PATTERNS OF BRAIN INJURY IN TERM NEONATAL ENCEPHALOPATHY

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Objectives To determine whether the pattern of brain injury in term neonatal encephalopathy is associated with distinct prenatal and perinatal factors and to determine whether the pattern of injury is associated with 30-month neurodevelopmental outcome.

Study design A total of 173 term newborns with neonatal encephalopathy from 2 centers underwent magnetic resonance imaging (MRI) at a median of 6 days of age (range, 1-24 days). Patterns of injury on MRI were defined on the basis of the predominant site of injury: watershed predominant, basal ganglia/thalamus predominant, and normal.

Results The watershed pattern of injury was seen in 78 newborns (45%), the basal ganglia/thalamus pattern was seen in 44 newborns (25%), and normal MRI studies were seen in 51 newborns (30%). Antenatal conditions such as maternal substance use, gestational diabetes, premature rupture of membranes, pre-eclampsia, and intra-uterine growth restriction did not differ across patterns. The basal ganglia/thalamus pattern was associated with more severe neonatal signs, including more intensive resuscitation at birth ($P = .001$), more severe encephalopathy ($P = .0001$), and more severe seizures ($P = .0001$). The basal ganglia/thalamus pattern was associated with the most impaired motor and cognitive outcome at 30 months.

Conclusion The patterns of brain injury in term neonatal encephalopathy are associated with different clinical presentations and neurodevelopmental outcomes. Measured prenatal risk factors did not predict the pattern of brain injury. *(J Pediatr 2005;146:453-60)*

Neonatal encephalopathy occurs in 1 to 6 of every 1000 live term births and is a major cause of neurodevelopmental disability in term infants.[1] As many as 20% of affected infants die during the newborn period, and another 25% sustain permanent deficits of motor and cognitive function.[2,3] Despite this prevalence, identifying the causes and predicting the long-term outcome of these newborns remains a considerable challenge. This understanding is critical to applying and evaluating emerging strategies to protect the neonatal brain from injury, such as systemic or selective cerebral hypothermia.[4,5]

Neonatal encephalopathy has primarily been related to antenatal risk factors, and intrapartum factors account for only a minority of cases.[6,7] Magnetic resonance imaging (MRI) has emerged as a valuable tool for determining the timing and etiology of neonatal brain injury. In a large cohort of term newborns with encephalopathy, signs of recent brain injury were commonly seen on MRI, whereas longstanding antenatal injury was distinctly rare.[8] This observation suggests that brain injury in most newborns with encephalopathy occurs at or near the time of birth and may be amenable to post-natal interventions.

MRI can also be applied to better understand the heterogeneity of brain injury associated with neonatal encephalopathy. In a primate model of term neonatal brain injury, the specific regional distribution of injury was associated with different durations and severities of ischemia: partial asphyxia caused cerebral white matter injury, and acute and

MRI	Magnetic resonance imaging	LLUCH	Loma Linda University Children's Hospital
MDI	Mental Development Index	IUGR	Intra-uterine growth restriction
UCSF	University of California San Francisco		

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profound asphyxia produced deep gray nuclei (basal ganglia and thalamus) injury.[9,10] A comparable regional vulnerability is observed in the term newborn, resulting in 2 major patterns of injury detectable by MRI: a watershed predominant pattern involving the white matter, particularly in the vascular watershed, extending to cortical gray matter when severe; and a basal ganglia/thalamus predominant pattern involving the deep gray nuclei and perirolandic cortex, extending to the total cortex when severe.[1,11-13] It is unclear whether these patterns in the human newborn are associated with different antenatal risk factors or timing of injury. The first aim of this cohort study of term neonatal encephalopathy was to determine the antenatal and perinatal risk factors for the watershed and basal ganglia/thalamus patterns of brain injury. If watershed injury follows relatively prolonged and milder insults and basal nuclei injury follows more abrupt severe insults, we hypothesized that the watershed pattern would be more strongly associated with long-standing antenatal risk factors, whereas the basal ganglia/thalamus pattern of injury would be more strongly associated with acute intrapartum risk factors.

