Intraventricular Hemorrhage and Neurodevelopmental Outcomes in Extreme Preterm Infants

AUTHORS: Srinivas Bolisetty, MD, FRACP,[a,b] Anjali Dhawan, MD, FRACP,[a] Mohamed Abdel-Latif, FRACP, MRCPCH, MPH, MScEpid,[c] Barbara Bajuk, MPH,[d] Jacqueline Stack, FRACP,[e] Kei Lui, MD, FRACP,[a,b] on behalf of the New South Wales and Australian Capital Territory Neonatal Intensive Care Units' Data Collection

[a]Division of Newborn Services, Royal Hospital for Women, Sydney, Australia; [b]School of Women's and Children's Health, University of New South Wales, Sydney, Australia; [c]Neonatal Intensive Care Unit, Centenary Hospital, Canberra, Australia; [d]New South Wales Pregnancy and Newborn Services Network (PSN), Sydney, Australia; and [e]Neonatal Intensive Care Unit, Liverpool Hospital, Sydney, Australia

KEY WORDS

infant, extremely premature, intraventricular hemorrhage, neurodevelopmental outcomes

ABBREVIATIONS

ACT—Australian Capital Territory
BSIDII-MDI—Bayley Scales of Infant Development-II Mental Development Index
CI—confidence interval
GMDS-GQ—Griffiths Mental Developmental Scale General Quotient
IVH—intraventricular hemorrhage
MDI—mental developmental index
NICUS—Neonatal Intensive Care Units database
NSW—New South Wales
PVL—periventricular leukomalacia
ROP—retinopathy of prematurity

Dr Bolisetty conceptualized and designed the study, coordinated and supervised data analyses, and reviewed and revised the manuscript; Dr Dhawan contributed to the initial concept and design of the study and to analysis and interpretation of data and drafted the initial manuscript; Dr Abdel-Latif contributed to the initial concept and design of the study and contributed substantially to data analysis and review of the initial draft of the manuscript; Ms Bajuk contributed to the initial concept and design of the study, acquisition of data, and critical review of the manuscript; Dr Stack contributed to the initial concept and design of the study and critical review of the manuscript; Dr Lui contributed to the initial concept and design of the study, assisted with data analysis and interpretation, and assisted with critical review of the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Cranial ultrasound is routinely used in identifying cerebral abnormalities in premature infants. Grade III and IV intraventricular hemorrhages, cystic periventricular leukomalacia, and late ventriculomegaly are all known predictors of adverse neurodevelopmental sequelae in these infants.

WHAT THIS STUDY ADDS: We reviewed neurodevelopmental outcomes among 2414 extreme preterm infants. Infants with grades I and II intraventricular hemorrhage had increased rates of neurosensory impairment, developmental delay, cerebral palsy, and deafness at 2 to 3 years' corrected age.

abstract

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OBJECTIVE: Not many large studies have reported the true impact of lower-grade intraventricular hemorrhages in preterm infants. We studied the neurodevelopmental outcomes of extremely preterm infants in relation to the severity of intraventricular hemorrhage.

METHODS: A regional cohort study of infants born at 23 to 28 weeks' gestation and admitted to a NICU between 1998 and 2004. Primary outcome measure was moderate to severe neurosensory impairment at 2 to 3 years' corrected age defined as developmental delay (developmental quotient >2 SD below the mean), cerebral palsy, bilateral deafness, or bilateral blindness.

RESULTS: Of the 1472 survivors assessed, infants with grade III–IV intraventricular hemorrhage (IVH; n = 93) had higher rates of developmental delay (17.5%), cerebral palsy (30%), deafness (8.6%), and blindness (2.2%). Grade I–II IVH infants (n = 336) also had increased rates of neurosensory impairment (22% vs 12.1%), developmental delay (7.8% vs 3.4%), cerebral palsy (10.4% vs 6.5%), and deafness (6.0% vs 2.3%) compared with the no IVH group (n = 1043). After exclusion of 40 infants with late ultrasound findings (periventricular leukomalacia, porencephaly, ventricular enlargement), isolated grade I–II IVH (n = 296) had increased rates of moderate-severe neurosensory impairment (18.6% vs 12.1%). Isolated grade I–II IVH was also independently associated with a higher risk of neurosensory impairment (adjusted odds ratio 1.73, 95% confidence interval 1.22–2.46).

