Brain Injury and Altered Brain Growth in Preterm Infants: Predictors and Prognosis

WHAT'S KNOWN ON THIS SUBJECT: Term MRI can assist in identifying the nature and extent of brain injury in preterm infants. However, brain injury detected by MRI does not fully account for neurodevelopmental impairments, particularly cognitive and behavioral impairments, common in preterm survivors.

WHAT THIS STUDY ADDS: In addition to brain injury, an assessment of brain growth by using one-dimensional measurements on MRI is helpful for predicting neurodevelopment. Two different patterns of impaired brain growth are observed that relate independently to early cognitive development in preterm infants.

AUTHORS: Hiroyuki Kidokoro, MD,[a] Peter J. Anderson, PhD,[b,c,d] Lex W. Doyle, MD,[b,c,d,e] Lianne J. Woodward, PhD,[f] Jeffrey J. Neil, MD, PhD,[g] and Terrie E. Inder, MBChB, MD[f]

[a]Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan; [b]Murdoch Children's Institute, Royal Children's Hospital, Melbourne, Australia; Departments of [c]Pediatrics, and [d]Obstetrics and Gynecology and [e]Research Office, The Royal Women's Hospital, University of Melbourne, Melbourne, Australia; [f]Department of Pediatric Newborn Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and [g]Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts

abstract

BACKGROUND: To define the nature and frequency of brain injury and brain growth impairment in very preterm (VPT) infants by using MRI at term-equivalent age and to relate these findings to perinatal risk factors and 2-year neurodevelopmental outcomes.

METHODS: MRI scans at term-equivalent age from 3 VPT cohorts (n = 325) were reviewed. The severity of brain injury, including periventricular leukomalacia and intraventricular and cerebellar hemorrhage, was graded. Brain growth was assessed by using measures of biparietal width (BPW) and interhemispheric distance. Neurodevelopmental outcome at age 2 years was assessed across all cohorts (n = 297) by using the *Bayley Scales of Infant Development, Second Edition* (BSID-II) or *Bayley Scales of Infant and Toddler Development, Third Edition* (Bayley-III), and evaluation for cerebral palsy.

RESULTS: Of 325 infants, 107 (33%) had some grade of brain injury and 33 (10%) had severe injury. Severe brain injury was more common in infants with lower Apgar scores, necrotizing enterocolitis, inotropic support, and patent ductus arteriosus. Severe brain injury was associated with delayed cognitive and motor development and cerebral palsy. Decreased BPW was related to lower gestational age, inotropic support, patent ductus arteriosus, necrotizing enterocolitis, prolonged parenteral nutrition, and oxygen at 36 weeks and was associated with delayed cognitive development. In contrast, increased interhemispheric distance was related to male gender, dexamethasone use, and severe brain injury. It was also associated with reduced cognitive development, independent of BPW.

CONCLUSIONS: At term-equivalent age, VPT infants showed both brain injury and impaired brain growth on MRI. Severe brain injury and impaired brain growth patterns were independently associated with perinatal risk factors and delayed cognitive development. *Pediatrics* 2014;134:e444–e453

With progress in perinatal and neonatal care of the preterm infant, the incidence of cerebral palsy (CP) has been diminishing,[1,2] yet rates of cognitive and behavioral challenges remain stable and high with 50% to 60% of extremely preterm infants displaying disability in these domains.[3–5] The neuropathology underlying these cognitive and behavioral challenges remains unclear, and it is difficult to predict them on the basis of brain injury. For example, whereas the 2 most common forms of brain injury described for preterm infants, periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH), are associated with adverse cognitive and motor outcomes, particularly CP, their presence does not fully account for all adverse neurodevelopmental outcomes. MRI can identify more subtle forms of injury, such as punctate or diffuse white matter injury, which are difficult to detect by cranial ultrasound.[6,7] A growing body of research supports improved prediction of motor[8] and cognitive outcomes by using MRI methods.[9,10] However, most studies linking neonatal MRI findings with outcome have been based on scoring systems that combine measures of both brain injury and growth, making it difficult to assess their relative contributions to later risk.

Volumetric MRI studies provide support for the importance of neonatal brain growth, in addition to injury, in predicting longer-term outcomes for children born very preterm (VPT).[11–13] However, volumetric approaches require complex methodologies that are not readily adaptable to clinical practice. Therefore, an alternative, simpler biometric approach has been proposed to evaluate early brain growth in preterm infants.[14,15] These brain metrics, applied at term-equivalent postmenstrual age (TEA), correlate reasonably with three-dimensional volumetric measures[14] and are readily used in a clinical setting. We applied these brain metrics along with a new grading system to assess brain injury on conventional MRI to char-acterize the patterns of brain injury and impaired brain growth in VPT infants at TEA. We evaluated the relationships of injury and growth impairment to perinatal risk factors and subsequent neurodevelopmental outcome.

METHODS

Subjects

Data from 448 preterm infants from 3 geographically different cohorts were collected by using similar study designs initiated by 1 investigator (T.E.I.). Infants ≤32 weeks' gestation were recruited between 1998 and 2000 at Christchurch Women's Hospital in Christchurch, New Zealand (n = 110); infants <30 weeks' gestation or <1250 g at birth were recruited between 2001 and 2003 at the Royal Women' Hospital in Melbourne, Australia (n = 227); and infants <30 weeks' gestation were recruited between 2007 and 2010 at St Louis Children's Hospital in St Louis, Missouri (n = 121). For the current study, 325 survivors (73%) satisfied the inclusion criteria of being born at <30 weeks' gestation, having an MRI scan at TEA (≥37 to ≤42 weeks' postmenstrual age), and having neither congenital nor chromosomal abnormalities. All study protocols were approved by each site's human research and ethics committee, and written informed consent was obtained from all parents.

MRI Acquisition

MRI data for the New Zealand and Australian cohorts were obtained by using 1.5-T Sigma LX Echospeed systems (GE Healthcare, Milwaukee, WI) with previously documented sequences.[16] In the St Louis cohort, magnetic resonance images were acquired by using a 3-T TIM Trio system (Siemens, Erlangen, Germany). MRI scanning in St Louis included anatomic images obtained with an axial magnetization–prepared rapid gradient echo T1-weighted sequence (TR/TE 1500/3 milliseconds; voxel size: $1 \times 0.7 \times 1$ mm^3) and a turbo spin echo T2-weighted sequence (TR/TE 8600/160 milliseconds; voxel size: $1 \times 1 \times 1$ mm^3; echo train length: 17). All of the images were obtained without sedation.