The American College of Obstetricians and Gynecologists task force on neonatal encephalopathy and cerebral palsy concluded that an acute intrapartum event could only result in cerebral palsy of the spastic quadriplegic or dyskinetic type and could not account for cognitive deficits alone.[14] Our clinical experience and data suggest that the outcome of neonatal encephalopathy is not homogeneous and may include cognitive deficits in the absence of cerebral palsy.[15] The second aim of this study was to discriminate the specific deficits associated with each of the patterns of brain injury on neonatal MRI. This is important to target appropriate rehabilitative services to newborns.

METHODS

Two cohorts of term newborns were studied at the University of California San Francisco (UCSF) and at Loma Linda University Children's Hospital (LLUCH). The Committees on Human Research at each site approved the protocol.

The UCSF cohort consists of 121 newborns studied with MRI (1994-2000), all of whom had neonatal encephalopathy or a marker of perinatal depression: umbilical artery pH <7.1, umbilical artery base deficit >10, or a 5-minute Apgar score ≤5. These inclusion criteria were chosen to include the entire range of neonatal encephalopathy and neurodevelopmental outcomes, from normal to severe impairment. Newborns were excluded when their gestational age was <36 weeks or there were suspected or confirmed congenital malformations, inborn errors of metabolism, or congenital infections on the basis of clinical examinations and laboratory studies. Infants with transient metabolic derangements such as hypoglycemia were not excluded from the study. The LLUCH cohort of 52 newborns was derived from newborns examined with MRI during the same period as part of a larger study of neonatal brain injuries.[16] The UCSF inclusion and exclusion criteria were applied at LLUCH.

MRI

MRI was acquired comparably at both centers at a median of 6 days of life (range, 1-24 days) when newborns were stable for transport to the MR scanner and imaging time was available. At UCSF, MRI used a circularly polarized head coil on a 1.5Tesla Signa EchoSpeed system (GE Medical Systems) and included 4 mm (1 mm "gap") sagittal spin-echo (SE; 500/11/2 [TR/TE/excitations]), 4 mm (1 mm "gap") axial SE (500/11/2) images, and 4 mm (2 mm "gap") axial SE (3000/60,120/1) images through the entire brain. At LLUCH, MRI used a circularly polarized head coil on a 1.5T Magnetom SP4000 (Siemens Medical Systems) and included 5 mm sagittal SE (550/22/4), 5 mm axial triple SE imaging (3000 ms/22,60,120 ms/1), and 5 mm coronal SE (1800/22,90 and 90/ half Fourier acquisition).

At each institution, a neuroradiologist who was blinded to the subjects' clinical condition reviewed the MRI scans. With a previously validated system for acute and subacute signal abnormalities, the severity of injury in the watershed region was scored from 0 to 5, and in the basal ganglia/thalamus region, the severity of injury was scored from 0 to 4.[11] Both neuroradiologists independently interpreted 10 MRI studies with a Kappa of 0.85, suggesting good reliability of the scoring at both sites. The intraobserver reliability of these scores was reported previously in this cohort as ranging from a Kappa of 0.85 to 1.0.[11]

Newborns were grouped into 3 patterns of injury on the basis of the predominant site of injury on MRI: normal, watershed predominant, and basal ganglia/thalamus predominant. Newborns had the watershed pattern when the watershed scores were higher than the basal ganglia/thalamus scores. Newborns were classified as basal ganglia/thalamus when the basal ganglia/thalamus scores were as high as or higher than the watershed scores. The basal ganglia/thalamus pattern included newborns with total brain injury (maximum basal ganglia/thalamus score and watershed score), because extensive deep gray nuclei injury was often accompanied by cerebral cortical injury that was not limited to a watershed pattern. In previous work, isolated hyperintensity of the lateral thalamus on T1 weighted images was found to be a normal variant and was classified with the normal pattern.[11]