CONCLUSIONS: Grade I–II IVH, even with no documented white matter injury or other late ultrasound abnormalities, is associated with adverse neurodevelopmental outcomes in extremely preterm infants. *Pediatrics* 2014;133:55–62

Cranial ultrasound is the most readily available and commonly used imaging technique for the diagnosis of cerebral lesions in preterm infants. Intraventricular hemorrhage (IVH) is the most commonly recognized cerebral lesion on ultrasound in extremely preterm infants.[1] Papile classification is commonly used to grade the severity of IVH.[2] Grade III–IV IVH and other lesions noted on ultrasound including periventricular leukomalacia (PVL), porencephaly, and ventriculomegaly are well documented to be associated with adverse neurodevelopmental outcomes.[3–7] However, the true impact of lower-grade IVH on the neurodevelopment of these extreme preterm infants has not been well described. IVH originates in the germinal matrix, which is the source of future neuronal and glial cells in the immature brain. The germinal matrix that initially surrounds the whole fetal ventricular system in the previable gestation gradually involutes to reside over the body of the caudate between 24 and 28 weeks' gestation and at the level of the head of the caudate nucleus between 28 and 32 weeks' gestation. It is therefore logical to suspect that even smaller hemorrhages within the germinal matrix at this gestation may have an impact on the future neuronal and glial cell migration within the immature brain.

We therefore undertook this study to investigate the long-term neurodevelopmental outcomes in relation to the severity of IVH in a large cohort of extremely preterm infants admitted to any of the 10 NICUs within New South Wales (NSW) and the Australian Capital Territory. We hypothesized that preterm infants with any grade of IVH have poorer neurodevelopmental outcomes compared with those without IVH.

METHODS

This was a retrospective cohort study using prospectively collected data from all 10 tertiary NICUs in NSW and the Australian Capital Territory (ACT). The study included all infants born between 23^{+0} and 28^{+6} weeks' gestation and admitted to the NICU between January 1998 and December 2004. Infants with major congenital malformations and those who died before an ultrasound was obtained were excluded. A full description of the NSW and ACT neonatal service organization and networking and the validity of the Neonatal Intensive Care Units (NICUS) database has been described.[8,9]

In NSW and ACT NICUs, cranial ultrasound is the standard screening test used to detect IVH and other cranial pathologies for all preterm infants born before 32 weeks' gestation. The standard policy in the network is to perform head ultrasounds during days 1 through 4 of life, days 10 through 14 of life, and 4 to 8 weeks of age and at 36 to 40 weeks' corrected age. The interpretation of the head ultrasound was based on the reports of radiologists and/or neonatologists at each hospital. Papile classification is used to grade the severity of IVH on ultrasound.[2] Porencephalic cysts are defined as parenchymal lesions corresponding to grade IV intraventricular hemorrhage. PVL refers to the ischemic brain injury affecting the periventricular white matter in the boundary zones supplied by terminal branches of both the centripetal and centrifugal arteries. Encephaloclastic porencephaly refers to the late development of extensive echo-dense and cystic lesions involving the periphery of the cerebrum. Interobserver reliability and accuracy in interpreting cranial ultrasounds in NSW and ACT has previously been validated and reported.[10] Overall agreement among the reporters was found to be 88%. Multirater agreement for individual grades of IVH found in this report were as follows: normal ultrasounds, 78%; grade I, 45%; grade II, 41%; grade III, 38%; and grade IV, 70%. Intraobserver reliability ranged from 78% to 90%.[10]

For all preterm infants of $<$29 weeks' gestation, the standard practice among the NICUs in this region is to perform a neurodevelopmental assessment by a developmental team at 2 to 3 years of age, corrected for prematurity, including the administration of the Griffiths Mental Developmental Scale General Quotient (GMDS-GQ) or Bayley Scales of Infant Development-II Mental Development Index (BSIDII-MDI). Follow-up assessment results are included in the NICUS database.

Data for this study extracted from the NICUS Data Collection included all relevant clinical information, hospital outcomes and follow-up information at 2 to 3 years of age, corrected for prematurity. The primary outcome measure was moderate to severe neurosensory impairment at 2 to 3 years' corrected age. Moderate neurosensory impairment was defined as the presence of developmental delay (GMDS-GQ or BSIDII-MDI between 2 and 3 SD below the mean), moderate cerebral palsy (able to walk with the assistance of aids), or deafness (requiring amplification with bilateral hearing aids or unilateral/bilateral cochlear implant). Severe neurosensory impairment was defined as developmental delay (GMDS-GQ or BSIDII-MDI $\geq$3 SD below the mean), severe cerebral palsy (unable to walk with the assistance of aids), or bilateral blindness (visual acuity of $<$6/60 in the better eye).[11]

Statistical analyses were performed by using Predictive Analytics SoftWare Statistics (version 20; IBM SPSS Statistics, IBM Corporation, Armonk, NY). Multivariate analysis using logistic regression models adjusted for significant clinical characteristics were performed to determine the relationship between the study groups (no IVH, IVH grade I–II, and IVH grade III–IV) and neurodevelopmental outcome. In multiple group comparisons, where appropriate, χ^2 for larger contingency table, analysis of variance, or Kruskal-Wallis tests were used to test for between group differences. A no-IVH group was used as controls for all subsequent post hoc 2-group comparisons.

