Neurobehavior at Term and White and Gray Matter Abnormalities in Very Preterm Infants

Nisha C. Brown, PhD, Terrie E. Inder, MD, Merilyn J. Bear, BN, Rod W. Hunt, PhD, Peter J. Anderson, PhD, and Lex W. Doyle, MD

Objective To examine the relationship between very preterm infant neurobehavior at term and concurrent magnetic resonance-defined cerebral abnormalities.

Study design 168 very preterm infants (birth weight <1250 g or gestation <30 weeks) were examined at term with 2 standardized neurobehavioral assessments, the Revised Hammersmith Neonatal Neurological Examination and the Neonatal Intensive Care Unit Network Neurobehavioral Scale. The relationship between composite neurobehavioral scores and qualitative white and gray matter abnormalities on magnetic resonance imaging was determined.

Results Poorer neurobehavioral performance related to magnetic resonance-defined cerebral abnormalities. Composite neurobehavioral scores related to the total grade of white matter abnormality, and worse neurobehavior related most strongly to 2 components of this grade: white matter signal abnormalities and reduction in white matter volumes. Neurobehavior was not related to the total grade of gray matter abnormality. However, delayed gyral maturation, a component of the total gray matter grade, was related to poorer performance on both neurobehavioral scales.

Conclusion Very preterm infant neurobehavior at term is related to concurrent cerebral abnormalities in both white and gray matter defined by qualitative magnetic resonance imaging. *(J Pediatr 2009;155:32-8)*.

Very preterm infants have excessive rates of neonatal neurobehavioral problems,[1-4] neurodevelopmental impairment,[5-7] and cerebral palsy.[7-9] Perinatal brain injury is the most significant contributor to later neurological morbidity in very preterm survivors,[10] particularly non-cystic white matter (WM) abnormalities[11-16] that have been related to neuromotor abnormalities at term,[14] Prechtl's general movements at 1 and 3 months' corrected age,[17] developmental delay at 18 and 24 months' corrected age,[12,13] and executive functioning at preschool.[18] There is also a growing belief that diffuse WM abnormalities may account for the more subtle cognitive difficulties experienced by many preterm infants in later childhood.[10,14,19] Although prematurity predominantly results in alterations to the cerebral WM, there may also be injury to the immature subplate neurons or a secondary impact on the developing cortical gray matter (GM) in association with WM injury.[13,20,21] However, the relationship of such neonatal abnormalities with concurrent functional capacity has not been clearly delineated in preterm infants.

The aim of this study was to examine the relationship, at term, between qualitatively defined magnetic resonance imaging (MRI) abnormalities and concurrent neurobehavior in a large prospective cohort of very preterm infants. The neurobehavioral performance of this cohort of very preterm infants was previously compared with term-born infants, with preterm infants overall demonstrating poorer (or altered) neurobehavior.[4] Although we previously described the influence of perinatal factors on the neurobehavior of this preterm infant cohort,[4] it is imperative that we also understand the underlying neuropathological mechanisms and their specific relationships to the different facets of the neurobehavioral evaluation.

Methods

One hundred and eighty-two very preterm infants, with birth weights <1250 g or gestational ages <30 weeks, were recruited from the Royal Women's Hospital neonatal unit in Melbourne, Australia (July 2001-April 2004), before term age. Infants with any congenital abnormalities were excluded. The Research and

APIB	Assessment of Preterm Infant Behavior
GM	Gray matter
HNNE	Hammersmith Neonatal Neurological Examination Scale
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NNNS	Neonatal Intensive Care Unit Network Neurobehavioral Scale
WM	White matter

From the Victorian Infant Brain Studies, Murdoch Children's Research Institute, Melbourne, Australia (N.B., T.I., M.B., R.H., P.A., L.D.); Departments of Obstetrics and Gynecology (N.B., P.A., L.D), Psychology (P.A.), Pediatrics (L.D.) and Howard Florey Institute (T.I.), University of Melbourne, Melbourne, Australia; Newborn Research, Royal Women's Hospital, Melbourne, Australia (N.B., L.D.); Department of Neonatal Medicine, Royal Children's Hospital, Melbourne, Australia (R.H.); and Department of Pediatrics, Neurology, and Radiology, St Louis Children's Hospital, Washington University, St Louis, MO (T.I.)