Neonatal Condition

Prenatal, perinatal, and postnatal variables thought *a priori* to be associated with neonatal brain injury were collected prospectively at UCSF. Two investigators who were blinded to the MRI and outcomes then retrospectively reviewed the obstetric and neonatal charts at LLUCH for these data. Maternal substance use was defined as drug, ethanol, or cigarette use because of the high frequency of concurrent recreational drug and ethanol use in mothers who smoke cigarettes during pregnancy.[17] Furthermore, previous work has demonstrated that, in infants exposed to cocaine *in utero*, maternal cigarette smoking was predictive of an abnormal neurologic examination, whereas the cocaine exposure itself was not.[17] A maternal inflammatory condition

was considered to be present when a treating physician diagnosed chorioamnionitis or endometritis on the basis of clinical symptoms or when antepartum or peripartum maternal fever or infection were documented. Intra-uterine growth restriction (IUGR) was defined as a birth weight <2 SDs below the mean for the gestational age at birth. Maternal thyroid studies were not systematically collected. Caesarean section was classified as emergent or elective on the basis of the clinical indication. Complicated vaginal delivery was defined as arrest of descent and failed vacuum delivery. Fetal distress included fetal bradycardia and variable or late decelerations documented by the treating physician. Placental/cord insults included abruptio placentae, vasa previa, cord prolapse, nuchal cord, cord rupture, or uterine rupture. The amount of resuscitation at birth was summarized by using a resuscitation score: 1 = no intervention, 2 = blow-by oxygen, 3 = endotracheal suctioning, 4 = bag-mask positive pressure ventilation, 5 = endotracheal intubation with positive pressure ventilation, and 6 = endotracheal intubation with ventilation and medication (sodium bicarbonate with or without epinephrine). The severity of neonatal seizures was graded from [0] no documented seizure to [10] severe seizures by using a previously developed score measuring seizure frequency and onset, electroencephalogram abnormalities, and the number of anticonvulsant medications used.[18] The severity of neonatal encephalopathy was graded from 0 (no encephalopathy) to 6 (severe encephalopathy) by using a validated score on the basis of alertness, feeding, tone, respiratory status, reflexes, and seizure activity.[19]

Developmental Examinations

The UCSF cohort was followed prospectively to 12- and 30-months of age. At both assessments, cognitive development was assessed by the Mental Development Index (MDI) of the Bayley Scales of Infant Development II.[20] At each assessment, a pediatric neurologist who was blinded to the neonatal course and imaging results performed a standardized neurological examination. The neurologist scored neuromotor outcome with a validated score: 0 = normal, 1 = abnormal tone *or* reflexes, 2 = abnormal tone *and* reflexes, 3 = decreased power in addition to tone or reflex abnormality (functional deficit of power), 4 = cranial nerve involvement with motor abnormality, and 5 = spastic quadraparesis.[21] The LLUCH cohort was not prospectively observed for neurodevelopmental outcomes.

Data Analysis

Statistical analysis was performed with Stata software version 8 (Stata Corporation, College Station, Texas). Variables were compared across the 3 patterns of injury with the Kruskal-Wallis tests for continuous variables and the Fisher exact tests for categorical variables. A P value $\leq .05$ was considered to be significant. Univariate comparisons of antenatal and perinatal variables with the MRI scores were made with linear regression. Variables associated with MRI scores on univariate analysis with a P value <.2 were included in multivariate models. Because of the categorical nature of the outcome variable, we investigated non-normality of the outcome variables using bootstrap modeling (5000 repetitions). Because these variables modeled similarly with and without bootstrap modeling, we present results without the bootstrap methods. The Spearman rank correlation (ρ) was used to compare MRI scores with scores for resuscitation, seizures, and encephalopathy.

