with severe IVH that required shunt insertion. It is concerning that children with severe IVH that required shunt insertion had a disproportionate risk for severe impairment compared with their peers as reflected in the 86% rate of NDI in our cohort (92% among those with grade 4 IVH and 78% among those with grade 3 IVH); however, 14% of our infants who required shunt insertion had no evidence of NDI at 18 to 22 months as defined by our study definition.

Previous studies have shown that ELBW infants are at significant risk for adverse neurocognitive outcome.[1,4,6,27–29] In this study, infants with no IVH had a lower rate of impairment and higher mean MDI and PDI scores compared with the other groups; however, it is equally important to note that even for infants with no hemorrhage, the mean Bayley MDI and PDI scores were 81 and 85, respectively, at the 18-month assessment. These data highlight the background rate of brain injury and abnormal functioning in this population of ELBW infants in early childhood. Severe IVH alone represents a significant risk factor for poor neurodevelopmental outcome in this already high-risk population (Table 4). Severe IVH that requires shunt insertion represents an additional differential risk factor that has an additional adverse impact on neurodevelopmental outcome above the baseline risk. Compared with infants with no IVH, infants in our cohort with grade 3 IVH that did not require shunt insertion had average decreases of 5 and 7 points in their mean MDI and PDI scores of cognitive and motor function, and those with grade 3 IVH that required shunt insertion had average decreases of 13 and 20 points. Those with grade 4 IVH that did not require shunt insertion had average decreases of 7 and 11 points in their mean MDI and PDI scores, and those who required shunt insertion had average decreases of 20 and 30 points.

The predictive value of neurodevelopmental outcome studies in early infancy has been questioned; however, when low Bayley scores are combined with the presence of severe grades 3 to 4 IVH, the ability to predict abnormal functioning at school age improves.[5] Hack et al[30] demonstrated that in the absence of neurosensory impairment, a significant percentage of ELBW infants will have improved neurodevelopmental functioning at school age. In contrast, children with severe cranial ultrasound abnormalities were less likely to have improved cognitive functioning over time, even in the neurosensory intact subgroup. Similarly, children

who were enrolled in the Indomethacin IVH prevention clinical trial were evaluated at 4.5 and 12 years of age. At 12 years of age, children with a history of grades 3 to 4 IVH were more likely to have abnormal neurocognitive functioning, including 60% with CP, 70% with mental retardation, and 92% who required special school services.[5,31,32]

The subset of patients in our cohort who had severe IVH and shunts and had a normal neuromotor assessment at 18 months is intriguing. Additional long-term follow-up of this subgroup to school age will be important in determining whether they remain unscathed.

In our study, we attempted to evaluate potential confounders that may influence outcome. The use of postnatal steroids was similar among children with grade 3 IVH with and without shunts and among those with grade 4 IVH with and without shunts. Those who required shunt insertion were more likely to have a diagnosis of meningitis at some point during their initial hospital stay than children in the other groups; however because of data collection limitations, we are unable to determine the timing of infection in relation to shunt insertion for all infants. Future studies are needed for better evaluation of the risk of meningitis associated with shunt insertion and subsequent impact on neurodevelopmental outcome in this patient population. Withdrawal of life-sustaining treatment is often discussed with parents of ELBW infants with severe IVH; therefore, we evaluated outcomes of infants who died before hospital discharge and could not be included in the neurodevelopmental follow-up. Among infants who died before hospital discharge, the primary cause of death was severe IVH in 5% and RDS with severe IVH in 12%. A higher percentage of these infants had a diagnosis of severe IVH compared with the cohort studied who attended follow-up (40% vs 13%). Among infants who either died after initial discharge but before the follow-up visit or were lost to follow-up, the rates of severe IVH were similar to those in the studied cohort (17% and 11% vs 13%).