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Ethics Committees at the Royal Women's Hospital approved this study, and informed written consent was obtained from the parents of all participating infants. The study protocol included an MRI scan and 2 concurrent standardized neurobehavioral examinations of infants at term equivalent age.

Term Magnetic Resonance Imaging

MRI was performed at term without the use of sedation or anesthesia, at the Royal Children's Hospital, with established MRI sequences and post-acquisition analyses, as previously described.[13,19] Two different imaging modes were applied for the acquisition of the primary magnetic resonance (MR) data, and included: 1) a 3-dimensional Fourier transform T1 spoiled gradient recalled sequence (thickness of coronal slices was 1.5mm, with 45-degree flip angle; repetition time, 35 msec; echo time, 5 msec; 18-cm field of view; 256 x 256 matrix acquisition; 124 slices; voxel dimensions 0.7 x 0.7 x 1.5 mm), and 2) a double-echo (proton density and T2-weighted) spin-echo sequence (dual-echo; thickness of axial slices was 3 mm; repetition time, 3000 msec; echo times, 36 and 162 msec; an 18-cm field of view; 256 x 256 matrix acquisition; 68 slices; interleaved acquisition; voxel dimensions 0.7 x 0.7 x 3 mm).

The qualitative MR scoring system applied in this study was described earlier.[19,22] Cerebral WM was assessed on a 3-point scale (graded 1-3) across 5 domains: WM signal abnormality (a combination of T2- and T1- weighted abnormalities scored for presence and severity of extent); reduction in WM volume; cystic abnormality; ventricular dilatation; and corpus callosum and maturation of myelination (posterior limb of the internal capsule). WM abnormality scores were then summed to produce a composite score. The minimum score possible (indicating no abnormality) was 5, and the maximum score possible (indicating abnormality) was 15. WM abnormality was then further classified in 4 grades of severity, with the composite scores of the 5 domains: 1 indicating no WM abnormality (composite scores of 5-6), 2 indicating mild WM abnormality (composite scores of 7-9), 3 indicating moderate to severe non-cystic WM abnormality (composite scores of 10-12), and 4 indicating moderate to severe cystic WM abnormality (composite scores of 13-15). Cerebral GM abnormality was also assessed on a 3-point scale, across 3 domains: size of subarachnoid space, cortical GM signal abnormality, and cortical gyration maturation. Total scores of 3 to 5 indicated normal GM, and scores of 6 to 9 indicated abnormal GM. All MRI scans were scored without the assessors' knowledge of the infants' clinical status or neurobehavioral assessment results. Scans were scored independently by a neonatal neurologist (T.I.) and experienced neonatologist (R.H.). Interrater agreement for category assignment was 94% (Kappa 0.90; $P < .001$).

Term Neurobehavioral Evaluations

On the same day as the MRI, at term equivalent age, infants were examined with 2 standardized neonatal evaluations: the Hammersmith Neonatal Neurologic Examination (HNNE)[23] and the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS).[24] Both evaluations were designed to include the assessment of high-risk infants. Because of the absence of a gold-standard, 2 different evaluations were used. The HNNE is briefer and more neurologically based, whereas the NNNS is neurobehaviorally based.

The HNNE comprises 34 individual items that are grouped in 6 subtotals: tone, tone patterns, reflexes, spontaneous movements, abnormal signs, and behavior. The sum of these 6 subtotals produces a total HNNE score. Because there currently are no "optimum" preterm infant scores determined for the HNNE, scores were re-coded as previously described,[4] on the basis of term infant "optimality scores,"[25] while taking into consideration the scores for a low-risk preterm population published by Mercuri et al.[3] Higher (composite) scores on the HNNE indicate a "better" performance, and lower (composite) scores indicate a "poorer" performance.