MRI Analysis

Injury Classification

Brain injury was diagnosed on the basis of the qualitative assessment of MRI at TEA by a single operator (H.K.) blinded to clinical data. A new system for the grading of PVL and cerebellar hemorrhage (CBH) was developed, and the IVH classification was based on that of Papile et al[17] (Fig 1).

PVL

Grades 1 and 2 PVL were defined by the presence of punctate lesions ≤3 mm in individual size in periventricular white matter on either or both of the T1/T2-weighted images. Grade 2 PVL was distinguished from grade 1 by the presence of lesions in bilateral corticospinal tracts or, more extensively, with ≥3 lesions per hemisphere. Grade 3 PVL was defined as the presence of extensive lesions along the wall of lateral ventricles with high signal on T1-weighted images. Grade 4 PVL was defined as the presence of cystic lesions in periventricular white matter.

IVH

Grade 1 IVH was defined as the presence of hemosiderin deposits or post hemorrhagic cysts within the thalamo-caudal notches. Grade 2 IVH was defined as the presence of hemosiderin deposits outside the region of the thalamo-caudal notches along the ventricular wall without ventricular dilatation. Grade 3 IVH was defined as ventricular dilatation >97th percentile with evidence of previous ventricular hemorrhage. Grade 4 IVH was defined as the presence of parenchymal hemorrhagic lesions or post-hemorrhagic cystic encephalomalacia.

CBH

Grade 1 CBH consisted of unilateral punctate lesions ≤3 mm in size; grade 2
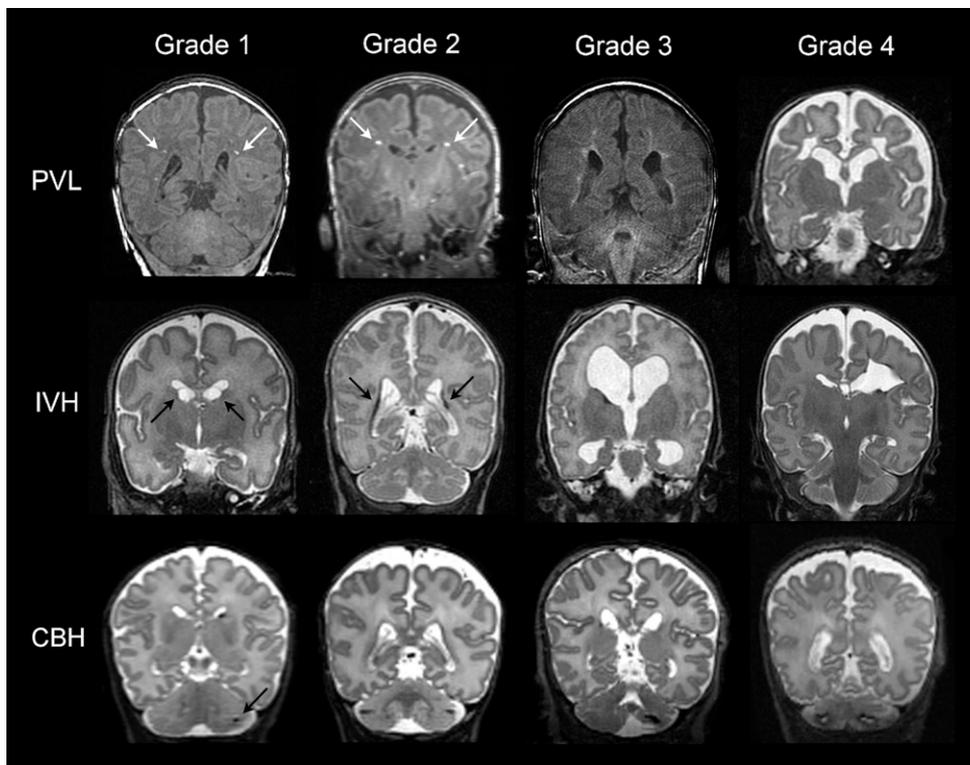
FIGURE 1
Classification of brain injury. Representative T1- and T2-weighted magnetic resonance images of each grade of PVL (upper panel), IVH (middle panel), and CBH (lower panel). Note the areas of high signal intensity on T1-weighted images in subjects with grades 1 to 3 PVL. Note also that both IVH and CBH appear dark on T2-weighted images, as shown in the middle and lower panels.

consisted of bilateral punctate lesions; grade 3 consisted of a unilateral lesion >3 mm in size; and grade 4 was present when extensive lesions were observed bilaterally.

When infants had 2 different grades of the same category of injury, they were assigned the higher grade. High-grade injury (ie, grades 3 and 4) in any category was classified as severe brain injury.

Brain Growth

Brain growth was evaluated by using 2 measures assessed by a single operator (H.K.): biparietal width (BPW) and interhemispheric distance (IHD). These measures were taken from coronal images by using a DICOM browser (Syngo fastView; Siemens) with the bilateral cochlea and basilar truncus as standard landmarks (Fig 2). BPW was defined as the maximal horizontal brain width of frontal lobes. IHD was defined as the horizontal distance between the tops of the crowns of the superior frontal gyri.

By using these measures, 2 patterns of impaired brain growth were identified. The first, the small BPW brain pattern, was defined as a BPW z score of less than −0.5 among the VPT infants in each cohort (equivalent to less than −1 SD below the mean of MRI-determined total brain volume in healthy term-born infants).[18] The second, the increased IHD brain pattern, was defined by an IHD ≥4.0 mm (>2 SDs above the mean of healthy term infants).[19] BPW z score was calculated from a linear regression model, adjusted for postmenstrual age at MRI scan and gender. Interobserver reliabilities (intraclass correlation coefficients) from 30 scans read by 2 different observers (H.K. and T.E.I.) were >0.90 for injury assessment and >0.98 for growth measurements. Intraobserver reliabilities calculated from 30 scans measured a month apart by 1 author (H.K.) were >0.90 for injury assessment and >0.96 for growth measurements.