RESULTS

Patterns of Injury

MRI findings consistent with acute or subacute brain injury were common in this cohort, particularly the watershed predominant pattern. At UCSF, 63 newborns had the watershed pattern (52%), 26 had the basal ganglia/thalamus pattern (22%), and 32 had normal MRI results (26%). At LLUCH, 15 newborns had the watershed pattern (29%), 18 had the basal ganglia/thalamus pattern (35%) and 19 had normal MRI results (37%). The predominant region of injury was often accompanied by lesser damage to the other region. Twenty-four newborns with the watershed predominant pattern (31%) had some deep gray nuclei injury. Twenty newborns with the basal ganglia/thalamus predominant pattern (45%) had total brain injury, and another 9 newborns (20%) had some watershed injury.

The day of life for MRI did not differ by the pattern of injury ($P = .8$). Only 11 newborns underwent their MRI study in the first 2 days of life (6.3%), including 2 newborns who underwent an MRI on their first day of life. Of the 11 newborns who underwent early imaging, 2 had normal scan results, 4 had the watershed predominant pattern, and 5 had the basal ganglia/thalamus predominant pattern. The basal ganglia/thalamus scores were significantly higher in the group studied in the first 2 days (median, 2) relative to the remainder of the cohort (median, 0; $P = .02$), whereas the watershed scores did not differ significantly ($P = .1$).

Most antenatal and perinatal variables associated with neonatal encephalopathy were similar across the 3 MRI patterns, except that emergent Caesarian section delivery was most common in the basal ganglia/thalamus predominant pattern (Table I). Although other prenatal and perinatal conditions were common in the cohort, in particular maternal inflammatory condition and fetal distress, these factors were similar in newborns with normal MRI scan results and newborns with brain injury. The antenatal and perinatal variables measured were similar in newborns with total brain injury as compared with the other newborns with the basal ganglia/thalamus predominant pattern (all $P > .2$).

Newborns with the watershed pattern had lower birthweights, but did not differ in gestational age, head circumference, or body length. The clinical presentation of the normal and watershed patterns was similar, whereas newborns with the basal ganglia/thalamus pattern had more severe clinical signs. Only 2 newborns in the entire cohort did not require resuscitation at birth (1 with normal MRI results and

Table I. Clinical characteristics by magnetic resonance imaging pattern

	Normal	Watershed predominant	Basal ganglia/thalamus predominant	*P* value
Number	51	78	44	
Male sex	27 (54%)	51 (65%)	24 (56%)	
Antenatal				
Substance use	8 (16%)	11 (14%)	11 (25%)	.3
Gestational diabetes	4 (8%)	9 (12%)	6 (14%)	.6
Preeclampsia	2 (4%)	6 (8%)	3 (7%)	.7
Prolonged rupture of membranes	6 (12%)	16 (21%)	8 (19%)	.4
Intra-uterine growth restriction	0	4 (5%)	2 (5%)	.3
Maternal inflammatory state	19 (37%)	35 (45%)	12 (28%)	.2
Perinatal				
Fetal distress	33 (66%)	51 (66%)	23 (56%)	.5
Complicated vaginal delivery	8 (16%)	17 (18%)	10 (23%)	.7
Caesarian section delivery	24 (47%)	42 (54%)	22 (50%)	.7
Emergent Caesarian section	18 (75%)	29 (69%)	22 (100%)	.006
Placenta/cord insult	16 (31%)	21 (27%)	15 (34%)	.7
Postnatal				
Gestational age (weeks)	40 (36-42)	40 (36-42)	40 (36-42)	.5
Birthweight (kg)	3.5 (2.2-5.2)	3.2 (2.0-5.4)	3.4 (1.6-4.9)	.01
Head circumference (cm)	35 (32-38)	35 (31-44)	35 (29-39)	.4
Length (cm)	51 (38-56)	51 (41-59)	51 (44-56)	.9
Resuscitation score (1-6)	4 (1-6)	4 (2-6)	5 (1-6)	.001
Five-minute Apgar score	6 (1-9)	5 (1-9)	4 (0-9)	.0005
Meconium aspiration	14 (28%)	17 (22%)	10 (23%)	.8
Encephalopathy score (0-6)	2 (0-6)	3 (1-6)	5 (1-6)	.0001
Clinical seizures (yes/no)	14 (28%)	34 (44%)	36 (82%)	.0001
Seizure score (0-10)	0 (0-6)	0 (0-8)	4.5 (0-9)	.0001

Data is presented as median (range) or number (%). *P* values refer to comparisons across the 3 groups.