The NNNS is a neurobehavioral assessment comprising 45 individual items that are clustered into state-dependent "packages" (with an additional 21 summary items), designed to evaluate the neurological integrity, behavioral functioning, and stress (or abstinence) responses of high-risk infants.[26] The habituation items and the stress/abstinence scale were not used in this study (the length of time required was not practical, because of the extensive study protocol at term). The behavioral components of the NNNS were based on the well-known Neonatal Behavioral Assessment Scale.[27] The NNNS has norms based on 125 full-term healthy infants (38-41 weeks' gestational age at birth).[28] Individual scores were coded and computed into 11 subscales/summary scores: attention, handling, quality of movement, regulation, non-optimal reflexes, arousal, hypertonicity, hypotonicity, asymmetrical reflexes, excitability, and lethargy. Higher scores for NNNS attention, quality of movement, and regulation subscales indicated a "better" performance, whereas higher scores for non-optimal reflexes, handling, hypotonicity, asymmetrical reflexes, excitability, and lethargy subscales indicated a "poorer" performance. Arousal and hypertonicity were not included in statistical analyses because the scores were previously found not to be clinically helpful.[4]

All assessments were video-recorded to enable review of examinations when necessary to clarify assessment scores. The examiner (N.B.) did not have knowledge of infants' MRI results or neonatal histories at the time of the examinations.

Statistical Analysis

All data were analyzed by SPSS for Windows software (version 16.0, SPSS, Chicago, Illinois). Differences in mean HNNE and NNNS composite scores across WM and GM abnormality grades were tested with 1-way analysis of variance, including a test for linearity. Again with analysis of variance, the relationships between the individual components of the WM and GM abnormality scores and neurobehavior were assessed. A conservative significance level of <.01 was adopted to account for multiple comparisons.

Results

Of the 182 preterm infants recruited into this study, 168 (92%) had complete neurobehavioral and MRI data acquired at term-corrected age (40.2 weeks ± 1.2 SD). Perinatal and neonatal characteristics are described in Table I.

MRI scans for all 168 preterm infants were graded as follows: 38% (n = 63) had no WM abnormality, 46% (n = 78) had mild WM abnormality, 13% (n = 22) had moderate WM abnormality, and 3% (n = 5) had severe WM abnormality. Thirty-seven preterm infants (22%) had GM abnormality.

White Matter Abnormality and Neurobehavior

At term-corrected age, there was a significant ($P = .002$) linear relationship between worse performance on the HNNE and increasing severity of WM abnormality (Table II). Of the subtotal HNNE scores, spontaneous movements and behavior also had a significant linear relationship with grade of WM abnormality (Table II). None of the NNNS composite scores exhibited a significant linear relationship with the total grade of WM abnormality.

Neurobehavior on both the HNNE and the NNNS related to some individual components of WM abnormality. More than half the preterm infants demonstrated WM signal abnormality, and more than half demonstrated reduced WM (Table III). Increasing WM signal abnormality related significantly to lower total HNNE scores and poorer HNNE spontaneous movement scores and the presence of NNNS non-optimal reflexes. Reduced WM volume related to poorer scores for the HNNE behavior subscale. The presence of cysts was found in only 5% of the preterm infants and did not relate significantly to neurobehavior. Ventricular dilatation was common, with most infants (64%) found to have mild-moderate dilatation of their ventricles (grade 2). Ventricular dilatation did not relate significantly to any neurobehavioral measure. Less than a quarter of the preterm infants (24%) displayed delayed posterior limb of the internal capsule myelination, thinning of the corpus callosum, or both. Again, this did not relate significantly to concurrent neurobehavior at term.