Clinical Risk Factors

Clinical variables were collected from maternal and infant hospital records, including gestational age, small for gestational age (birth weight of less than −2 SDs for gestational age), gender, multiple birth, any course of antenatal corticosteroids, chorioamnionitis (identified by using clinical criteria consisting of maternal fever and/or elevated inflammatory markers on laboratory testing), mode of delivery, 5-minute Apgar score, inotropic agents (used according to clinical needs for maintaining systemic blood pressure), confirmed postnatal sepsis (defined as culture-positive sepsis), necrotizing enterocolitis (defined according to Bell's criteria[20] of stage II or greater), and treated patent ductus arteriosus (PDA; including pharmacologic and/or surgical treatment). Considering presumed timing of insult, additional variables were collected for impaired growth: days of parenteral
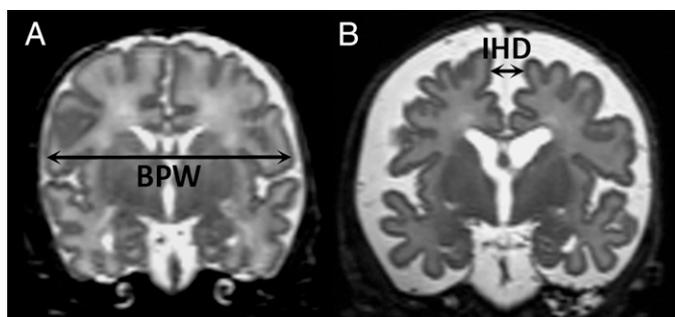
FIGURE 2
Growth measurements using brain metrics. BPW (A) and IHD (B) shown on coronal T2-weighted images. These measurements were made at the level of the third ventricle, cochlea, and basilar artery. Note the representative samples of the small BPW (A) and increased IHD (B) patterns.

nutrition, need for oxygen at 36 weeks' postmenstrual age, and dexamethasone use. Apart from risk factors, head circumference z score (controlled for postmenstrual age at MRI scan and gender) at TEA was calculated.

Neurodevelopmental Outcome

In the Christchurch and Melbourne cohorts, neurodevelopmental outcome at 2 years' corrected age was assessed by using the *Bayley Scales of Infant Development, Second Edition* (BSID-II).[21] The Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI) were used for this analysis. Each scale has a normative mean (SD) of 100 (15). The St Louis cohort is more recent, and the *Bayley Scales of Infant and Toddler Development, Third Edition* (Bayley-III), was used to assess neurodevelopment at 2 years.[22] Given the significant differences between the BSID-II and Bayley-III scales[23] and concerns with the Bayley-III underestimating developmental delay,[24] the neurodevelopmental outcomes were analyzed separately. Children who were too severely impaired to be assessed with the Bayley scales were assigned values of 40.

Children also underwent a standardized neurologic evaluation to assess the quality of their motor skills, coordination, gait, and behavior. CP was diagnosed by using standard criteria, including the location of the impairment or body part affected and abnormal muscle tone and reflexes; severity was based on the Gross Motor Function Classification System.[25]

Statistical Analyses

Data were analyzed with SPSS version 17.0 software (IBM SPSS Statistics, IBM Corporation, Armonk, NY). Analysis of variance with Bonferroni post hoc tests or t tests was used when continuous variables were compared between 2 groups. χ^2 Tests were used with categorical variables, and odds ratios and 95% confidence intervals were calculated for the association between clinical risk factors and patterns of MRI abnormality. Logistic regression models were used to examine associations between clinical risk factors and patterns of MRI abnormality after adjustment for center. Finally, forced-entry linear regression models were used to examine the association between the 2 brain growth measures and neurodevelopmental scores after adjusting for the clinical risk factors listed in Table 5, maternal education and center. Two-sided P values <.05 were used to assess statistical significance.

RESULTS

Subjects

The demographic characteristics of the 325 infants from the 3 cohorts are shown in Table 1. The St Louis cohort had a greater number of infants born small for gestational age, lower rates of an-

tenatal corticosteroid use and postnatal sepsis, higher rates of chorioamnionitis, lower mean Apgar scores, and a higher incidence of prolonged parenteral nutrition. The Melbourne cohort had more multiple births. Of 244 infants from the Melbourne and Christchurch cohorts, 3 died and 9 were lost to follow-up by age 2 years. Thus, the remaining 232 infants had neurodevelopmental evaluation at age 2 years. Of 81 infants from the St Louis cohort, 65 had neurodevelopmental evaluation at age 2 years.

Patterns of Brain Injury: Prevalence, Risks, and Outcomes

Of 325 infants from the 3 cohorts, 107 (33%) showed some form of brain injury. PVL was diagnosed in 40 infants (12%; grade 1, $n = 16$; grade 2, $n = 12$; grade 3, $n = 6$; grade 4, $n = 6$), IVH in 62 infants (19%; grade 1, $n = 17$; grade 2, $n = 31$; grade 3, $n = 2$; grade 4, $n = 12$), and CBH in 31 infants (10%; grade 1, $n = 17$; grade 2, $n = 7$; grade 3, $n = 3$; grade 4, $n = 4$). Of 107 infants with brain injury, 24 had >1 form of injury, although no infant had >1 pattern of severe (grade ≥3) injury. Severe injuries of any type were observed in 33 infants (10%). Rates of severe PVL and IVH injury were similar across cohorts, whereas CBH was more common in the St Louis cohort (Table 1).

The risk factors for high-grade PVL or IVH are shown in Table 2. Because of the small number of infants with high-grade CBH ($n = 7$), the risk factors for any grade of CBH were investigated. Necrotizing enterocolitis was a strong risk factor for high-grade PVL, whereas lower gestational age decreased the risk of high-grade PVL. High-grade IVH occurred in the infants with lower Apgar scores. Lower gestational age, inotropic use, and treated PDA increased the risk of any grade of CBH.

The neurodevelopmental consequences of each form and grade of brain injury are shown in Tables 3 and 4. The results of these analyses are presented