1 with the basal ganglia/thalamus pattern); each of these newborns had clinical seizures at presentation. Newborns with the basal ganglia/thalamus pattern had at birth the most intensive need for resuscitation and the most severe clinical encephalopathy and seizures. Among newborns with the basal ganglia/thalamus pattern, newborns with total brain injury had more severe clinical seizures, but did not have a significantly different need for resuscitation ($P = .7$), 5-minute Apgar score ($P = 1.0$), or severity of encephalopathy ($P = .06$). The median seizure score in newborns with total brain injury was 5, whereas that of the other newborns with the basal ganglia/thalamus pattern was 3 ($P = .01$).

Antenatal and Perinatal Predictors of the Severity of Brain Injury in Each Region

Antenatal and perinatal predictors of the severity of brain injury in each region were determined. Birthweight was the only measured variable associated with the watershed score on univariate analysis (Table II). Maternal substance use was associated with the basal ganglia/thalamus region score on univariate analysis. In a multivariate model adjusting for maternal substance use, maternal inflammatory state, and prolonged rupture of membranes, newborns of lower birthweight had higher watershed scores (Table II). Adjusting for these factors, newborns with maternal inflammatory conditions had lower basal ganglia/thalamus scores compared with newborns without a maternal inflammatory condition.

Severity of Brain Injury in Each Region and the Neurological Syndrome

The basal ganglia/thalamus score was significantly correlated with the intensity of resuscitation at birth ($\rho = 0.32$; $P < .0001$), the severity of encephalopathy ($\rho = 0.42$; $P < .0001$), and the severity of seizures ($\rho = 0.41$; $P < .0001$). In contrast, the watershed score was less strongly correlated with the intensity of resuscitation at birth ($\rho = 0.21$; $P = .006$), the severity of encephalopathy ($\rho = 0.32$; $P < .0001$), and the severity of seizures ($\rho = 0.29$; $P = .0001$).

Neurodevelopmental Outcome

Of the UCSF cohort, 89 infants (74%) were observed to 30 months of age. The basal ganglia/thalamus predominant pattern was associated with more impaired cognitive and

Table II. Antenatal and perinatal predictors of the severity of brain injury measured by the magnetic resonance imaging scores

Predictor	Change in watershed score	95% CI	*P* value	Change in basal ganglia/ thalamus score	95% CI	*P* value
Univariate analysis						
Birthweight (per 100-gram decrease)	0.06	0.02-0.11	.006	0.02	−0.01-0.06	.17
Maternal substance use	0.54	−0.24-1.32	.18	0.70	0.1-1.3	.02
Maternal inflammatory state	−0.27	−0.88-0.34	.40	−0.38	−0.85-0.09	.11
Prolonged rupture of membranes	0.71	−0.07-1.48	.07	0.30	−0.30-0.91	.30
Diabetes mellitus	−0.57	−1.51-0.38	.24	−0.02	−0.76-0.71	.90
Pre-eclampsia	0.73	−0.48-1.94	.24	0.33	−0.61-1.28	.50
Fetal distress	0.11	−0.26-0.48	.60	−0.06	−0.35-0.22	.70
Caesarean section	0.21	−0.8-0.38	.50	−0.01	−0.48-0.48	1.0
Multivariate analysis						
Birthweight (per 100 gram decrease)	0.06	0.01-0.10	.01	0.02	−0.01-0.05	.26
Maternal substance use	0.30	−0.49-1.08	.45	0.60	−0.01-1.21	.06
Maternal inflammatory state	−0.42	−1.02-0.18	.17	−0.48	−0.95-0.01	.05
Prolonged rupture of membranes	0.63	−0.14-1.41	.11	0.25	−0.36-0.87	.42