The definition of IVH is well defined in the literature[11]; however, the lack of central readings is one of the limitations of our study because it introduces the possibility of inconsistent classifications, particularly across study centers. In addition, the definition of PHH is not standardized in the literature or in our study population. PHH is typically diagnosed in the clinical scenario of increasing ventricular width on coronal and sagittal images from serial imaging studies in an infant with a history of IVH and increasing HC or increasing fullness or size of the anterior fontanel[7]; however, again, we acknowledge that there may have been some variability in interpretation among radiologists. In addition, we noted significant variability by center on rates of shunt insertion among infants with grade 3 or 4 IVH. These findings highlight the need for more uniform and objective criteria for shunt insertion, and future studies would need to explore this observation further.

Previous studies and our data help us appreciate that the preterm brain is vulnerable to injury. The mean GA for most ELBW infants is coincident with critical periods in fetal brain development. The majority of IVH occurs in the highly cellular germinal matrix, which is also the site of origin for cerebral precursor cells for both the gray and white matter. Injury to these important tissues may disrupt the maturation process of other developing CNS tissues. Data from Patra et al[33] showing lower developmental functioning even in preterm infants with grades 1 to 2 IVH help one understand the vulnerability of the developing brain even in the absence of severe IVH. Vasileiadis et al[34] postulated that injury to these progenitor cells secondary to uncomplicated germinal matrix hemorrhage may result in disruption of neural development and reduction in cortical brain volumes. Using volumetric MRI technology, they demonstrated that preterm infants with uncomplicated grades 1 to 2 hemorrhage had a 16% reduction in cortical gray matter volumes at near-term gestation compared with preterm infants with normal cranial sonograms. Correlation with neurodevelopmental outcomes in early infancy are needed to determine the clinical relevance of these MRI findings; however, these data augment the concern regarding the risk for brain injury in infants with more severe degrees

of IVH. Our study is limited to assessment of cranial ultrasounds, which likely underestimate the extent of brain injury; however, on the basis of current data, one could speculate that infants with severe hemorrhage are even more likely to have abnormalities in brain development in the white matter and cortical and subcortical regions of the developing brain. White matter injury is an important predictor of neurodevelopmental outcome and must be included in a risk assessment. Our limited ability to evaluate the full extent of white matter injury in infants with severe IVH may have affected our results. It is interesting that a significant proportion of infants with severe IVH that did not require shunts were noted to have a HC <10th percentile at 18 to 2 months (Table 5). This delayed head growth suggests the possibility of porencephaly and impaired brain growth. Future research projects, including MRI assessment of children with severe IVH, will better delineate the extent of injury to the surrounding white matter and the impact on long-term development.

The pathophysiology of brain injury in patients with severe IVH is most likely multifactorial. Ischemia, pressure on the surrounding tissues, and inflammation all contribute to the risk for brain injury.[35,36] Animal data suggest that IVH initiates the inflammatory cascade. The developing oligodendrocytes seem to be particularly vulnerable to cytotoxic injury, resulting in an increased risk for white matter injury. The role of inflammatory mediators in patients with PHH has not been completely delineated; however, it appears that various mediators shown to be important in CNS development may be affected. Schmitz et al[36] compared serial CSF cytokine concentrations in 27 preterm infants who had PHH with control infants who received a lumbar puncture as part of a sepsis evaluation. Interleukin-1β, a well-described proinflammatory mediator, was elevated during the acute phase in patients who developed PHH. IL-18 is another proinflammatory mediator that is thought to have an important role in white matter injury. In this study, IL-18 levels were not elevated acutely but were increased in samples that were collected at the time of definitive shunt insertion. In contrast to previous reports,[37] interferon-γ levels, which have been shown to be elevated in adult demyelinating disorders such as multiple sclerosis, were elevated in patients who had PHH and evidence of white matter injury.[34] Savman et al[38] compared cytokine levels in a group of 24 infants with PHH with control subjects. Patient with PHH had significantly increased levels of tumor necrosis factor α, IL-1β, IL-6, and IL-8; however, these levels did not correlate to severity of adverse outcome. This study may not have been powered to detect a difference, and additional investigation is warranted.

