ORIGINAL ARTICLE

Neonatal MRI to Predict Neurodevelopmental Outcomes in Preterm Infants

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ABSTRACT

BACKGROUND

Very preterm infants are at high risk for adverse neurodevelopmental outcomes. Magnetic resonance imaging (MRI) has been proposed as a means of predicting neurodevelopmental outcomes in this population.

METHODS

We studied 167 very preterm infants (gestational age at birth, 30 weeks or less) to assess the associations between qualitatively defined white-matter and gray-matter abnormalities on MRI at term equivalent (gestational age of 40 weeks) and the risks of severe cognitive delay, severe psychomotor delay, cerebral palsy, and neurosensory (hearing or visual) impairment at 2 years of age (corrected for prematurity).

RESULTS

At two years of age, 17 percent of infants had severe cognitive delay, 10 percent had severe psychomotor delay, 10 percent had cerebral palsy, and 11 percent had neurosensory impairment. Moderate-to-severe cerebral white-matter abnormalities present in 21 percent of infants at term equivalent were predictive of the following adverse outcomes at two years of age: cognitive delay (odds ratio, 3.6; 95 percent confidence interval, 1.5 to 8.7), motor delay (odds ratio, 10.3; 95 percent confidence interval, 3.5 to 30.8), cerebral palsy (odds ratio, 9.6; 95 percent confidence interval, 3.2 to 28.3), and neurosensory impairment (odds ratio, 4.2; 95 percent confidence interval, 1.6 to 11.3). Gray-matter abnormalities (present in 49 percent of infants) were also associated, but less strongly, with cognitive delay, motor delay, and cerebral palsy. Moderate-to-severe white-matter abnormalities on MRI were significant predictors of severe motor delay and cerebral palsy after adjustment for other measures during the neonatal period, including findings on cranial ultrasonography.

CONCLUSIONS

Abnormal findings on MRI at term equivalent in very preterm infants strongly predict adverse neurodevelopmental outcomes at two years of age. These findings suggest a role for MRI at term equivalent in risk stratification for these infants.

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Very preterm birth has profound ramifications for public health and education worldwide. Infants born before 32 weeks of gestation now represent more than 2 percent of all live births, and their survival rates exceed 85 percent.[1] Follow-up studies have revealed high rates of neurodevelopmental disability among very preterm infants who survive, with 5 to 15 percent having cerebral palsy, severe neurosensory impairment, or both and 25 to 50 percent having cognitive, behavioral, and social difficulties that impede progress in school and require special educational support.[2-4]

A major issue confronting clinicians who work with preterm infants and their families is the identification of infants who are most at risk for subsequent neurodevelopmental disability and who may benefit from early intervention services. Several factors (including bronchopulmonary dysplasia, sepsis, surgery, the postnatal use of corticosteroids, and evidence on ultrasonography of intraventricular hemorrhage and periventricular leukomalacia) are recognized to increase neurodevelopmental risks. However, risk indexes for neonates that incorporate these factors have shown limited effectiveness in identifying infants who are at high risk for poor neurodevelopmental outcomes.[5,6]

One tool that may assist early prognostic evaluations of the preterm infant is magnetic resonance imaging (MRI) during the neonatal period. Currently, the most widely used imaging technique is cranial ultrasonography. This method is useful for the detection of intraventricular hemorrhage and cystic periventricular leukomalacia, but it has poor sensitivity for diffuse white-matter abnormalities detected by MRI.[7,8] Neonatal MRI studies have revealed that the majority of very preterm infants have white-matter abnormalities, including signal abnormalities, loss of volume, cystic abnormality, enlarged ventricles, thinning of the corpus callosum, and delayed myelination.[9-11] Gray-matter abnormalities, including decreased cerebral gray-matter volume and delayed cortical gyration, have also been reported in very preterm infants at term equivalent (gestational age of 40 weeks) with the use of neuroanatomical MRI techniques.[12,13] In smaller studies of preterm infants, such abnormalities have been found to be correlated with impaired working memory[14] and early neurodevelopmental delay.[15,16]

We performed a prospective longitudinal study of very preterm infants studied from birth to two years of age, to examine associations between qualitatively defined cerebral white-matter and gray-matter abnormalities on MRI at term equivalent and neurodevelopmental outcomes at two years of age. We also compared the predictive value of MRI findings with that of findings derived from other assessments during the neonatal period, such as cranial ultrasonography, that are currently used to predict neurodevelopmental risk.