TABLE 1 Demographic Characteristics of VPT Infants

Characteristics	All (N = 325)	Christchurch (n = 60)	Melbourne (n = 184)	St Louis (n = 81)	P
Gestational age at birth, mean (SD), wk	27.5 (2.0)	27.0 (1.8)	26.9 (1.5)	26.5 (1.7)	.11
Birth weight, mean (SD), g	959 (237)	987 (266)	966 (227)	922 (238)	.23
Male, n (%)	152 (47)	27 (45)	87 (47)	38 (47)	.95
SGA, n (%)	24 (7)	4 (7)	8 (4)	12 (15)	.011
Multiple birth, n (%)	130 (40)	19 (32)	85 (46)	26 (32)	.038
Antenatal corticosteroids, n (%)	280 (86)	49 (82)	169 (92)	62 (77)	.002
Chorioamnionitis, n (%)	72 (22)	11 (19)	27 (15)	34 (43)	<.001
Cesarean delivery, n (%)	229 (71)	42 (70)	132 (72)	55 (68)	.82
Five-minute Apgar score of <7, n (%)	69 (21)	14 (23)	17 (9)	38 (47)	<.001
Inotropic support, n (%)	127 (39)	26 (44)	75 (41)	26 (32)	.29
Treated PDA, n (%)	137 (42)	31 (52)	70 (38)	36 (44)	.16
Postnatal sepsis, n (%)	122 (38)	22 (37)	81 (44)	19 (24)	.006
Parenteral nutrition ≥14 days, n (%)	121 (37)	13 (22)	58 (32)	50 (62)	<.001
Postnatal dexamethasone, n (%)	30 (9)	8 (13)	14 (8)	8 (10)	.40
Oxygen at 36 weeks, n (%)	117 (36)	25 (42)	62 (34)	30 (37)	.52
Necrotizing enterocolitis, n (%)	18 (6)	4 (7)	8 (4)	6 (7)	.55
Gestational age at scan, mean (SD), wk	39.6 (1.4)	39.6 (1.0)	40.1 (1.1)	38.4 (1.4)	<.001
High-grade PVL, n (%)	12 (3.7)	2 (3.3)	7 (3.8)	3 (3.7)	.99
High-grade IVH, n (%)	14 (4.3)	2 (3.3)	8 (4.3)	4 (6.7)	.90
High-grade CBH, n (%)	7 (2.2)	1 (1.7)	0	6 (7.4)	.001
Small BPW, n (%)	101 (31)	16 (27)	55 (30)	30 (37)	.37
Increased IHD, n (%)	106 (33)	18 (30)	60 (33)	28 (35)	.85
Maternal education[a]					<.001
Less than high school	51 (16)	21 (35)	28 (15)	2 (3)	
High school graduate	153 (48)	30 (50)	94 (51)	29 (38)	
College/university graduate	116 (36)	9 (15)	62 (34)	45 (59)	
Two-year outcomes, n	297	56	176	65	
MDI or cognition/language score,[b] mean (SD)	85.3 (19.0)	87.1 (16.4)	84.8 (19.7)	85.9 (9.2)/89.7 (10.4)	ND
PDI or motor score,[c] mean (SD)	88.0 (17.5)	88.3 (16.5)	87.9 (17.9)	84.1 (10.4)	ND
CP, n (%)	33 (11)	9 (15)	15 (8)	9 (14)	.18

ND, not done; SGA, small for gestational age.

[a] Data were missing for 5 infants in St Louis.

[b] MDI in the Christchurch and Melbourne cohorts; cognition/language in the St Louis cohort.

[c] PDI in the Christchurch and Melbourne cohorts; motor in the St Louis cohort.

separately for Australasian and St Louis children given the different versions of the Bayley scales used. In the Christchurch and Melbourne cohorts, infants with high-grade PVL or IVH had lower MDI and PDI scores and a higher in-cidence of CP. In contrast, infants with low grades of brain injury had similar neurodevelopmental outcomes at age 2 years to those without brain injury, except for grade 2 PVL, which was associated with an increased risk of CP. In the St Louis cohort, infants with high-grade PVL or IVH displayed a similar trend. CBH was not related to any neurodevelopmental outcome.

Patterns of Impaired Brain Growth: Prevalence, Risks, and Outcomes

The 2 patterns of impaired brain growth, small BPW and increased IHD, were observed in 101 (31%) and 106 (34%) infants, respectively. Twenty-two infants (7%) showed both patterns of impaired growth. Rates for each of these patterns were similar across cohorts (Table 1). Head circumference

TABLE 2 Clinical Risk Factors for Brain Injuries

Characteristics	Grade 3 or 4 PVL (n = 12)		Grade 3 or 4 IVH (n = 14)		Any Grade CBH (n = 31)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Gestational age <27 weeks	0.13 (0.016–0.98)	.048	1.1 (0.37–3.2)	.88	3.2 (1.4–7.2)	.005
SGA	1.2 (0.14–9.7)	.89	NA	NA	2.5 (0.85–7.4)	.094
Male gender	0.37 (0.097–1.4)	.14	1.5 (0.52–4.5)	.43	1.7 (0.79–3.7)	.18
Multiple birth[a]	0.73 (0.21–2.5)	.61	2.1 (0.70–6.2)	.19	0.55 (0.23–1.3)	.17
Antenatal corticosteroids	NA	NA	0.36 (0.10–1.3)	.11	0.70 (0.27–1.9)	.48
Chorioamnionitis[a]	0.67 (0.14–3.3)	.62	0.51 (0.11–2.5)	.41	1.0 (0.43–2.4)	.97
Cesarean delivery	0.83 (0.24–2.8)	.77	1.1 (0.32–3.5)	.93	1.1 (0.47–2.6)	.82
Five-minute Apgar score of <7	0.29 (0.034–2.5)	.26	5.3 (1.6–17.8)	.008	2.1 (0.89–4.9)	.093
Inotropic support[a]	0.77 (0.23–2.6)	.67	0.87 (0.28–2.7)	.81	8.0 (3.2–20.2)	<.001
Treated PDA	0.26 (0.056–1.2)	.089	0.76 (0.25–2.3)	.64	2.9 (1.3–6.5)	.009
Postnatal sepsis	0.81 (0.24–2.8)	.74	0.44 (0.12–1.6)	.22	1.3 (0.56–2.9)	.55
Necrotizing enterocolitis	6.8 (1.6–28.0)	.008	NA	NA	2.8 (0.79–10.0)	.11

Data were adjusted for center. CI, confidence interval; NA, not assessed (all infants with grade 3 or 4 PVL received antenatal corticosteroids, and all infants with grade 3 or 4 IVH were not SGA and did not have necrotizing enterocolitis); OR, odds ratio; SGA, small for gestational age.

[a] Data were missing on multiple births for 1 infant, on chorioamnionitis for 2 infants, and on inotropic support for 1 infant.