Gray Matter Abnormality and Neurobehavior

There were no significant relationships between composite neurobehavioral scores, on either the HNNE or the NNNS, and the overall grade of GM abnormality on qualitative MR analysis (Table IV; available at www.jpeds.com).The most common GM abnormalities were increased subarachnoid space and delayed gyral maturation (Table V). Delayed gyral maturation was the only component of the GM abnormality score that was related to neurobehavior. Delayed gyral maturation was associated with worse scores on the HNNE tone and spontaneous movements subscales, and the HNNE total score, and the NNNS non-optimal reflexes subscale.

Table I. Characteristics of very preterm infant study sample

Characteristics (n = 168)	Mean (SD)	Range
Birth weight, g	969 (223)	450-1500
Birth weight z score	−0.7 (1.0)	−4.0-1.8
Gestational age, weeks	27.7 (2.0)	22-32
Post-menstrual age at neurobehavioral assessment, weeks	40.2 (1.2)	38.0-42.9
	N (%)	
Males	87 (51.9)	
Multiple births	72 (42.9)	
IUGR (birth weight z score <-2SD)	20 (11.9)	
Maternal antenatal steroids	148 (88.1)	
Oxygen dependency at 36 weeks' post-menstrual age	51 (30.4)	
Grade III/IV IVH (cranial ultrasound scanning)	10 (6.0)	
Moderate-severe WM abnormality (grade III/IV) on MRI	27 (16.1)	
GM abnormality on MRI	37 (22.0)	

IUGR, Intrauterine growth restriction; *IVH,* intraventricular hemorrhage.

Discussion

We demonstrate specific relationships between neurobehavioral functioning and concurrent MRI-defined cerebral abnormalities in a large unselected cohort of very preterm infants at term-corrected age. The more complex neurobehavioral items of behavior and spontaneous movements were more strongly related to the extent of WM abnormality. In comparison, the simple motor abnormalities, such as tone, demonstrated impairment in only the severely affected infants. Increasing WM signal abnormality and reduced WM volume were the specific WM abnormalities that related to abnormal neurobehavior. This was similar for gyral delay in the GM scale. Both the HNNE and NNNS scales showed impaired performance across many domains in infants with severe WM abnormality, although the number of affected infants in this group was small (n = 5). Overall, structural abnormalities on MR were statistically more related to the HNNE than the NNNS. This may be because the HNNE has more emphasis on neurological items than the NNNS.

Preterm infant brain development is different in the ex-utero environment, compared with brain development in infants who have remained in-utero to term.[19,29] This study defines relationships between altered brain development at term, specifically cerebral structural changes to the white and cortical GM, and functional capacity, adding further support to the concept that MR is not only useful as a research tool, but is also clinically relevant in the newborn period. Functional relationships with subcortical and infratentorial structures have not been a focus of this study and would be worthy of investigation in the future. The overall functional performance of preterm infants, as defined by the total score on the HNNE, declined significantly with increasing grades of WM abnormality, and this relationship was also significant for the HNNE spontaneous movements and behavior subscales.

The spontaneous movements subscale was 1 of the major areas of disturbed neurobehavior in the preterm infant

Table II. Relationship of neurobehavioral performance to total white matter abnormality, at term-equivalent age