Table III. Neurodevelopmental outcome of newborns observed to 30 months of age by magnetic resonance imaging pattern

	Normal	Watershed predominant	Basal ganglia/ thalamus predominant	*P* value
Number	**20**	**48**	**21**	
Died *	0	3	5	.01
30-month MDI	101 (77-121)	84 (50-116)	62.5 (50-104)	.0007
12-month MDI	93 (53-109)	91.5 (50-120)	58 (50-109)	.006
30-month NMS	0 (0-2)	1 (0-5)	5 (0-5)	.0001
12-month NMS	0 (0-3)	1 (0-5)	5 (0-5)	.0008
30-month head circumference	50 (47-57)	50 (41-53)	47 (39-51)	.005

Data is presented as median (range) or number (%). *P* values refer to comparisons across the 3 groups.
NMS=Neuromotor score.
*All infants died before 12 months of age.

motor outcomes at 30 months of age, with the watershed predominant pattern having an intermediate outcome (Table III; Figure). None of the newborns with normal MRI results had an MDI score <70 (2 SD below the mean) or functional motor deficits (neuromotor score ≥3). Eight newborns with the basal ganglia/thalamus pattern (50% of survivors) had an MDI score <70, and 9 newborns with the basal ganglia/thalamus (56% of survivors) had functional motor deficits (spastic quadraparesis in all). In newborns with the basal ganglia/thalamus predominant pattern, the median MDI and neuromotor scores were not significantly different in those with isolated deep gray nuclei injury compared with those with deep gray nuclei and watershed injury ($P > .1$). Similarly, the median MDI and neuromotor scores were not significantly different in newborns with total brain injury compared with the remainder of the basal ganglia/thalamus predominant group ($P > .1$). Eight newborns with the watershed predominant pattern (18% of survivors) had an MDI score <70, and 5 newborns with the watershed predominant pattern (11% of survivors) had functional motor deficits (spastic quadraparesis in 3, spastic hemiparesis in 1, and spastic triparesis in 1). Three of the 5 newborns with a watershed pattern and functional motor deficits had isolated watershed injury without deep gray nuclei abnormalities. Of the 32 newborns lost to follow-up at 30 months of age, 20 were examined at 12 months (5 with normal MRI results [16%], 10 with the watershed predominant pattern [16%], and 5 with the basal ganglia/thalamus predominant pattern [19%]); the outcomes at 12 months of this group were similar to that of the cohort observed to 30 months. In the infants evaluated at both times, the MDI of infants with the watershed pattern was significantly lower at 30 months than at 12 months ($P = .0007$), but did not differ with time in the infants with normal MRI results ($P = .5$) or basal ganglia/thalamus