TABLE 3 Outcomes in Infants With Different Types and Grades of Brain Injuries in the Christchurch and Melbourne Cohorts

Pattern and Grade	n	Mean (SD) MDI Score	MDI <70, n (%)	Mean (SD) PDI Score	PDI <70, n (%)	CP, n (%)
PVL						
Grade 4	3	40.0 (0)***	3 (100)**	40.0 (0)***	3 (100)**	3 (100)**
Grade 3	5	61.2 (20.4)**	3 (60)*	55.6 (29.4)	4 (80)***	4 (80)***
Grade 2	7	89.1 (13.8)	0	91.3 (9.4)	0	2 (29)*
Grade 1	9	82.8 (21.7)	2 (22)	82.3 (17.9)	1 (11)	1 (11)
IVH						
Grade 4	9	72.2 (26.3)*	4 (44)	68.4 (18.3)***	4 (44)*	3 (33)***
Grade 3	1	68	1 (100)	84	0	0
Grade 2	15	86.5 (15.7)	1 (7)	89.8 (10.8)	0	1 (7)
Grade 1	11	95.0 (14.2)	0	95.0 (10.9)	0	1 (9)
CBH						
Grade 4	1	84	0	84	0	0
Grade 3	0	—	—	—	—	—
Grade 2	1	88	0	103	0	0
Grade 1	10	85.8 (15.4)	2 (20)	94.0 (10.9)	1 (10)	1 (10)
No injury	168	87.2 (17.7)	21 (13)	90.0 (15.5)	16 (10)	10 (6)

$n = 232$. *$P < .05$, **$P < .01$, ***$P < .001$ versus no injury (by t test or χ^2 test). Eight infants had >1 form of injury among lower grade injuries. Those infants were counted twice.

TABLE 4 Outcomes in Infants With Different Type and Grade of Brain Injuries in the St Louis Cohort

Pattern and Grade	n	Cognition	Language	Motor	Cognition <80, n (%)	Language <80, n (%)	Motor <70, n (%)	CP, n (%)
PVL								
Grade 4	1	75	91	79	1 (100)	0	0	1 (100)
Grade 3	1	75	86	64	1 (100)	0	1 (100)	1 (100)
Grade 2	3	78.3 (5.8)	85.0 (3.5)	85.0 (6.0)	2 (67)	0	0	0
Grade 1	4	81.3 (12.5)	81.0 (11.9)	75.3 (8.6)	2 (50)	2 (50)	1 (25)	1 (25)
IVH								
Grade 4	2	80.0 (14.1)	86.5 (10.6)	68.5 (14.8)	1 (50)	1 (50)	1 (50)	2 (100)
Grade 3	1	75	89	67	1 (100)	0	1 (100)	1 (100)
Grade 2	10	92.5 (8.6)	92.8 (13.6)	86.0 (8.5)	1 (10)	1 (10)	0	1 (10)
Grade 1	4	78.8 (7.5)	87.3 (8.5)	79.8 (16.3)	3 (75)	0	1 (25)	1 (25)
CBH								
Grade 4	3	90.0 (5.0)	91.7 (10.3)	82 (5.2)	0	0	0	1 (33)
Grade 3	2	82.5 (10.6)	93.0 (14.1)	86.5 (14.8)	1 (50)	0	0	0
Grade 2	6	90.8 (15.3)	89.8 (20.8)	87.2 (14.6)	1 (17)	3 (50)	1 (17)	0
Grade 1	4	86.3 (4.8)	87.3 (5.3)	82.0 (4.2)	1 (25)	0	0	1 (25)
No injury	34	86.1 (7.8)	88.7 (8.7)	86.3 (8.5)	10 (29)	9 (27)	4 (12)	1 (3)

$n = 65$. Data are presented as mean (SD) for Cognition, Language and Motor categories.

z score at TEA was smaller in infants with a small BPW than in those without (mean difference: -0.57; $P = .003$), whereas it was not different between infants with and without an increased IHD (mean difference: 0.18; $P = .35$).

Associations between a range of clinical risk factors and each brain growth pattern are shown in Table 5. The small BPW brain pattern was associated with lower gestational age, inotropic support, treated PDA, necrotizing enterocolitis, oxygen at 36 weeks, and prolonged parenteral nutrition. In contrast, the increased IHD brain pattern was associated with male gender, dexamethasone use, and high-grade brain injury.

Tables 6 and 7 describe the 2-year outcomes of infants with small BPW and/or increased IHD relative to the remainder of infants without these brain patterns. In the Christchurch and Melbourne cohorts, VPT infants with either the small BPW or increased IHD brain pattern had lower MDI but not PDI scores than did infants without these brain growth findings. Neither pattern was associated with CP. The most developmentally impaired infants were those with both small BPW and increased IHD on neonatal MRI, with these infants obtaining the lowest MDI and PDI scores at age 2 years. In contrast, no associations were found between neonatal brain growth and neurodevelopmental outcomes in the St Louis cohort.

Neonatal Brain Growth and Outcomes After Adjustment for Clinical and Social Risk

Table 8 summarizes the results of regression analyses examining associations between the 2 growth parameters (IHD and BPW) and children's MDI and PDI scores at age 2 years after adjustment for the effects of child gender, brain injury, maternal education, and

TABLE 5 Clinical Risk Factors for Small BPW or IHD Brain Patterns

Characteristics	Small BPW (n = 101)		Increased IHD (n = 106)	
	OR (95% CI)	P	OR (95% CI)	P
Gestational age <27 weeks	2.4 (1.5–3.9)	<.001	0.94 (0.59–1.5)	.81
SGA	2.2 (0.95–5.2)	.064	0.65 (0.25–1.7)	.37
Male gender	1.2 (0.73–1.9)	.51	2.0 (1.3–3.2)	.003
Multiple birth[a]	1.3 (0.78–2.0)	.35	0.83 (0.51–1.3)	.44
Antenatal corticosteroids	0.94 (0.47–1.9)	.85	0.61 (0.32–1.2)	.14
Chorioamnionitis[a]	1.3 (0.71–2.2)	.43	1.0 (0.57–1.8)	.97
Cesarean delivery	1.0 (0.60–1.7)	.99	0.84 (0.51–1.4)	.49
Five-minute Apgar score of <7	1.4 (0.74–2.5)	.33	0.92 (0.49–1.7)	.78
Inotropic support[a]	2.6 (1.6–4.3)	<.001	1.3 (0.82–2.1)	.26
Treated PDA	1.7 (1.0–2.7)	.039	0.91 (0.57–1.5)	.71
Postnatal sepsis[a]	1.6 (0.96–2.6)	.070	0.96 (0.59–1.6)	.86
Necrotizing enterocolitis	12.9 (3.6–45.9)	<.001	0.57 (0.18–1.8)	.34
Dexamethasone	1.3 (0.61–2.9)	.48	2.3 (1.1–4.9)	.034
Oxygen at 36 weeks	2.2 (1.3–3.6)	.002	1.1 (0.69–1.8)	.64
Parenteral nutrition ≥14 days	2.3 (1.4–3.8)	.001	1.2 (0.73–2.0)	.46
High-grade injury (grade 3 or 4)	1.4 (0.68–3.0)	.35	2.1 (1.0–4.4)	.048