All *P* values were 2-sided, and the significance level was not changed when multiple comparisons were performed.

The study was approved by the South Eastern Sydney Illawarra Area Health Services Northern Hospital Network Human Research Ethics Committee.

RESULTS

During the study period, 2701 extremely preterm infants (23–28 weeks; gestational age) were registered in the NICUS database, and 133 infants died before head ultrasound screening (Fig 1). Of the survivors, 152 infants had major congenital malformations and were excluded from the study. Another 2 surviving infants who did not have ultrasound examination were excluded. The study population comprised 2414 infants of whom 819 (33.9%) were diagnosed with IVH, 515 (21.3%) grade I–II IVH and 304 (12.6%) Grade III–IV IVH. Of these, 446 infants died. Infants with III–IV IVH had a significantly higher mortality rate (62.2%) compared with I–II IVH (15.7%) and the no-IVH groups (11%).

Of the 1968 survivors, 1472 (74.8%) infants were assessed at 2 to 3 years of age, corrected for prematurity. Of these, 1043 had no IVH. Grade I, II, III, and IV IVH was found in 232, 104, 56, and 37 infants, respectively. Table 1 compares infants who were followed up with those lost to follow-up. Infants lost to follow-up had less neonatal morbidity compared with infants who were followed-up.

Perinatal characteristics of the IVH and no-IVH group are summarized in Table 2. Pregnancy-induced hypertension, antenatally detected intrauterine growth restriction, and antenatal steroids were significantly associated with a lower incidence of IVH. Caesarean delivery (with or without labor) is associated with lower incidence of IVH. Outborn infants (delivery outside a tertiary perinatal center), male gender, and low Apgar scores were associated with a higher risk of III–IV IVH.

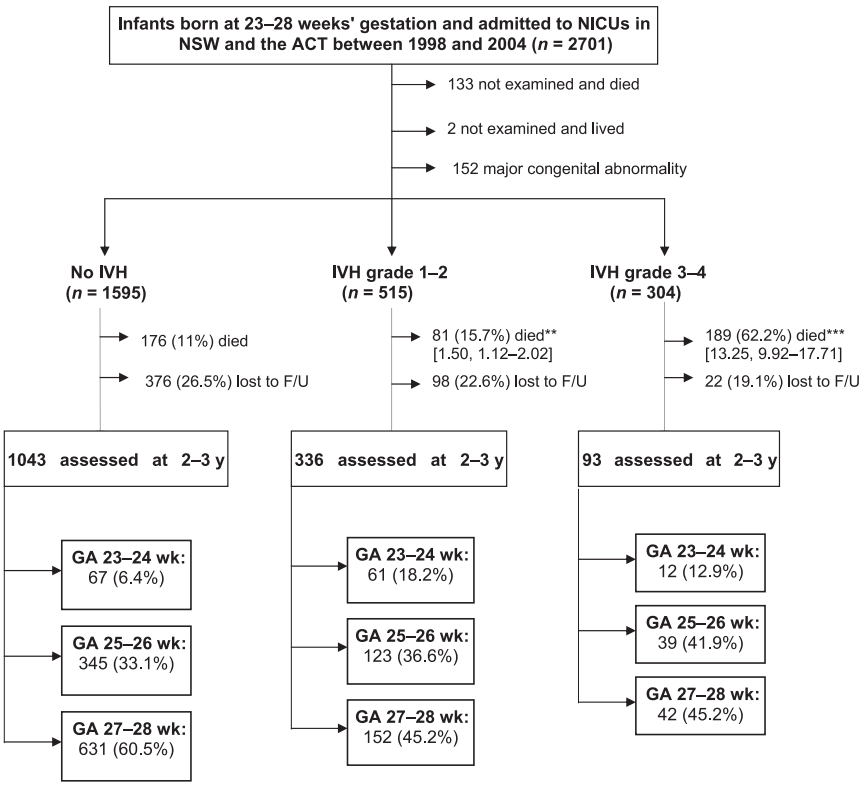

FIGURE 1
Profile of study group from admission to follow-up assessment. *$P < .05$, **$P < .01$, ***$P < .001$. F/U, follow-up.

Major morbidities including chronic lung disease, postnatal steroid therapy, patent ductus arteriosus, necrotizing enterocolitis, sepsis and severe retinopathy of prematurity (ROP) were significantly more common in infants with IVH of any grading. Pneumothorax was associated with higher incidence of Grade III–IV IVH. Compared with no-IVH infants (Table 2), significantly more IVH infants had abnormal 6-week ultrasound findings including PVL, porencephalic cyst, and hydrocephalus (ventricular dilatation >97th percentile). In particular, these cerebral abnormalities were found in 64 (69%) of the grade III–IV infants.