Our findings regarding growth impairment in this population are interesting. In some respects, oral motor dysfunction serves as a surrogate marker for poor motor coordination. Given the high rate of NDI among infants with severe IVH that required shunt insertion, one could speculate that many of these infants also had oral-motor dysfunction. These finding are consistent with previously published reports showing association between growth impairment and adverse neurodevelopmental outcome.[19,27,39] The importance of adequate energy and mineral intake during the period of critical brain development during the first year of life cannot be underestimated.

Recent data suggest that the increased overall survival rate of ELBW infants has also been associated with an increased rate of disability and NDI.[4] Studies that evaluated neurodevelopmental outcome in early childhood suggested that these children are at higher risk for abnormal neurocognitive functioning and delayed school performance, particularly those with a history of severe IVH.[6,28,29,32] The lifetime costs to care for a child with severe IVH are significant. These data highlight the importance of delineating neonatal morbidities associated with poor long-term neurodevelopmental outcome. Although the clinician is unable to determine which infants will progress to require shunt insertion, current data regarding the neurodevelopmental outcome of surviving ELBW infants who have severe IVH that requires shunt insertion provides valuable information to help guide medical decision-making and

counseling. Furthermore, our data show that infants with severe IVH with or without shunt insertion are at significant risk for adverse neurodevelopmental outcome in early infancy. Long-term follow-up to school age and correlation to MRI findings are needed.

CONCLUSION

Infants with severe IVH associated with PHH that requires shunt insertion are at significant risk for cognitive and motor impairment. Although a small subset of these patients seem unaffected at 18 to 22 months, extended follow-up to school age is necessary before considering them unscathed. Neurodevelopmental outcomes in early childhood of infants with severe IVH that requires shunt insertion seem more promising than those reported from the 1980s; however, these patients continue to represent an extremely high-risk group of infants for adverse neurodevelopmental outcome.

What's Known on This Subject

Premature infants with severe intraventricular hemorrhage are at higher risk for adverse neurodevelopmental outcome.

What This Study Adds

This study evaluates the neurodevelopmental outcome data of a contemporary cohort of extremely low birth weight infants with severe intraventricular hemorrhage and posthemorrhagic hydrocephalus. An incremental increased risk for adverse outcome is associated with an increasing severity of intraventricular hemorrhage and the need for shunt insertion.

Abbreviations

ELBW	extremely low birth weight
IVH	intraventricular hemorrhage
GA	gestational age
PHH	posthemorrhagic hydrocephalus
GDB	Generic Database
ROM	rupture of membranes
HC	head circumference
RDS	respiratory distress syndrome
PDA	patent ductus arteriosus
PVL	periventricular leukomalacia
CLD/BPD	chronic lung disease or bronchopulmonary dysplasia
NEC	necrotizing enterocolitis
PCA	postconceptional age
CSF	cerebrospinal fluid
MDI	Mental Development Index
PDI	Psychomotor Development Index

NDI	neurodevelopmental impairment
CP	cerebral palsy
RR	relative risk
CI	confidence interval
IL	interleukin

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TABLE 1

Incidence of IVH and Shunt Insertion Among Study Population

Parameter	Infants With IVH, *n* (%)	Shunt Required, *n* (%)
Grade 1 IVH	1003/7693 (13)	13/1003 (1)
Grade 2 IVH	529/7693 (7)	5/529 (1)
Grade 3 IVH	562/7693 (7)	103/562 (18)
Grade 4 IVH	436/7693 (6)	125/436 (29)
Total	2530/7693 (33)	246/2530 (10)