Data were adjusted for center. CI, confidence interval; OR, odds ratio; SGA, small for gestational age.
[a] Data were missing on multiple births for 1 infant, on chorioamnionitis for 2 infants, on inotropic support for 1 infant, and on postnatal sepsis for 1 infant.

other clinical risk factors correlated with brain growth in Table 5. This analysis was confined to the Christchurch and Melbourne cohorts. As shown, a higher BPW z score and lower IHD were predictive of higher MDI (P = .002) and PDI (P = .003) scores independent of high-grade brain injury, clinical variables, and maternal education. Additionally, for infants without the increased IHD brain pattern, BPW z score prominently influenced outcome for MDI scores (P < .001), but influenced PDI scores less (P = .05) (Fig 3). On the other hand, IHD correlated negatively with MDI scores (P < .001), but not with PDI scores (P = .08), in univariate analysis (Fig 3). The multivariable analyses revealed that both BPW z score and IHD were predictors of MDI scores (P = .001 in BPW, P < .001 in IHD) (Table 8). In the St Louis cohort, both z scores of BPW and IHD were not predictors for cognitive, language, and motor scores.

DISCUSSION

This study assists in defining the nature and frequency of brain injury and impaired brain growth in VPT infants as detected by conventional MRI at TEA. The study also identifies risk factors and neurodevelopmental consequences of these imaging abnormalities.

Both brain injury and altered development were found in these cohorts. The data also confirmed that severe brain injury is relatively uncommon (10%) in VPT survivors but is related to neurodevelopmental impairments at age 2 years. Identified risk factors for high-grade PVL, IVH, or any grade of CBH are similar to those described in previous studies.[16,26–28] and are consistent with our pathophysiological understanding of these forms of injury in the preterm brain.[29] However, of importance, less severe injuries in any category, which were more frequently observed in our cohorts, also affect neurodevelopmental outcome, but to a lesser degree, at least to age 2 years.

Most VPT survivors (90%) did not have severe brain injury apparent on conventional MRI. However, they commonly showed 2 patterns of impaired brain growth, termed small BPW and increased IHD brain (31% and 34%, respectively). The small BPW brain pattern represents insufficient brain growth in absolute volume by TEA, whereas the increased IHD brain pattern reflects disproportionally impaired brain growth relative to skull growth, resulting in both hemispheres being surrounded by a large amount of extracerebral fluid.

TABLE 6 Outcomes in Infants With Small BPW and/or Increased IHD Brain Patterns in the Christchurch and Melbourne Cohorts

Infants and Brain Patterns	n	Mean (SD) MDI Score	MDI <70, n (%)	Mean (SD) PDI	PDI <70, n (%)	CP, n (%)
Overall infants	232					
Small BPW and increased IHD	15	72.8 (23.0)**	7 (47)*	72.7 (23.5)**	5 (33)	3 (20)
Small BPW only	54	81.8 (16.2)**	9 (17)	86.5 (14.8)	6 (11)	6 (11)
Increased IHD only	54	79.9 (22.6)**	17 (32)*	88.2 (19.2)	8 (15)	6 (11)
Remainder	109	91.6 (15.4)	7 (6)	90.7 (15.9)	10 (9)	8 (7)
Infants with high-grade injury	19					
Small BPW and increased IHD	1	40	1 (100)	40	1 (100)	1 (100)
Small BPW only	5	62.6 (19.3)	2 (40)	62.0 (21.0)	3 (60)	2 (40)
Increased IHD only	7	56.7 (24.0)	4 (57)	58.7 (25.8)	5 (71)	5 (71)
Remainder	6	79.7 (22.8)	2 (33)	70.2 (21.9)	2 (33)	2 (33)
Infants without high-grade injury	213					
Small BPW and increased IHD	14	74.1 (22.1)**	6 (43)*	75.1 (22.5)**	4 (29)	2 (14)
Small BPW only	49	83.7 (14.7)*	6 (12)	89.0 (11.7)	3 (6)	4 (8)
Increased IHD only	47	83.4 (20.5)*	12 (26)*	92.6 (13.7)	3 (6)	1 (2)
Remainder	103	92.3 (14.7)	5 (5)	91.9 (14.8)	8 (8)	6 (6)

n = 232. *P < .05, **P < .01 versus the remainder group in each row by Bonferroni post hoc tests.

TABLE 7 Outcomes in Infants With Small BPW and/or Increased IHD Brain Patterns in the St Louis Cohort

Infants and Brain Patterns	n	Cognition	Language	Motor	Cognition <80, n (%)	Language <80, n (%)	Motor <70, n (%)	CP, n (%)
Overall infants	65							
Small BPW and increased IHD	6	81.7 (9.3)	85.2 (7.4)	73.5 (11.9)	3 (50)	2 (33)	3 (50)	4 (67)
Small BPW only	19	86.1 (8.9)	90.4 (10.0)	85.3 (10.7)	4 (21)	3 (16)	2 (11)	3 (16)
Increased IHD only	16	91.4 (9.0)	92.9 (11.4)	88.1 (8.1)	3 (19)	3 (19)	0	1 (6.3)
Remainder	24	83.1 (8.3)	88.0 (10.6)	83.2 (9.9)	12 (50)	(21)	4 (17)	1 (4.2)
Infants without high-grade injury	54							
Small BPW and increased IHD	2	90.0	84.0 (14.1)	83.5 (2.1)	0	1 (50)	0	0
Small BPW only	16	85.9 (9.7)	89.5 (9.4)	84.6 (11.3)	4 (25)	2 (13)	2 (13)	3 (19)
Increased IHD only	15	91.5 (9.3)	92.8 (11.8)	88.7 (8.0)	3 (20)	3 (20)	0	0
Remainder	21	83.3 (8.1)	88.4 (11.3)	84.1 (10.3)	10 (49)	5 (24)	4 (19)	0

n = 65. Data are presented as mean (SD) for Cognition, Language and Motor categories.