Neurodevelopmental Outcomes at 2 to 3 Years, Corrected for Prematurity

Higher rates of moderate-severe neurosensory impairment were seen with increasing grades of IVH, being 12.1% for no-IVH ($n = 1043$); 21.1% for Grade I ($n = 232$); 24% for grade II ($n = 104$); 41% for grade III ($n = 56$) and 46% for grade IV ($n = 37$). After exclusion of ultrasound abnormalities including PVL, porencephalic cyst, and ventricular enlargement, moderate-severe neurosensory impairment rates were 17.6% for isolated grade I ($n = 205$); 20.9% for isolated grade II IVH ($n = 91$); 36.8% for isolated IVH III ($n = 19$), and 40% for isolated IVH IV ($n = 10$). The comparable rates of impairment for grades I and II and for grades III and IV allow grouping into 2 IVH groups, grade I–II and III–IV, for subsequent analyses. Thus, infants with III–IV IVH had the highest rate (43.0%) of moderate-severe neurosensory impairment (Table 3). Infants with grade I–II IVH were twice as likely to have a moderate-severe neurosensory impairment (22.0%) compared with the no-IVH group (12.1%). Infants with grade I–II IVH had a significantly higher rate of cerebral palsy than the no-IVH group (10.4% v 6.5%. odds ratio

TABLE 1 Comparison of Infants Followed Up and Lost to Follow-Up

Characteristics	Followed Up (n = 1472)	Lost Follow-Up (n = 496)
Maternal age, y	30 (26–34)	27 (22–32)***
Aboriginal	38 (2.6%)	52 (10.5%)
Assisted conception	213 (14.4%)	34 (6.8%)
Multiple pregnancy	392 (26.6%)	114 (23%)
Pregnancy-induced hypertension	26 (17.7%)	50 (10.1%)***
Vaginal breech delivery	149 (10%)	41 (8.3%)
Caesarean delivery	473 (32.1%)	122 (24.6%)***
Outborn	105 (7.1%)	82 (16.5%)***
Gestational age, wk	27 (26–28)	27 (26–28)
Birth wt, g	945 (776–1110)	1024.5 (1185–1865.7)***
Birth wt <10th percentile	152 (10.3%)	26 (5.2%)***
Apgar <7 at 5 min	281 (19.2%)	86 (17.4%)
PDA treated	647 (43.9%)	190 (38.3%)*
NEC	110 (7.5%)	33 (6.7%)
CLD	596 (40.5%)	133 (26.8%)***
Postnatal steroid	408 (27.7%)	78 (11.7%)***
Home oxygen	306 (20.8%)	58 (11.7%)***
Systemic infection	595 (40.4%)	141 (28.4%)***
Any IVH	429 (29%)	120 (24%)*
IVH grade III or IV	93 (6.3%)	22 (4.4%)
IVH grade I or II	336 (22.8%)	98 (19.7%)
ROP grade ≥3	187 (12.7%)	36 (7.3%)***
Abnormal HUS at 6 wk	120 (8.2%)	21 (4.2%)**

Data are presented as median (interquartile range) or n (%). CLD, chronic lung disease defined as respiratory support at 36 weeks' corrected age; HUS, head ultrasound; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus. *P < .05; **P < .01; ***P < .001.

[OR] 1.72, 95% confidence interval (CI) 1.11–2.67). Both IVH groups had higher incidence of hearing loss in comparison with no-IVH group.

After controlling for confounding factors by multivariate analysis (Table 4), the adjusted OR for moderate-severe impairment for infants with I–II IVH was 1.61 (95% CI 1.14–2.28) compared with no IVH, and for III–IV IVH, it was 3.81 (95% CI 2.30–6.30). Small for gestational age, male gender, PVL, chronic lung disease, and ROP independently predicted significant adverse outcomes. In view of the high incidence of hearing loss in grade I–II IVH, multivariate analysis was repeated with the exclusion of infants with isolated hearing loss. Grade I–II IVH remained an independent risk factor for moderate-severe neurosensory impairment (adjusted OR 1.45, 95% CI 1.003–2.112, P = .048).

Of the 336 grade I–II IVH, 40 had other ultrasound abnormalities including PVL, porencephalic cyst, or late ventricular dilatation detected at 6-week ultrasound. Table 5 shows the neurodevelopmental outcome of 296 "isolated grade I–II IVH" stratified by gestation. Moderate to severe neurosensory impairment was significantly higher in I–II "isolated IVH" compared with no IVH in both 23 to 25 weeks' gestation (24.3% vs 18%) and 26 to 28 weeks' gestation groups (15.5% vs 10%), representing a consistent 5% impairment rate difference between no-IVH and isolated IVH grade I–II infants (Table 5). After multiple logistic regression analysis controlled for male gender, small for gestational age, chronic lung disease, and ROP, variables that were found independently significant from Table 4, moderate to severe impairment was still significantly increased for isolated I–II IVH.