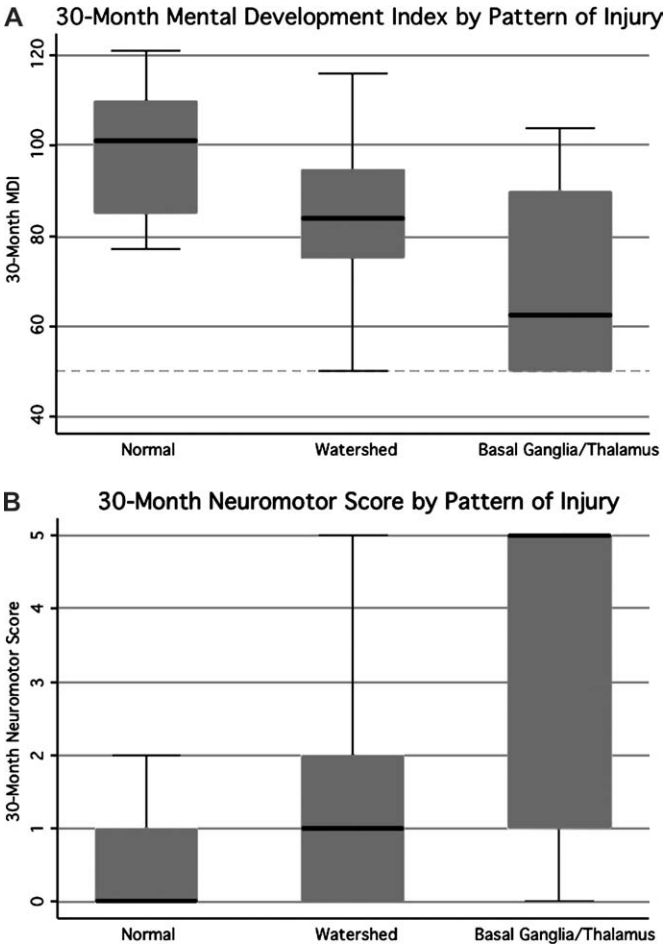

Figure. (A) Box plot of the 30-month Mental Development Index by the pattern of injury. MDI was lowest in the infants with the basal ganglia/thalamus predominant pattern, with intermediate scores in infants with the watershed pattern (P = .0007). The thick line represents the median, with the 25th and 75th percentiles as the lower and upper limits of the box; whiskers indicate the 5th and 95th percentiles. The dashed line indicates the lowest attainable MDI score. (B) Box plot of the 30-month neuromotor score by the pattern of injury. Neuromotor impairments were most severe in the infants with the basal ganglia/thalamus pattern (P = .0001).

patterns (P = 1.0). The neuromotor scores did not change significantly from 12 to 30 months in any group (all P >.3)

DISCUSSION

In this cohort representative of the spectrum of severity of term neonatal encephalopathy, the watershed predominant injury pattern was most common, seen in 45% of the cohort, and was often accompanied by less severe basal ganglia/thalamus injury. The basal ganglia/thalamus predominant pattern was less common, seen in 25% of the cohort, and was frequently accompanied by more diffuse cortical injury. These patterns are consistent with the regional vulnerability of the term neonatal brain.[1,11-13,22]

In an earlier study of risk factors for neonatal encephalopathy, 69% of cases had antepartum risk factors, 24% had both antepartum and intrapartum risks, and 5% only had intrapartum risks.[6,7] In our cohort, although Caesarian section delivery was common in all 3 MRI patterns, emergent Caesarian delivery was significantly more common in the basal ganglia/thalamus pattern. Although many risk factors are clearly prenatal,[7] recent evidence from prospective cohorts of neonatal encephalopathy using MRI demonstrate that the brain injury actually happens close to the time of birth.[8] The MRI findings in our cohort were also consistent with recent rather than chronic brain injury, and the antenatal conditions measured were remarkably similar in newborns with normal and abnormal MRI scan results. These observations highlight the potential of interventions to ameliorate brain injury in the newborn.

The association of lower birthweight with the severity of watershed injury supports our hypothesis that antenatal risk factors are more strongly associated with this pattern of injury. However, lower birthweight may be a marker for multiple risk factors of neonatal encephalopathy.[23] We were also unable to attribute more severe brain injury to a maternal inflammatory condition. The failure to identify the specific antenatal risk factors associated with the pattern and severity of brain injury suggests that either we did not measure the relevant antenatal risk factors or that better antenatal markers need to be identified.

The intensity of resuscitation, the severity of encephalopathy, and the severity of seizures were associated more strongly with the basal ganglia/thalamus predominant pattern than with the watershed pattern. This is consistent with previous observations relating deep gray nuclei injury with profound asphyxia and severe encephalopathy.[13] The surprising observation of more severe seizures in newborns with the basal ganglia/thalamus pattern as compared with the watershed pattern may relate to an overall increased severity of injury, including the cerebral cortex. This is supported by the observation that seizures were most severe in newborns with total brain injury. The dissociation of antenatal risk factors from the severity of the clinical presentation supports the hypothesis that the etiology of brain injury in neonatal encephalopathy is distinct from these antenatal risk factors.