METHODS

SUBJECTS

The study population included 167 very preterm infants (born at 30 weeks of gestation or less) at either Christchurch Women's Hospital, New Zealand, between November 1998 and December 2000 (81 children) or at the Royal Women's Hospital, Melbourne, Australia, between July 2001 and May 2002 (86 children). Fifty infants, all in the Christchurch cohort, received some early intervention services. Referral for these services was based on ultrasonographic findings, gestational age at birth, clinical history, and assessment of physical therapy; MRI results were not used to make referral decisions, nor were they made available to early intervention providers.

In Christchurch, 92 percent of all eligible infants were enrolled. In Melbourne, 95 percent of eligible infants were approached, with a recruitment rate of 70 percent. Nonparticipation was primarily due to family circumstances or involvement in other studies. There were no significant ($P<0.05$) differences in perinatal characteristics between infants who were recruited and those who were not recruited. At two years of age corrected for prematurity, sample retention was high, with 95 percent of Christchurch children and 98 percent of Melbourne children being assessed. Written informed consent was obtained from all parents or guardians, and the studies were approved by hospital or regional ethics committees, or both. Table 1 lists the characteristics of the infants at each study center.

MRI

At term equivalent, all infants underwent MRI. Prior to undergoing MRI, each infant was fed, wrapped, and placed, unsedated, in a Vac Fix beanbag designed to keep the infant still and supported in the scanner. We performed MRI using a 1.5-tesla General Electric Signa System (GE Medical Systems) with previously documented sequenc-

es.[10] All scans were scored independently by one of the authors and by a pediatric neuroradiologist (Christchurch) or neonatologist (Melbourne). Raters were unaware of the infants' perinatal history and ultrasonographic findings. We used a standardized scoring system, developed in this study and consisting of eight 3-point scales (Fig. 1).[10,17] White-matter abnormality was graded according to five scales, which assessed the nature and extent of white-matter signal abnormality, the loss in the volume of periventricular white matter, and the extent of any cystic abnormalities, ventricular dilatation, or the thinning of the corpus callosum. Gray-matter abnormality was graded according to three scales, which assessed the extent of gray-matter signal abnormality, the quality of gyral maturation, and the size of the subarachnoid space (see Supplementary Appendix 1, available with the full text of this article at www.nejm.org). Composite white-matter scores and composite gray-matter scores were created and used to categorize infants according to the extent of their cerebral abnormalities.[10,17] The categories of white-matter abnormality were none (a score of 5 to 6), mild (a score of 7 to 9), moderate (a score of 10 to 12), and severe (a score of 13 to 15). Gray matter was categorized as normal (a score of 3 to 5) or abnormal (a score of 6 to 9). Interrater agreement for the category assignments was 96 percent.

Table 1. Neonatal Clinical Characteristics of the Infants.*

Characteristic	Christchurch Cohort (N=81)	Melbourne Cohort (N=86)
Birth weight (g)	1014±297	948±220
Gestational age at birth (wk)	27.3±2.0	27.1±1.7
Male sex (%)	51	44
Singleton (%)	69	57
Small size for gestational age (%)†	6	7
CRIB score‡	3.4±3.0	3.3±3.2
Antenatal corticosteroid use (%)	83	87
Postnatal corticosteroid (dexamethasone) use (%)	7	6
Dexamethasone dose (mg/kg of body weight)	0.14±0.57	0.09±0.38
Oxygen therapy at 36 wk (%)	38	33
Patent ductus arteriosus (%)	52	51
Any intraventricular hemorrhage (%)	20	15
Grade III or IV intraventricular hemorrhage (%)	6	5
Cystic periventricular leukomalacia (%)	3	2

* Plus–minus values are means ±SD. There were no significant differences between groups.
† Small size for gestational age was defined as a birth weight more than 2 SD below the mean for gestational age and sex.
‡ The Critical Risk Index for Babies (CRIB) score is a measure of clinical risk and the severity of illness at birth. Scores can range from 1 to 10, with higher scores indicating higher risk.

CRANIAL ULTRASONOGRAPHY

We also performed cranial ultrasonography through the anterior fontanelle, with a 7.5- or 8.5-MHz transducer (Acuson-Siemens), according to a standardized protocol.[18] We acquired images within the first 48 hours of life, at five to seven days of age, and again at four to six weeks of age. If an abnormality was detected, more frequent ultrasonography was performed as clinically indicated. The scans were assessed for the presence and extent of white-matter echolucency or cystic periventricular leukomalacia and the highest grade of intraventricular hemorrhage.