TABLE 8 Multivariate Linear Regression Models in the Christchurch and Melbourne Cohorts

	B	SE	β	P
MDI score				
Constant	90.7	7.6		<.001
High-grade injury (no = 0, yes = 1)	−21.0	4.1	−0.31	<.001
IHD (mm)	−2.7	0.74	−0.23	<.001
z Score of BPW	3.4	1.2	0.18	.005
Gender (male = 1, female = 2)	5.7	2.4	0.15	.016
Maternal education (college/university = 0, high school graduate = 1, less than high school = 2)	−3.5	1.7	−0.13	.040
PDI score				
Constant	85.9	7.0		<.001
High-grade injury (no = 0, yes = 1)	−26.7	3.8	−0.42	<.001
z Score of BPW	2.6	1.1	0.15	.021
Dexamethasone use (no = 0, yes = 1)	−9.7	4.4	−0.15	.029

n = 232. Table represents results of forced-entry multivariate linear regression analysis with significant variables after testing the association between brain injuries, growth measurements, and the clinical variables, including all of the variables listed in Table 5, maternal education, and center. R^2 = 0.30 or 0.30 for MRI or PDI scores, respectively.

Both of these patterns represent impairment in brain growth, either influencing skull and brain growth (small BPW) or relatively greater in relation to skull growth (increased IHD). This difference is of importance, because the expected growth of an infant's brain volume can vary, as in linear growth, by a factor of at least 2, and comparison of brain growth with skull size may compensate for this difference to some degree. The increased IHD brain pattern was common (34%) in the VPT infants regardless of the cohort, and was not necessarily accompanied by smaller BPW. Importantly, impaired brain growth on both BPW and IHD parameters was found in only 7% of infants. Both growth parameters were associated with neurodevelopmental outcome at age 2 years, especially cognitive development, with those infants who were impaired on both growth parameters exhibiting the poorest outcomes. The existence of an increased IHD brain pattern may explain why head circumference at TEA is not always well correlated with subsequent cognitive outcome.[30,31]

In human brain development, the third trimester of gestation is a critical period during which global and regional brain volume increases three- to fourfold.[32,33] Histologically, there are cytoarchitectonic changes involving (1) neuronal organization and elaboration of dendrites, (2) glial cell proliferation and maturation, and (3) myelination of corticospinal tracts. Each of these cellular processes may be vulnerable to environmental influences in the NICU, and thereby their impairment may disrupt brain growth. Many previous studies have suggested that several risk factors within the NICU relate to adverse cognitive outcomes, including postnatal infection,[34,35] bronchopulmonary dysplasia,[36] suboptimal nutrition,[37] postnatal dexamethasone,[38] and stress.[39,40] However, few have defined the neuroanatomical pathway by which such exposures influence cognitive outcome. Our study contributes to this literature by confirming the importance of inotrope exposure, oxygen at 36 weeks, necrotizing enterocolitis, treated PDA, and prolonged parenteral nutrition as factors associated with the small BPW brain pattern at TEA, which, in turn, is associated with adverse cognitive development at age 2 years. In contrast, male gender, dexamethasone use, and severe brain injury are risk factors for the increased IHD brain pattern, which is also associated with later cognitive impairments. Relationships between clinical factors and patterns of impaired brain growth provide us with a better understanding of the potential pathway (s) to adverse outcome, particularly in the absence of severe brain injury.

Our study has some limitations. First, three-dimensional volumetry is a gold standard to quantitatively evaluate brain volume. However, the simple brain metrics we used are widely available and show reasonable correlations with three-dimensional volumetric measurements.[14] Additionally, several investigations suggest that the premotor or sensorimotor areas of the brain are the most vulnerable areas for reductions in volume, and that the volume reduction correlates with later neurodevelopmental outcomes.[11,18] Thus, brain measurements in specific regions may be crucial, as was done in the current study.
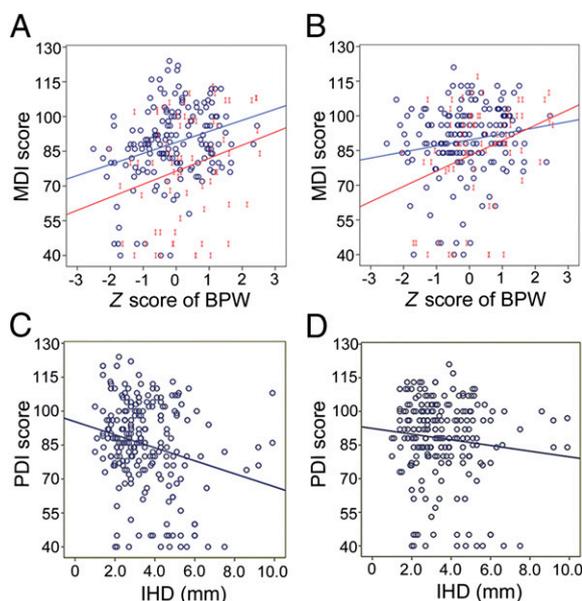
FIGURE 3
MDI or PDI scores in infants with different growth measurements in the Christchurch and Melbourne cohorts. A and B, The x-axes show the BPW z score after adjustment for postmenstrual age at MRI scan and gender. Subjects with the increased IHD brain pattern (red vertical bars) are separated from those without (blue circles). The solid lines are regression lines for subjects with (red) or without (blue) the increased IHD brain pattern. C and D, Negative linear correlation was observed between IHD and MDI scores but not between IHD and PDI scores.

The second limitation is the inclusion of infants from 3 regionally different cohorts. Each cohort was independently recruited for population-based studies in a similar manner. However, the number of infants in each cohort is different, and their perinatal and postdischarge environments and treatments may differ. Additionally, infants were recruited over more than a decade. Some neonatal practices, including nutritional management, varied over the time period. The third limitation is the definition of brain injury with MRI at term. Mild form of injuries and ventricular dilatation may resolve by TEA, resulting in underestimation of the extent of brain injury. Finally, direct comparison of relations between neonatal brain findings and neurodevelopmental outcome between the Christchurch and Melbourne cohorts and the St Louis cohort was difficult because the St Louis cohort was tested by using the Bayley III (versus BSID-II), was subject to more socioeconomic adversity, and had higher rates of brain injury and altered brain growth. These measurement and sample differences, in addition to the smaller sample size, may also have influenced observed associations between brain injury/growth and outcome.

CONCLUSIONS

Severe brain injury in VPT survivors is uncommon but has a major influence on neurodevelopmental outcomes in multiple domains. Impaired brain growth at discharge from the NICU is related to adverse neurodevelopmental outcomes at age 2 years, particularly cognitive development, even in preterm infants without severe brain injury. The MRI assessment of both brain injury and brain growth is relevant to understanding the pathway from preterm birth to subsequent neurodevelopmental outcomes in VPT survivors. Our findings suggest that neonatal brain injury is important for later motor function, whereas both brain injury and brain growth affect later cognitive function. The contribution of these 2 neuropathological mechanisms to later adverse behavioral and mental health outcomes associated with preterm birth is an issue for future research.