TABLE 2

Maternal and Neonatal Characteristics of Study Population

Characteristic[a]	Group, *n* (%)				
	No IVH/No Shunt (*n* = 5163)	IVH 3/No Shunt (*n* = 459)	IVH 3/Shunt (*n* = 103)[b]	IVH 4/No Shunt (*n* = 311)	IVH 4/Shunt (*n* = 125)[c]
Maternal					
Age ≤19 y	791/5161 (15)	84/459 (18)	17/103 (17)	55/310 (18)	26/125 (21)
ROM >24 h	1199/5062 (24)	98/443 (22)	19/102 (19)	66/297 (22)	20/120 (17)
Antenatal antibiotics	3290/5154 (64)	312/455 (69)	78/103 (76)	201/310 (65)	72/121 (60)
Antenatal steroids	3999/5157 (78)	297/456 (65)	75/102 (74)	186/310 (60)	67/122 (55)
Cesarean section	3368/5157 (65)	208/458 (45)	54/103 (52)	148/309 (48)	75/125 (60)[e]
Caregiver education: high school graduate[d]	3897/5093 (77)	328/456 (72)	81/102 (79)	226/311 (73)	94/124 (76)
Neonatal					
Birth weight, g					
401–500	88/5163 (2)	9/459 (2)	0/103 (0)	3/311 (1)	2/125 (2)
501–750	1817/5163 (35)	210/459 (46)	38/103 (37)	162/311 (52)	50/125 (40)
751–1000	3258/5163 (63)	240/459 (52)	65/103 (63)	146/311 (47)	73/125 (58)
GA, wk					
<25	835/5162 (16)	151/459 (33)	33/103 (32)	114/311 (37)	28/124 (23)[e]
25–28	3567/5162 (69)	288/459 (63)	67/103 (65)	183/311 (59)	92/124 (74)
29–32	724/5162 (14)	20/459 (4)	3/103 (3)	13/311 (4)	4/124 (3)
≥33	36/5162 (1)	0/459 (0)	0/103 (0)	1/311 (<1)	0/124 (0)
SGA at birth	1019/5162 (20)	38/459 (8)	5/103 (5)	25/311 (8)	6/124 (5)
HC at <10th percentile at birth	784/5007 (16)	31/448 (7)	6/101 (6)	22/294 (7)	8/119 (7)
Male	2308/5163 (45)	245/459 (53)	63/103 (61)	162/311 (52)	60/125 (48)
Race					
Black	2280/5161 (44)	207/459 (45)	48/103 (47)	149/311 (48)	64/125 (51)
White	2026/5161 (39)	163/459 (36)	42/103 (41)	105/311 (34)	49/125 (39)
Hispanic	698/5161 (14)	75/459 (16)	13/103 (13)	48/311 (15)	10/125 (8)
Other	157/5161 (3)	14/459 (3)	0/103 (0)	9/311 (3)	2/125 (2)

SGA indicates small for gestational age.

[a] Information was missing for mother's age (3), ROM at >24 hours before birth (137), antenatal antibiotics (18), antenatal steroids (14), cesarean section (9), caregiver high school degree (75), GA (2), SGA (2), HC at birth (192), and race (2).

[b] There were no statistically significant comparisons between IVH 3/shunt versus IVH 3/no shunt. Comparisons between IVH 3/shunt versus no IVH/no shunt were statistically significant for antenatal antibiotics ($P < .05$), cesarean section birth ($P < .01$), GA ($P < .001$), SGA ($P < .001$), HC at the <10th percentile ($P < .01$), and male gender ($P < .001$).

[c] Statistically significant comparisons between IVH 4/shunt versus IVH 4/no shunt are shown. Comparisons between IVH 4/shunt versus no IVH/no shunt were statistically significant for antenatal steroids ($P < .001$), GA ($P < .01$), SGA ($P < .001$), and HC < 10th percentile ($P < .01$).

[d] The mother was the caretaker for 91% of the infants.

[e] $P \leq .05$ for IVH 4/shunt versus IVH 4/no shunt by the χ^2 test.