Neurobehavioral scores at term	WM abnormality at term (n = 168) None (HNNE n = 63; NNNS n = 61) mean (SD)	Mild (HNNE n = 78; NNNS n = 77) mean (SD)	Moderate (HNNE n = 22; NNNS n = 22) mean (SD)	Severe (HNNE n = 5; NNNS n = 4) mean (SD)	Pearson correlation	*P* value linearity‖
HNNE						
Tone↑	7.7 (1.9)	7.2 (2.1)	7.5 (2.0)	5.9 (1.8)	−.13	.11
Tone patterns↑	4.3 (0.8)	4.0 (0.8)	4.3 (0.6)	3.4 (1.1)	−.14	.08
Reflexes↑	5.5 (0.6)	5.4 (0.8)	5.2 (0.8)	5.0 (1.1)	−.18	.024
Spontaneous movements↑	2.1 (0.9)	2.0 (0.9)	1.6 (1.0)	1.2 (1.1)	−.22	.004
Abnormal signs↑	2.4 (0.6)	2.4 (0.6)	2.2 (0.6)	2.3 (0.6)	−.12	.14
Behavior↑	5.5 (1.5)	5.4 (1.4)	4.8 (1.2)	3.8 (1.1)	−.21	.007
HNNE score↑	27.6 (4.2)	26.4 (4.3)	25.5 (3.4)	22.1 (3.4)	−.24	.002
NNNS						
Attention↑¶	5.7 (1.6)§	5.1 (1.7)	5.1 (1.3)*	4.1 (1.7)	−.15	.06
Handling↓¶	0.45 (0.2)‡	0.41 (0.2)†	0.42 (0.3)*	0.38 (0.3)	−.08	.30
Quality of movement↑¶	4.4 (0.9)*	4.6 (0.7)	4.3 (0.8)	3.8 (0.8)	−.09	.27
Regulation↑¶	5.3 (1.0)*	5.6 (1.3)	5.2 (1.1)	4.0 (0.6)	−.08	.32
Non-optimal reflexes↓	3.6 (2.5)	3.9 (2.2)	4.6 (1.3)	6.3 (2.2)	.19	.014
Hypotonicity↓	0.21 (0.5)	0.23 (0.5)	0.23 (0.4)	0.75 (1.0)	.09	.26
Asymmetrical reflexes↓	0.33 (0.7)	0.43 (0.7)	0.59 (0.7)	0.75 (1.5)	.14	.09
Excitability↓	3.5 (2.4)	2.9 (2.3)	4.0 (2.7)	5.0 (3.6)	.07	.39
Lethargy↓	3.6 (2.7)	4.0 (2.9)	3.6 (2.3)	6.5 (3.7)	.09	.27

*n = 1 missing because of minimum number of items required to calculate score.
†n = 4 missing because of minimum number of items required to calculate score.
‡n = 6 missing because of minimum number of items required to calculate score.
§n = 7 missing because of minimum number of items required to calculate score.
‖*P* value from weighted linearity test (1-way analysis of variance). Significance level for *P* value reduced to <.01 because of multiple testing.
¶Scales that require a minimum number of items.
↑Higher score = better neurobehavioral performance.
↓Higher score = poorer neurobehavioral performance.

with WM abnormalities and includes items assessing both the quantity and quality of spontaneous movements and the infant's head-raising ability in prone. Spontaneous whole body movements are observed for the patterns and sequences of movements rather than individual limb movements.[30] These whole body, general movements have been described and studied in detail by Prechtl et al.[31,32] Standardized observations of Prechtl's general movements, in preterm infants, were previously related to WM abnormalities[17] and neurodevelopmental outcome, in particular, cerebral palsy.[33] Although the evaluation of spontaneous movements is less complex on the HNNE than Prechtl's methods, the relationship of WM abnormality at term adds further strength to the theory that normative patterns of spontaneous movements reflect central nervous system integrity.

The behavior subscale was the second major area of disturbance in preterm infants at term with WM abnormalities and includes an assessment of the infant's eye movements, auditory and visual orientation abilities (turning to sound and visually tracking an object), level of alertness, irritability, quality of cry, and consolability. Preterm infants with more severe WM abnormality received scores reflecting greater irritability during the course of the examination. Such infants often had difficulty regulating their states of arousal and were hyper-reactive to handling. Poor HNNE behavior scores were also related to reductions in WM volumes, a component of the overall WM abnormality score.

In addition to the HNNE total score and spontaneous movements subscale score, the NNNS summary score non-optimal reflexes related significantly to the presence of WM signal abnormality on MR. The NNNS summary score for non-optimal reflexes comprises scores from 15 individual reflex items; infants who score poorly on this subscale demonstrate under-reactive or exaggerated reflex responses. Overall, the NNNS did not demonstrate the strength of relationship to the WM and GM abnormalities that was found with the HNNE, which may reflect the development of the NNNS for a different population principally focused on the in-utero drug-exposed infant.