DISCUSSION

Our regional study of a recent and large sample of 1472 very premature survivors revealed that presence of IVH, even for grade I–II, was associated with poor neurodevelopmental outcomes. Moderate-severe neurosensory impairment was significantly higher in the I–II IVH group than the no-IVH group (22% vs 12%). After excluding other ultrasound abnormalities including PVL, porencephaly, and ventricular enlargement, it was 19% and 12%, respectively, representing a 7% impairment rate difference between no-IVH and isolated IVH I–II infants. After adjusting for confounding perinatal variables, isolated grade I–II IVH remains a significant independent risk factor associated with poor outcomes (adjusted OR 1.73, 95% CI 1.22–2.46). It is noteworthy that a 5% increase in the neurosensory impairment rate persisted even when the infants were stratified by gestational age, indicating that the presence of isolated grade I–II IVH can be associated with poor outcomes. There was a relatively high incidence of hearing loss in grade I–II IVH, which could have contributed to the adverse neurosensory outcomes. However, even after excluding infants with isolated hearing loss, grade I–II IVH remained a risk factor for increased neurosensory adverse outcomes.

Our findings add to the growing number of studies from different populations reporting similar concerns with isolated low grades of IVH.[12–15] The EPIPAGE study from France involving 942 preterm infants of <32 weeks' gestation born in 1997 found that isolated grade I–II IVH occurred in 16% of infants and was associated with a 5.5% risk of cerebral palsy at 2 years' corrected age.[13] When other ultrasound abnormalities were included, the rates of CP increased to 8.1% for grade I IVH and 12.2% for grade II IVH. Patra and colleagues from United States, in an institutional study of extremely low birth weight infants born from 1992 to 2000, reported that the 104 infants with isolated grade I–II IVH had a significantly lower mean mental developmental index (MDI) score than the 258 infants with a normal cranial ultrasound (mean 74 vs 79). They had significantly higher rates of low MDI <70 (45% vs 25%; OR 2.00), major neurologic abnormality (13% vs 5%; OR 2.60), and

TABLE 2 Perinatal Characteristics and Morbidities Among 1472 Infants

Characteristics	No IVH (n = 1043), 71%	All IVH (n = 429), 29%	IVH I–II (n = 336), 23%	Isolated IVH I–II[a] (n = 296), 20%	IVH III–IV (n = 93), 6%
Maternal					
Maternal age, y	31(26–35)	30 (23–34)	30 (25–34)	30 (25–34)	30 (23–34)
Aboriginal ethnicity	41 (3.9)	13 (3.0)	11 (3.3)	7 (2.4)	2 (2.1)
Assisted conception	152 (14.6)	65 (15.1)	49 (14.6)	44 (14.8)	16 (17.2)
Pregnancy-induced hypertension	214 (20.5)	47 (10.9)***	41 (12.2)***	37 (12.5)***	6 (6.5)***
ROM >24 h	255 (24.4)	118 (27.5)	94 (28.0)	86 (29)	24 (25.8)
APH	300 (28.8)	139 (32.4)	106 (31.5)	97 (32.7)	33 (35.5)
IUGR	103 (9.9)	23 (5.3)**	17 (5.1)**	13 (4.4)**	6 (6.5)
Multiple pregnancy	288 (27.6)	104 (24.2)	81 (24.1)	71 (23.9)	23 (24.7)
Antenatal steroids	945 (90.4)	377 (87.8)	301 (89.5)	270 (91.2)	76 (81.7)*
Delivery					
Fetal distress	191 (18.3)	76 (17.7)	57 (17.0)	51 (17.2)	19 (20.4)
Breech delivery	90 (8.6)	59 (13.7)**	46 (13.7)**	42 (14.2)**	13 (14.0)
Caesarean section	643 (61.6)	169 (39.3)***	130 (38.6)***	115 (38.8)***	39 (41.9)***
Outborn	68 (6.5)	40 (9.3)	25 (7.4)	22 (7.4)	15 (16.1)***
Apgar <7 at 5 min	181 (17.3)	100 (23.3)*	70 (20.8)	62 (20.9)	30 (32.2)***
Neonatal					
GA, wk	27(2)	26 (2)	26 (2)	26 (2)	26 (2)
Birth wt, g	956 (329)	915 (342)*	895 (349)*	889 (344)*	960 (348)
Birth wt <10th percentile	121 (11.6)	31 (7.2)*	25 (7.4)*	20 (6.7)*	6 (6.5)
HC <10th percentile	85 (8.1)	33 (7.7)	28 (8.3)	26 (8.7)	5 (5.4)
Male gender	532 (51.0)	254 (59.2)**	195 (58.0)*	175 (59.1)*	59 (63.4)*
Surfactant	722 (69.2)	328 (76.4)**	245 (72.9)	218 (73.6)	83 (89.2)***
CLD	377 (36.1)	219 (51)***	164 (48.8)***	146 (49.3)***	55 (59.1)***
Postnatal steroids	256 (24.5)	151 (35)***	111 (33.0)**	97 (32.7)**	40 (43.0)***
Home oxygen	199 (19.1)	107 (24.9)*	84 (25.0)*	73 (24.6)*	23 (24.7)
PDA treated	427 (40.9)	220 (51.3)***	170 (50.6)**	167 (56.4)**	50 (53.8)*
NEC	62 (5.9)	48 (11.2)***	34 (10.1)**	25 (8.4)	14 (16.1)**
ROP grade ≥3[b]	110/103 (10.7)	77/425 (18.1)***	56/332 (16.7)**	48 (16.2)**	21/93 (22.6)**
Systemic infection	383(36.7)	212 (49.4)***	159 (47.3)***	139 (46.9)***	53 (57.0)***
PVL	9/999 (0.9)	24/425 (5.6)***	14/332 (4.2)***	0/296	10/93 (10.7)***
Porencephalic or other cysts	5/999 (0.5)	23/425 (5.4)***	8/332 (2.4)**	0/296	15/93 (16.1)***
Ventricle size >97th	8/999 (0.8)	68/425 (16)***	18/332 (5.4)***	0/296	50/93 (53.8)***