REFERENCES

1. Platt MJ, Cans C, Johnson A, et al. Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. *Lancet*. 2007;369(9555):43–50

2. Robertson CMT, Watt MJ, Yasui Y. Changes in the prevalence of cerebral palsy for children born very prematurely within a population-based program over 30 years. *JAMA*. 2007;297(24):2733–2740

3. Anderson P, Doyle LW; Victorian Infant Collaborative Study Group. Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s. *JAMA*. 2003;289(24):3264–3272

4. Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N. Outcomes in young adulthood for very-low-birth-weight infants. *N Engl J Med*. 2002;346(3):149–157

5. Hutchinson EA, De Luca CR, Doyle LW, Roberts G, Anderson PJ; Victorian Infant Collaborative Study Group. School-age outcomes of extremely preterm or extremely low birth weight children. *Pediatrics*. 2013;131(4). Available at: www.pediatrics.org/cgi/content/full/131/4/e1053

6. Maalouf EF, Duggan PJ, Counsell SJ, et al. Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm infants. *Pediatrics*. 2001;107(4):719–727

7. Rademaker KJ, Uiterwaal CS, Beek FJ, et al. Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm. *Arch Dis Child Fetal Neonatal Ed*. 2005;90(6):F489–F493

8. Spittle AJ, Spencer-Smith MM, Eeles AL, et al. Does the Bayley-III Motor Scale at 2 years predict motor outcome at 4 years in very preterm children? *Dev Med Child Neurol.* 2013;55(5):448–452

9. Woodward LJ, Clark CA, Bora S, Inder TE. Neonatal white matter abnormalities an important predictor of neurocognitive outcome for very preterm children. *PLoS ONE.* 2012;7(12):e51879

10. Woodward LJ, Clark CA, Pritchard VE, Anderson PJ, Inder TE. Neonatal white matter abnormalities predict global executive function impairment in children born very preterm. *Dev Neuropsychol.* 2011;36(1):22–41

11. Peterson BS, Vohr B, Staib LH, et al. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. *JAMA.* 2000;284(15):1939–1947

12. Nosarti C, Al-Asady MHS, Frangou S, Stewart AL, Rifkin L, Murray RM. Adolescents who were born very preterm have decreased brain volumes. *Brain.* 2002;125(pt 7):1616–1623

13. Inder TE, Warfield SK, Wang H, Hüppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. *Pediatrics.* 2005;115(2):286–294

14. Nguyen The Tich S, Anderson PJ, Shimony JS, Hunt RW, Doyle LW, Inder TE. A novel quantitative simple brain metric using MR imaging for preterm infants. *AJNR Am J Neuroradiol.* 2009;30(1):125–131

15. Tich SN, Anderson PJ, Hunt RW, Lee KJ, Doyle LW, Inder TE. Neurodevelopmental and perinatal correlates of simple brain metrics in very preterm infants. *Arch Pediatr Adolesc Med.* 2011;165(3):216–222

16. Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. *J Pediatr.* 2003;143(2):171–179

17. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr.* 1978;92(4):529–534

18. Thompson DK, Warfield SK, Carlin JB, et al. Perinatal risk factors altering regional brain structure in the preterm infant. *Brain.* 2007;130(pt 3):667–677

19. Garel C. MRI of the Fetal Brain. Berlin, Germany: Springer-Verlag; 2004

20. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis: therapeutic decisions based upon clinical staging. *Ann Surg.* 1978;187(1):1–7

21. Bayley N. The Bayley Scales of Infant Development. 2nd ed. New York, NY: Psychological Corporation; 1993

22. Bayley N. *Bayley Scales of Infant and Toddler Development.* 3rd ed. San Antonio, TX: Harcourt Assessment; 2006

23. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW; Victorian Infant Collaborative Group. Underestimation of developmental delay by the new Bayley-III scale. *Arch Pediatr Adolesc Med.* 2010;164(4):352–356

24. Vohr BR, Stephens BE, Higgins RD, et al. Are outcomes of extremely preterm infants improving? Impact of Bayley assessment on outcomes. *J Pediatr.* 2012;161(2):222–228.e3

25. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol.* 1997;39(4):214–223

26. Dyet LE, Kennea N, Counsell SJ, et al. Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. *Pediatrics.* 2006;118(2):536–548

27. Miller SP, Ferriero DM, Leonard C, et al. Early brain injury in premature newborns detected with magnetic resonance imaging is associated with adverse early neurodevelopmental outcome. *J Pediatr.* 2005;147(5):609–616

28. Limperopoulos C, Benson CB, Bassan H, et al. Cerebellar hemorrhage in the preterm infant: ultrasonographic findings and risk factors. *Pediatrics.* 2005;116(3):717–724

29. Volpe JJ.Hypoxic-ischemic encephalopathy: neuropathology and pathogenesis. In: Volpe JJ, ed. Neurology of the Newborn. Philadelphia, PA: W.B.Saunders; 2008:347–399

30. Hack M, Breslau N, Weissman B, Aram D, Klein N, Borawski E. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. *N Engl J Med.* 1991;325(4):231–237

31. Cheong JL, Hunt RW, Anderson PJ, et al. Head growth in preterm infants: correlation with magnetic resonance imaging and neurodevelopmental outcome. *Pediatrics.* 2008;121(6):e1534–e1540

32. Huppi PS, Warfield S, Kilinis R, et al. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. *Ann Neurol.* 1998;43:224–235

33. Kapellou O, Counsell SJ, Kennea N, et al. Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. *PLoS Med.* 2006;3(8):e265

34. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth weight infants with neonatal infection. *JAMA.* 2004;292(19):2357–2365

35. Shah DK, Doyle LW, Anderson PJ, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. *J Pediatr.* 2008;153(2):170–175, e1

36. Short EJ, Klein NK, Lewis BA, et al. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. *Pediatrics.* 2003;112(5). Available at: www.pediatrics.org/cgi/content/full/112/5/e359

37. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. *BMJ.* 1998;317(7171):1481–1487

38. Murphy BP, Inder TE, Huppi PS, et al. Impaired cerebral cortical gray matter growth after treatment with dexamethasone for neonatal chronic lung disease. *Pediatrics.* 2001;107(2):217–221

39. Smith GC, Gutovich J, Smyser C, et al. Neonatal intensive care unit stress is associated with brain development in preterm infants. *Ann Neurol.* 2011;70(4):541–549

40. Brummelte S, Grunau RE, Chau V, et al. Procedural pain and brain development in premature newborns. *Ann Neurol.* 2012;71(3):385–396