The gyral maturation of preterm infants at term was found on MR to be delayed in comparison with term infants, with the cerebral cortex of preterm infants having less cortical surface area and being less complex than term infants.[21] Gray matter abnormalities have been associated with neurosensory impairment at 2 years' corrected age.[13] Although composite neurobehavioral scores did not relate significantly to the overall grade of GM abnormality in this study, delayed gyral maturation was associated with worse scores for HNNE tone and spontaneous movements subscales, the HNNE total, and the NNNS non-optimal reflexes subscale. The differential impact of GM delay in maturation from that of WM abnormalities on neurobehavior and outcomes warrants further investigation.

Although abnormal muscle tone at term was related to gyral maturation, there was no relationship of WM abnormalities to tone. There are, however, plausible hypotheses as to why tone abnormalities may be difficult to identify correctly in preterm infants at term and may not appear to relate to

Table III. Relationship of neurobehavioral performance to items contributing to total white matter abnormality scores at term-equivalent age

		WM abnormality at term (n = 168)				
		WMSA, n	WMVL, n	CA, n	VD, n	CC/PLIC, n
Grade	**1**	77	71	159	51	128
	2	71	77	5	107	32
	3	20	20	4	10	8
Neurobehavioral Scores		*P**	*P**	*P**	*P**	*P**
HNNE (n = 168)						
Tone ↑		.014	.321	.413	.806	.34
Tone patterns ↑		.144	.208	.101	.852	.71
Reflexes ↑		.020	.270	.154	.762	.11
Spontaneous movements ↑		.001	.251	.028	.062	.03
Abnormal signs ↑		.025	.545	.732	.353	.31
Behavior ↑		.037	.006	.200	.012	.08
HNNE score ↑		.0001	.041	.041	.188	.046
NNNS (n = 164)						
Attention ↑† (n = 150)		.217	.190	.387	.185	.23
Handling ↓† (n = 153)		.266	.097	.742	.113	.56
Quality of movement ↑† (n = 163)		.036	.117	.101	.011	.23
Regulation ↑† (n = 163)		.086	.117	.025	.035	.016
Non-optimal reflexes ↓		.001	.414	.062	.604	.047
Hypotonicity ↓		.019	.085	.233	.108	.28
Asymmetrical reflexes ↓		.477	.562	.032	.157	.72
Excitability ↓		.159	.069	.069	.086	.06
Lethargy ↓		.754	.354	.747	.590	.14

WMSA, White matter signal abnormality; *WMVL*, periventricular white matter volume loss; *CA*, presence of any cystic abnormality; *VD*, ventricular dilatation; *CC/PLIC*, thinning of the corpus callosum and impaired PLIC (posterior limb of the internal capsule) myelination.
**P* value for between-group comparisons from 1-way analysis of variance. Significance level for *P* value reduced to <.01 because of multiple testing.
†Scales that require a minimum number of items.
↑Higher score = better neurobehavioral performance.
↓Higher score = poorer neurobehavioral performance.

Table V. Relationship of neurobehavioral performance to items contributing to total gray matter abnormality scores, at term-equivalent age

		GM abnormality at term (n = 168)		
		SS	GMSA	GyM
Grade	**1**	69	162	71
	2	63	5	77
	3	36	1	20
Neurobehavioral Scores		***P****	***P****	***P****
HNNE (n = 168)				
Tone↑		.521	.754	.006
Tone patterns↑		.942	.539	.12
Reflexes↑		.050	.155	.05
Spontaneous movements↑		.196	.571	.001
Abnormal signs↑		.307	.815	.03
Behavior↑		.043	.441	.016
HNNE score↑		.165	.847	.001
NNNS (n = 164)				
Attention↑† (n = 150)		.546	.019	.24
Handling↓† (n = 153)		.140	.196	.84
Quality of movement↑† (n = 163)		.176	.742	.07
Regulation↑† (n = 163)		.981	.162	.36
Non-optimal reflexes↓		.268	.405	.001
Hypotonicity↓		.210	.877	.19
Asymmetrical reflexes↓		.854	.579	.45
Excitability↓		.845	.084	.048
Lethargy↓		.705	.061	.65