TABLE 3

Clinical Characteristics of Study Population During Initial Hospitalization

Characteristic[a]	Group, *n* (%)				
	No IVH/No Shunt (*N* = 5163)	IVH 3/No Shunt (*N* = 459)	IVH 3/Shunt (*N* = 103)[b]	IVH 4/No Shunt (*N* = 311)	IVH 4/Shunt (*N* = 125)[c]
RDS	3076/5148 (60)	354/454 (78)	77/103 (75)	242/311 (78)	110/124 (89)[f]
CLD/BPD	2134/5152 (41)	238/455 (52)	65/103 (63)[e]	176/311 (57)	85/122 (70)[e]
PDA	2049/5161 (40)	284/459 (62)	52/103 (50)[e]	197/311 (63)	73/125 (58)
PVL	100/4727 (2)	50/457 (11)	23/103 (22)[f]	94/307 (31)	51/124 (41)[e]
Infection group[d]					
Uninfected	1931/5161 (37)	117/459 (25)	15/102 (15)[g]	66/311 (21)	18/125 (14)[g]
Clinical infection only	1248/5161 (24)	95/459 (21)	13/102 (13)	89/311 (29)	34/125 (27)
Sepsis alone	1466/5161 (28)	173/459 (38)	35/102 (34)	109/311 (35)	28/125 (22)
NEC with/without sepsis	366/5161 (7)	43/459 (9)	9/102 (9)	27/311 (9)	13/125 (10)
Meningitis	150/5161 (3)	31/459 (7)	30/102 (29)	20/311 (6)	32/125 (26)
Surfactant use	3874/5155 (75)	400/458 (87)	94/103 (91)	268/311 (86)	122/125 (98)[g]
Postnatal steroids	1828/5160 (35)	243/459 (53)	56/103 (54)	180/311 (58)	61/125 (49)
Weight <10th percentile at 36 wk	3142/4699 (67)	292/420 (70)	62/95 (65)	193/279 (69)	71/115 (62)
Head circumference at the <10th percentile at 36 wk	1724/4533 (38)	184/405 (45)	31/92 (34)[e]	126/271 (46)	38/114 (33)[e]

[a] Information was missing for RDS (21), CLD/BPD (18), PDA (2), PVL (443), infection group (3), surfactant use (9), postnatal steroids (3), weight at 36 weeks (553), and HC at 36 weeks (746).

[b] Statistically significant comparisons between IVH 3/shunt versus IVH 3/no shunt are shown. Comparisons between IVH 3/shunt versus no IVH/no shunt were statistically significant for RDS ($P < .01$), CLD/BPD ($P < .001$), PDA ($P < .05$), PVL ($P < .001$), infection group ($P < .001$), surfactant use ($P < .001$), and postnatal steroids ($P < .001$).

[c] Statistically significant comparisons between IVH 4/shunt versus IVH 4/no shunt are shown. Comparisons between IVH 4/shunt versus no IVH/no shunt were statistically significant for RDS ($P < .001$), CLD/BPD ($P < .001$), PDA ($P < .001$), PVL ($P < .001$), infection group ($P < .001$), surfactant use ($P < .001$), and postnatal steroids ($P < .01$).

[d] Of the 457 infants with NEC, 270 (59%) also had sepsis. Of the 265 infants with meningitis, 81 (31%) had meningitis alone, 154 (58%) had meningitis plus sepsis, 6 (2%) had meningitis plus NEC, and 24 (9%) had meningitis plus sepsis plus NEC.

[e] $P \leq .05$,

[f] $P \leq .01$,

[g] $P \leq .001$ for IVH 3/shunt versus IVH 3/no shunt or for IVH 4/shunt versus IVH 4/no shunt by the χ^2 test.

TABLE 4

Neurodevelopmental Outcomes at 18 to 22 Months' Corrected Age: Univariate Analyses