The MRI scoring system applied in this cohort was developed to better evaluate the severity of neonatal brain injury, particularly milder abnormalities, and discriminates abnormal neurodevelopmental outcomes at 12 months of age.[11] This is consistent with other studies demonstrating that the severity of brain lesions on MRI in the term newborn is predictive of neurodevelopmental outcome.[24-26] Although it is accepted that the risk of an abnormal neurodevelopmental outcome increases with the severity of the injury, the pattern of injury also conveys important prognostic information. The MRI patterns of injury were associated with impairments in different developmental domains. Similar to previous observations with computed tomography, the basal ganglia/thalamus predominant pattern was associated with severely impaired motor and cognitive outcomes at 30 months of age.[27] This is also consistent with the seminal observation that abnormal signal intensity in the posterior limb of the internal

capsule on MRI, a structure involved in the basal ganglia/thalamus predominant pattern, is an accurate predictor of neurodevelopmental impairment in term neonatal encephalopathy.[28] Because of the frequent occurrence of cerebral watershed injury with the basal ganglia/thalamus predominant pattern, cognitive deficits cannot be directly attributed to damage to the deep gray nuclei themselves. In contrast, the watershed pattern had predominantly cognitive impairments at 30 months that were not detected at 12 months of age. Cognitive deficits in this group often occurred without functional motor deficits. This highlights that abnormal outcome after neonatal encephalopathy is not limited to cerebral palsy and often requires follow-up beyond 12 months of age to be detected.[15]

A limitation of this study is that not all newborns underwent imaging at a uniform time after brain injury, so the extent of damage, particularly in the basal nuclei, may have been underestimated in some newborns.[29,30] However, the basal ganglia/thalamus scores were significantly higher in the group studied in the first 2 days compared with the remainder of the cohort. Althouth some injury in this group may have been underestimated, it is less likely that these newborns were inadvertently classified as normal or as watershed injury. Because of our sample size, we *a priori* included newborns with total brain injury with the basal ganglia/thalamus pattern. This was done because extensive deep gray nuclei injury was often accompanied by cerebral cortical injury not limited to a watershed pattern. We found that, besides more severe clinical seizures, the clinical presentation of newborns with total brain injury was similar to that of other newborns with the basal ganglia/thalamus pattern. Because of the broad inclusion criteria for this cohort, it is not surprising that a substantial number of the newborns had normal MRI study results. Although the cohort was recruited from 2 specialized care centers, the range of normal and abnormal MRI study results suggests that the entire severity spectrum of neonatal encephalopathy is represented. Incomplete follow-up at 30-months may have exaggerated the difference in cognitive outcome between the patterns because cognitive deficits in the watershed groups were most evident at 30 months. However, newborns "lost to follow-up" were evenly distributed across the MRI patterns.

Because newborns with more severe encephalopathy are more likely to be identified for research studies in the intensive care nursery and these newborns are more likely to have the basal ganglia/thalamus injury pattern, it is possible that prospective MRI studies of neonatal encephalopathy will over-represent perinatally acquired injury as compared with population-based epidemiological surveys. Because population-based retrospective studies identify a preponderance of antenatal risk factors and smaller prospective cohort studies identify the perinatal occurrence of brain injury,[8] our results indicate the pressing need to establish the mechanistic link between prenatal risk factors and etiology of brain injury. This is critical to the prevention of acquired neonatal brain injury and may be achieved with the development and application of more accurate in-utero measures of brain injury, such as fetal MRI.[31] Until MRI is routinely applied to study neonatal encephalopathy, it is likely that discrepancies across study designs will be related to the heterogeneity of the brain injury.

In conclusion, the pattern of brain injury in neonatal encephalopathy can distinguish associated risk factors and clinical presentation and can identify those newborns who are at a higher risk for abnormal outcomes. This is important when considering which newborns should be targeted for emerging strategies to protect the brain after injury. Knowing the pattern of brain injury can also help parents and physicians care for the survivors of neonatal encephalopathy by identifying newborns who may benefit from rehabilitative services, in particular, the developmental domains requiring specific attention.

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