SS, Subarachnoid space; *GMSA*, gray matter signal abnormality; *GyM*, gyral maturation.
**P* value for group comparisons from 1-way analysis of variance. Significance level for *P* value reduced to <.01 because of multiple testing.
†Scales that require a minimum number of items.
↑Higher score = better neurobehavioral performance.
↓Higher score = poorer neurobehavioral performance.

concurrent WM injury. First, hypotonia is a common finding in the neonatal period for preterm infants.[34-36] Thus, when infants are only examined at only 1 time point, they may appear to have a transient normalization of muscle tone as they move from preterm hypotonia to post-term hypertonia (eg, as with spastic cerebral palsy).[37] In addition, Stewart et al[38] suggested that hypertonicity may be difficult to identify in preterm infants because of its symmetry in diffuse WM injury.

Direct comparisons of this study with similar preterm infant populations are limited. Although Constantinou et al[39] recently reported term neurobehavioral performance with MRI findings, they do not report specifically on the relationship of the 2 forms of assessment. Miller et al[14] reported that preterm infants with moderate to severe MRI abnormalities in the newborn period had more abnormal neuromotor scores.Of greater similarity to this study, Woodward et al[22] compared the administration of the HNNE with qualitative MRI at term, but in a smaller cohort of very preterm infants (n = 66). Woodward et al,[22] however, did not examine behavior as extensively as this study, nor neurobehavioral relationships with the specific components contributing to overall WM and GM scores. Despite these limitations, the findings from Woodward et al[22] are in agreement with this study in that neurological functioning at term related significantly to cerebral abnormalities defined with qualitative MRI at term.

Hüppi et al[40] also reported qualitative MRI findings with the neurobehavioral assessment of preterm infants at term, by using the Assessment of Preterm Infant Behavior (APIB); however, the preterm infant sample size in their study was much smaller (n = 18). Direct relationships between the APIB and cerebral abnormalities were not reported; however, neurobehavioral function paralleled cerebral maturation across 2 time points, at 2 weeks' postnatal age (mean, 32.5 weeks' gestation) and at term-equivalent age.[40] In particular, significant maturational changes were reported for GM, WM, and myelination. In the same time span, functional maturation was also observed in all 5 functional APIB subsystems, including the autonomic, motor, state organization, attentional-interactive, and self-regulatory systems. Despite the small sample size, the findings of this study add further strength to the theory that preterm infant neurobehavioral functioning at term is related to cerebral development.

A limiting factor of this study is the lack of healthy preterm infant norms for calculating the composite or "'optimality" scores for both the HNNE and the NNNS. Because of the differences between very preterm and term infant neurobehavior at term,[4] this is clearly something that needs further attention. The study by Woodward et al[22] lends some support to the use of the HNNE term optimality scoring system for preterm

infants. However, outcomes on the NNNS have not been previously published with preterm infants, other than our own and "quasi norms" for infants at varying degrees of biological risk, social risk, or both (many of whom were exposed to drugs in-utero).[41] The development of preterm infant norms may help to improve the diagnostic usefulness of neurobehavioral examinations.[3,22] The assessment of functional status at a single time point could also be considered a limitation of this study. There is no doubt that serial neurobehavioral assessments provide greater information to the clinician, particularly for evolving/changing muscle tone.

In conclusion, this prospective study of very preterm infants has found that poor neurobehavioral performance at term was related to severity of cerebral abnormalities on concurrent MRI. Preterm infants with WM abnormality demonstrated poorer neurobehavioral functioning, most prominently in the complex domains of spontaneous movements and behavior. Because of the limitations of traditional neurological measures such as tone and reflexes, systematic neurobehavioral examinations may facilitate identification of the preterm infant with neuropathology and assist with the implementation of developmental interventions. Later neurodevelopmental outcomes are required to evaluate the predictive role of both MRI and early neurobehavioral assessments for later developmental outcomes. ■

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Reprint requests: Dr Nisha Brown, Newborn Research, 7th Floor, Royal Women's Hospital, Locked Bag 300, Parkville, Victoria, Australia 3052. E-mail: nisha.brown@thewomens.org.au.