Data are presented as median (interquartile range) or n (%). No-IVH group acted as the control group for all comparisons. APH, antepartum hemorrhage; CLD, chronic lung disease; IUGR, antenatal diagnosis of intrauterine growth restriction; IUGR, intrauterine growth restriction; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus. *P < .05; **P < .01; ***P < .001.

[a] Isolated grade I–II IVH, defined as grade I–II IVH without PVL, porencephaly, and ventricular enlargement >97th percentile.

[b] Denominator is number of infants examined.

neurodevelopmental impairment (47% vs 28%; OR 1.83) at 20 months' corrected age, even when adjusting for confounding factors.[14] Vavasseur and colleagues from Ireland demonstrated that infants with grade I–II IVH in the 24 to 26–week and the 27 to 29–week groups had significantly lower MDI and PDI scores. However, no significant difference in scores was noted in the 30 to 32 weeks' gestation subgroup.[15] Similarly, another recent institutional study from Austria by Klebermass-Schrehof and colleagues showed abnormal neurodevelopmental outcomes up to 5.5 years in preterm infants <32 weeks' gestation with grade I–II IVH.[16]

Despite these publications, there is generally less appreciation among clinicians of the neurodevelopmental impact resulting from lower grades of IVH. This is probably because of a high baseline of adverse outcomes noted in very premature infants even without IVH, and it requires a large sample size to appreciate a relatively small increase in impairment risks compared with no IVH. For example, in our 979 no-IVH infants without any ultrasound abnormalities, the baseline impairment rate was 11.6% and 18% in the 23 to 25 weeks' gestation high-risk subgroup. The NICHD Network showed that nearly 30% of the 1473 <1000-g infants cared for in 1996–1997 with normal cerebral ultrasounds had either CP or low MDI <70 at 2 years' corrected age.[17]

A number of studies reported IVH-related adverse outcomes extending into school age and beyond. In a study of preterm infants weighing <1000 g at birth, the Victorian Infant Collaboration Study Group reported at 8 years that no-IVH was associated with cerebral palsy rates of 6.7%, with no rise in association with grade I IVH (6.4%) but a marked elevation to 24% with grade II IVH.[18] A population-based national study from the Netherlands involving preterm infants with a gestational age of <32 weeks and/or a birth weight <1500 g reported that the risk of needing special

TABLE 3 Neurodevelopmental Outcomes of 1472 Infants at 2 to 3 Years' Corrected Age

Characteristic	No IVH (n = 1043)	All IVH (n = 429)	I–II IVH (n = 336)	Isolated I–II IVH (n = 296)	III–IV IVH (n = 93)
Moderate/severe neurosensory impairment	126 (12.1)	114 (26.6)*** [2.63, 1.96–3.53]	74 (22.0)*** [2.06, 1.48–2.86]	55 (18.6)** [1.66, 1.17–2.35]	40 (43.0)*** [5.49, 3.42–8.83]
CP	68 (6.5)	63 (15.1)*** [2.48, 1.71–3.61]	35 (10.4)* [1.72, 1.11–2.67]	22 (7.4)	28 (30.1)*** [5.99, 3.50–10.21]
MDI or GQ ≤2 SD	31/900 (3.4)	37/377 (9.8)*** [3.08, 1.83–5.19]	23/297 (7.8)** [2.37, 1.31–4.28]	15/263 (5.7) [1.69, 0.90–3.19]	14/80 (17.5)*** [6.00, 2.88–12.39]
Bilateral blindness	2 (0.2)	5 (1.2)* [6.14,1.06–45.77]	3 (0.9) [4.69, 0.64–40.16]	3 (1) [5.32, 0.88–32.04]	2 (2.2)* [11.44,1.14–114.92]
Bilateral hearing loss Isolated[a]	24 (2.3)	28 (6.5)*** [2.96, 1.64–5.36]	20 (6.0)** [2.69, 1.41–5.12]	16 (5.4)** [2.42, 1.27–4.63]	8 (8.6)** [4.0, 1.60–9.69]
	17 (1.6)	16 (3.7) [2.34, 1.17–4.67]	13 (3.9) [2.42, 1.16–5.05]	10 (3.4) [2.11, 0.96–4.66]	3 (3.2) [2.01, 0.58–6.99]