Outcome[a]	Group				
	No IVH/No Shunt (*N* = 5163)	IVH 3/No Shunt (*N* = 459)	IVH 3/Shunt (*N* = 103)[b]	IVH 4/No Shunt (*N* = 311)	IVH 4/Shunt (*N* = 125)[c]
MDI score					
Mean (SE)	80.6 (0.25)	74.1 (0.91)	66.2 (1.72)[d]	71.5 (1.09)	60.3 (1.57)[d]
Median	82	75	61	72	50
MDI < 70, *n* (%)	1318/4807 (27)	183/424 (43)	59/99 (60)[e]	143/295 (48)	87/115 (76)[d]
MDI = 49, *n* (%)	294/4805 (6)	70/424 (17)	32/99 (32)[d]	60/295 (20)	55/115 (48)[d]
PDI score					
Mean (SE)	84.7 (0.25)	77.4 (0.97)	64.1 (1.88)[d]	73.2 (1.17)	55.2 (1.24)[d]
Median	87	82	51	75	49
PDI < 70, *n* (%)	810/4741 (17)	140/417 (34)	65/100 (65)[d]	123/294 (42)	98/114 (86)[d]
PDI = 49, *n* (%)	313/4738 (7)	73/417 (18)	39/100 (39)[d]	76/294 (26)	74/114 (65)[d]
CP, *n* (%)	492/5125 (10)	103/457 (23)	58/102 (57)[d]	114/310 (37)	100/125 (80)[d]
Vision impairment, *n* (%)	465/5115 (9)	77/453 (17)	24/100 (24)	64/307 (21)	41/123 (33)[e]
Hearing impairment, *n* (%)	73/5091 (1)	25/446 (6)	2/101 (2)	12/304 (4)	6/119 (5)
NDI, *n* (%)	1690/4764 (35)	234/426 (55)	79/101 (78)[d]	189/299 (63)	114/124 (92)[d]

[a] Information was missing for MDI (421), PDI (495), CP (42); vision impairment (63), hearing impairment (100), and NDI (447).

[b] Statistically significant comparisons between IVH 3/shunt versus IVH 3/no shunt are shown. Comparisons between IVH 3/shunt versus no IVH/no shunt were statistically significant for all outcomes ($P < .001$) except hearing impairment ($P = .6$).

[c] Statistically significant comparisons between IVH 4/shunt versus IVH 4/no shunt are shown. Comparisons between IVH 4/shunt versus no IVH/no shunt were statistically significant for all outcomes ($P < .001$ for all, except hearing impairment $P < .01$).

[d] $P \leq .001$,

[e] $P \leq .01$ for IVH 3/shunt versus IVH 3/no shunt or for IVH 4/shunt versus IVH 4/no shunt by the χ^2 or Wilcoxon test.

TABLE 5

Growth Outcomes at 18 to 22 Months' Corrected Age: Univariate Analyses

Outcome[a]	Group				
	No IVH/No Shunt ($N = 5163$)	IVH 3/No Shunt ($N = 459$)	IVH 3/Shunt ($N = 103$)[b]	IVH 4/No Shunt ($N = 311$)	IVH 4/Shunt ($N = 125$)[c]
Weight *z* score					
Mean (SE)	−1.35 (0.02)	−1.43 (0.07)	−1.53 (0.15)	−1.47 (0.08)	−2.47 (0.13)[f]
Median	−1.32	−1.33	−1.63	−1.42	−2.32
Weight <10th percentile, *n* (%)	2594/5118 (51)	236/457 (52)	57/101 (56)	169/307 (55)	92/124 (74)[f]
Length *z* score					
Mean (SE)	−0.85 (0.02)	−0.88 (0.06)	−1.05 (0.12)	−0.89 (0.07)	−1.48 (0.12)[f]
Median	−0.80	−0.83	−1.15	−0.95	−1.55
Length at the <10th percentile, *n* (%)	1725/5112 (34)	161/457 (35)	43/99 (43)	121/307 (39)	68/123 (55)[e]
HC *z* score					
Mean (SE)	−0.51 (0.02)	−0.63 (0.06)	−0.90 (0.19)	−0.79 (0.09)	−1.66 (0.18)[f]
Median	−0.47	−0.64	−1.02	−0.81	−1.70
HC at the <10th percentile, *n* (%)	1245/5112 (24)	135/456 (30)	40/101 (40)[d]	108/306 (35)	76/125 (61)[f]

[a] Information was missing for weight (54), length (63), and HC (61).