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50 Years Ago in THE JOURNAL OF PEDIATRICS

Virus Isolation in Fatal Human Cases of Influenza (Comments on Current Literature)

Blattner RJ. J Pediatr 1959;55:113-5

Responding to sudden and unexplained deaths from Asian influenza in young persons in Cleveland in the fall of 1957, the medical community collaborated to collect autopsy tissue for examination and culture. Blattner reviewed reports of theses studies. Cultures from the trachea and lower respiratory tract yielded influenza virus, and tissues generally demonstrated inflammation, necrosis, and hemorrhage. Only a few extrapulmonary organ tissue samples revealed virus or inflammation. Culture-positive specimens were obtained from reticuloendothelial sites (which exhibited only congestion histologically) and from a single cardiac specimen (which exhibited fibrinoid degeneration of arterioles but no myocarditis). No virus was isolated from cardiac tissue from the few patients who had histological findings of myocardial inflammation. Remarkably, fulminant clinical disease with profound neurologic and cardiac dysfunction was associated with autopsy findings of edema, but not inflammation or necrosis and no virus isolation, in affected organs.

The mechanism behind fatal influenza after fulminant necrotizing influenza pneumonitis or complicating bacterial pneumonia was elusive in 1959 and remains somewhat so now. Blattner argued in favor of the hypothesis of "viremia in overwhelming cases" (which was not then and still has not been confirmed in many such cases). This writer weighs in on the side of virus-induced—and possibly in some cases nonsteroidal anti-inflammatory drug–abetted—cytokine storm.

Sarah S. Long, MD
Section of Infectious Diseases
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania
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Table IV. Total gray matter abnormality and neurobehavior at term-equivalent age

Neurobehavioral score	GM abnormality at term (n = 168)		
	No abnormality (HNNE n = 131; NNNS n = 128) mean (SD)	Abnormality (HNNE n = 37; NNNS n = 36) Mean (SD)	*P* value*
HNNE			
Tone↑	7.4 (2.1)	7.3 (1.9)	.77
Tone patterns↑	4.1 (.8)	4.1 (.9)	.75
Reflexes↑	5.4 (.8)	5.5 (.7)	.17
Spontaneous movements↑	2.0 (.9)	1.8 (1)	.32
Abnormal signs↑	2.4 (.6)	2.3 (.5)	.64
Behavior↑	5.4 (1.5)	5.0 (1.4)	.15
HNNE score↑	26.8 (4.3)	26.1 (3.9)	.42
NNNS			
Attention↑†	5.6 (1.6)§	5.5 (1.6)*	.69
Handling↓†	0.44 (.2) ¶	0.38 (.2)*	.12
Quality of movement↑†	4.5 (.8)*	4.3 (.8)	.23
Regulation↑†	5.4 (1)*	5.4 (1.7)	.84
Non-optimal reflexes↓	3.9 (2.4)	4.1 (1.9)	.76
Hypotonicity↓	0.22 (.5)	0.31 (.6)	.35
Asymmetrical reflexes↓	0.42 (.7)	0.42 (.8)	.97
Excitability↓	3.3 (2.4)	3.6 (2.6)	.44
Lethargy↓	3.9 (2.9)	3.6 (2.6)	.59

‡n = 1 missing because of minimum number of items required to calculate score.
**P* value for group differences from 1-way analysis of variance. Significance level for *P* value reduced to <.01 because of multiple testing.
†Scales that require a minimum number of items.
§n = 7 missing because of minimum number of items required to calculate score.
¶n =10 missing because of minimum number of items required to calculate score.
↑Higher score = better neurobehavioral performance.
↓Higher score = poorer neurobehavioral performance.