Data are presented as n (%) [OR, 95% CI]. CP, cerebral palsy; GQ, general quotient; MDI, mental developmental index. *$P < .05$; **$P < .01$; ***$P < .001$.

[a] Hearing loss without any other neurosensory deficit.

education for adolescents with grades I–II IVH increased twofold compared with those without IVH.[19] Lowe and colleagues in 1990 found that VLBW infants <1501 g with grades I–II IVH performed less well at 5 to 6 years of age than at 1 to 2 years of age because specific visual motor and tactile perceptual skills are difficult to assess at 1 to 2 years of age.[20]

The mechanism of brain injury in isolated grades I–II IVH during early gestation may result from impaired cortical development. The germinal matrix is a source of neuronal precursor cells at 10 to 20 weeks' gestation after which it is a source of glial precursor cells that are in the process of migration to cortical regions at about the time very low birth weight infants are born. These cells give rise to oligodendroglia, the absence of which may affect myelination, and astrocytic precursor cells, necessary for cortical development. It is suggested that when a small IVH occurs at a relatively early period of gestation, it may affect the neuronal migration and result in excessive brain injury.[2,21] Grades I–II IVH can also cause lesions in the head of the caudate nucleus as well as destroy cells that would otherwise migrate to the subcortical structures such as amygdala and the thalamus. Therefore, functions served by the subcortical areas may be negatively affected in low-grade IVH.[22] Indeed, an MRI study of 12 uncomplicated IVH infants, 7 grade I, 4 grade II, and 1 grade III, found that the cortical gray matter volume was reduced compared with the 11 no-IVH infants.[23] There are also several more determinants that may not be picked up by the ultrasound imaging. These include associated white matter injury, brainstem and hippocampal hypoxic injury, and cerebellar hemorrhage or ischemia.[24]

There are limitations to the study. This is a retrospective review, and grading of IVH and other ultrasound abnormalities were based on clinical information collected in the database and not under a prospective research protocol. It can be argued that a higher incidence of adverse outcomes in grade I–II IVH, even for some no-IVH infants, was probably due to white matter injury, which is not readily identified on ultrasound. The retrospective nature of the study would not allow us to determine the interobserver reliability and accuracy of ultrasound reporting. Second, studies of IVH grading reliabilities have generally showed good results for higher grades of IVH or the absence of IVH, but less so for grade I and II.[10,24–26] For example, the interobserver agreement in the Eunice Kennedy Shriver National Institute of Child Health and Development network report ranged from 48% to 68% for grade I–II IVH, which was not dissimilar to the previous data from 151 infants from our region[10] showing an overall κ of 70% to 77%. Considering the likely blurring of grades between lower IVH grades, we analyzed all 336 grade I and II infants as a group and found that low grades of IVH are also associated with increased risk of adverse outcomes.

Our neurodevelopmental follow-up rate was ~75%. However, those who were lost to follow-up in our region had fewer perinatal risk factors and less early neonatal morbidity compared with assessed infants. The ultrasound imaging in our NICUs is generally restricted to sagittal and coronal views through the anterior fontanel. It is not a standard practice among the NICUs to obtain mastoid views to improve the detection of any cerebellar or posterior fossa lesions. Paneth and colleagues found cerebellar lesions in 28% of preterm infants at autopsy. However, the importance of these lesions remains uncertain.[27] Finally, neurodevelopmental follow-up in our network is performed by a team including a developmental pediatrician, neonatologist, and/or psychologist certified to perform Griffiths and Bayley assessment. As a part of the case review,

TABLE 4 Multivariate Analysis to Determine Independent Factors Associated With Moderate-Severe Neurosensory Impairment