[b] Statistically significant comparisons between IVH 3/shunt versus IVH 3/no shunt are shown. Comparisons between IVH 3/shunt versus no IVH/no shunt were statistically significant for length (*z* score: $P = .02$; <10th percentile: $P = .04$) and for HC ($P < .01$ for *z* score and <10th percentile) but not for weight (*z* score: $P = .06$; <10th percentile: $P = .3$).

[c] Statistically significant comparisons between IVH 4/shunt versus IVH 4/no shunt are shown. Comparisons between IVH 4/shunt versus no IVH/no shunt were statistically significant for all outcomes ($P < .001$ for all).

[d] $P \leq .05$,

[e] $P \leq .01$,

[f] $P \leq .001$ for IVH 3/shunt versus IVH 3/no shunt or for IVH 4/shunt versus IVH 4/no shunt by the χ^2 or Wilcoxon test.

TABLE 6

Neurodevelopmental and Growth Outcomes at 18 to 22 Months' Corrected Age Assessed by RRs and 95% CI

Outcome	IVH 3/Shunt Versus IVH 3/No Shunt, Adjusted RR (95 CI)	IVH 3/Shunt Versus No IVH/ No Shunt, Adjusted RR (95% CI)	IVH 4/Shunt Versus IVH 4/No Shunt, Adjusted RR (95 CI)	IVH 4/Shunt Versus No IVH/ No Shunt, Adjusted RR (95% CI)
MDI < 70 (*n* = 5606)	1.19 (0.97–1.44)	1.41 (1.18–1.68)[c]	1.48 (1.24–1.78)[c]	1.72 (1.47–2.02)[c]
PDI < 70 (*n* = 5534)	1.61 (1.32–1.96)[c]	2.45 (2.06–2.91)[c]	1.94 (1.61–2.34)[c]	2.90 (2.45–3.43)[c]
Cerebral palsy (*n* = 5977)	2.08 (1.63–2.66)[c]	3.44 (2.76–4.29)[c]	1.83 (1.47–2.28)[c]	3.96 (3.19–4.92)[c]
Vision impairment (*n* = 5957)	1.26 (0.87–1.82)	1.65 (1.18–2.31)[b]	1.72 (1.19–2.46)[b]	2.39 (1.71–3.35)[c]
Hearing impairment (*n* = 5921)	0.33 (0.09–1.30)	0.88 (0.23–3.35)	1.41 (0.56–3.59)	2.13 (0.96–4.76)
NDI (*n* = 5579)	1.29 (1.11–1.48)[c]	1.57 (1.38–1.78)[c]	1.44 (1.27–1.64)[c]	1.81 (1.62–2.03)[c]
Weight at the <10th percentile (*n* = 5983)	1.12 (0.93–1.37)	1.10 (0.92–1.32)	1.34 (1.15–1.55)[c]	1.33 (1.17–1.51)[c]
Length at the <10th percentile (*n* = 5975)	1.30 (1.01–1.68)[a]	1.28 (1.02–1.62)[a]	1.41 (1.13–1.77)[b]	1.48 (1.22–1.80)[c]
Head circumference at the <10th percentile (*n* = 5976)	1.38 (1.07–1.80)[a]	1.43 (1.13–1.81)[b]	1.77 (1.41–2.22)[c]	2.02 (1.66–2.46)[c]

Neurodevelopmental outcome RRs were adjusted for study center, GA, birth weight, gender, race, cesarean section delivery, multiple birth, antenatal steroid exposure, postnatal steroid exposure, surfactant use, RDS, CLD/BPD, PDA, PVL, infection group, and caregiver's education. Growth outcome RRs were adjusted for study center, GA, birth weight, gender, race, mother's age, cesarean section delivery, multiple birth, antenatal antibiotic exposure, antenatal steroid exposure, postnatal steroid exposure, surfactant use, PDA, PVL, infection group, and caregiver's education. The *n* shown in row headings represent the total number of infants with nonmissing outcome and covariates who were included in each model from which RRs were derived.

[a] $P \leq .05$,

[b] $P \leq .01$,

[c] $P \leq .001$ by the χ^2 test.