	β Coefficient (SE)	Adjusted OR (95% CI)	*P* Value
IVH			
I–II IVH	0.48 (0.176)	1.61 (1.14–2.28)	.006
III–IV IVH	1.339 (0.257)	3.81(2.30–6.30)	<.001
23–25 vs 26–28 weeks' gestation	0.448 (0.173)	1.56 (1.12–2.19)	.01
SGA			
SGA<10th percentile	0.665 (0.295)	1.94 (1.09–3.46)	.024
SGA<3rd percentile	0.685 (0.348)	1.98 (1.00–3.92)	.049
Male gender	0.592 (0.159)	1.81 (1.32–2.47)	<0.001
Out born	−0.037 (0.305)	0.96 (0.53–1.75)	.904
PVL	2.176 (0.41)	8.81 (3.92–19.78)	<.001
Chronic lung disease	0.587 (0.17)	1.79 (1.29–2.49)	<.001
Pregnancy-induced hypertension	0.203 (0.22)	1.22 (0.79–1.88)	.358
Proven systemic infection	0.190 (0.239)	1.20 (0.88–1.65)	.239
NEC	0.087 (0.261)	1.09 (0.65–1.82)	.738
ROP grade 3–4	0.758 (0.197)	2.13 (1.44–3.14)	<.001

NEC, necrotizing enterocolitis; SGA, small for gestational age.

TABLE 5 Moderate-Severe Neurosensory Impairment in Isolated Grade I–II IVH Group in Comparison With No-IVH Group After Exclusion of Other Ultrasound Abnormalities

Gestation	No-IVH	Isolated I–II IVH	Adjusted OR [95% CI]
23–25 wk	35/194 (18%)	25/103 (24.3%)	1.45 (0.81–2.60)
26–28 wk	79/785 (10%)	30/193 (15.5%)	1.64 (1.04–2.58)*
Total	114/979 (11.6%)	55/296 (18.6%)	1.73 (1.22–2.46)**

Excluded PVL, porencephalic cyst, or late ventricular dilatation detected at 6-week ultrasound. Logistic regression models adjusted for male gender, small for gestational age, chronic lung disease, and ROP as identified from Table 4.
*$P < .05$, **$P < .01$

they are, however, aware of the child's ultrasound findings and the NICU course from the hospital discharge summary. We acknowledge the theoretical possibility of bias, but given that standardized objective measurement tools are used for neurodevelopmental assessment of these infants, we postulate that any bias of the developmental evaluators that might have been attributed to the positive findings in our study is negligible.

CONCLUSIONS

We found that even lower grades of IVH can adversely influence long-term neurodevelopmental outcomes in extremely preterm infants. In light of these findings and similar reports from various other populations, we suggest a more cautious approach by clinicians in counseling these families and highlight the importance of regular long-term follow-up and screening for adverse neurodevelopmental outcomes in this population.

ACKNOWLEDGMENTS

We thank the directors, the NICUS members, and the audit officers of all tertiary units in supporting this collaborative study: NICUS, Dr JenniferBowen (Chairperson), Barbara Bajuk (Coordinator), Sara Sedgley (Research Officer); Centenary Hospital for Women and Children, Associate Professor Zsuzsoka Kecskés (Director), Dr Hazel Carlisle, Lyn Barnes; John Hunter Children's Hospital, Dr Paul Craven (Acting Director), Dr Chris Wake, Dr Rebecca Glover, Lynne Cruden, Alissa Argomand; Royal Prince Alfred Hospital, A/Prof Nick Evans (Director), Dr A/Prof David Osborn, Girvan Malcolm, Dr Ingrid Rieger, Shelley Reid; Liverpool Hospital, Dr Jacqueline Stack (Acting Director), Dr Ian Callander, Kathryn Medlin, Kate Marcin; Nepean Hospital, Dr Vijay Shingde (Acting Director), Dr Basiliki Lampropoulos, Mee Fong Chin; The Children's Hospital at Westmead, Professor Nadia Badawi (Director), Dr Alison Loughran-Fowlds, Caroline Karskens; Royal North Shore Hospital, Dr Mary Paradisis (Director), A/Prof Martin Kluckow, Claire Jacobs, Glynis Howard; Sydney Children's Hospital, Dr Andrew Numa (Director), Dr Gary Williams, Janelle Young; Westmead Hospital, Dr Mark Tracy (Director), Dr Melissa Luig, Jane Baird; and Royal Hospital for Women, A/Prof Kei Lui (Director), Dr Julee Oei, Dr Lee Sutton, Diane Cameron. We also thank the infants and their families and the nursing and midwifery, obstetric, and medical records staffs of the obstetric and children's hospitals in NSW and the ACT.

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(Continued from first page)

www.pediatrics.org/cgi/doi/10.1542/peds.2013-0372

doi:10.1542/peds.2013-0372

Accepted for publication Oct 1, 2013

Address correspondence to Srinivas Bolisetty, MD, FRACP, Division of Newborn Services, Royal Hospital for Women, Barker Street, Locked Bag 2000, Randwick, 2031 NSW, Australia. E-mail: Srinivas.Bolisetty@sesiahs.health.nsw.gov.au

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics 2014;133;55
DOI: 10.1542/peds.2013-0372 originally published online December 30, 2013;

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