NEURODEVELOPMENTAL OUTCOMES AT TWO YEARS OF AGE

Within two weeks either before or after their second birthday (corrected for prematurity), children underwent a comprehensive neurodevelopmental assessment conducted by examiners who were unaware of the MRI findings and the perinatal course. The examiners assessed the cognitive and psychomotor development using the Bayley Scales of Infant Development (BSID-II)[19]: the Mental Development Index assesses environmental responsiveness and sensory and perceptual abilities, memory, learning, and early language and communication abilities; the Psychomotor Development Index assesses both gross and fine motor skills. The six children who had standard scores below 50 were assigned a score of 45, and the two children who were unable to be tested owing to impaired perceptual or cognitive ability were assigned a score of 40. A mild delay in development was defined by a score that was more than 1 SD below the normative mean, and a severe delay was defined by a score that was more than 2 SD below the normative mean.

Each child also underwent a standardized pediatric neurologic evaluation to assess the quality of their motor skills, coordination, gait, and behavior.[20] Cerebral palsy was diagnosed with the use of standard criteria, including the location or body parts impaired (e.g., hemiplegia or diplegia), the degree of impairment of muscle tone and reflexes, and the effects of the condition on ambulation.[21] Finally, evaluations of vision and hearing

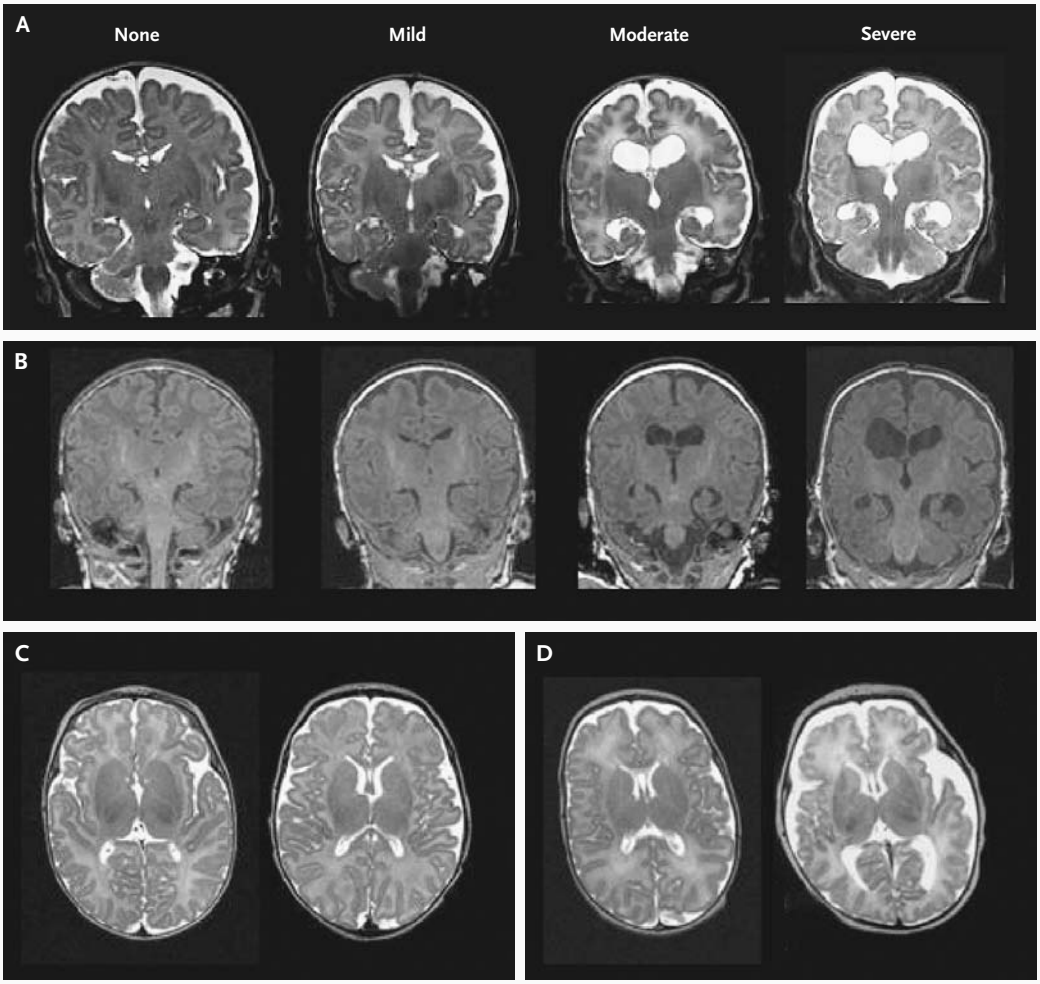

Figure 1. Representative MRI Scans of Children in the Study.

Representative coronal T_2-weighted MRI (Panel A) and T_1-weighted MRI (Panel B) show the four grades of white-matter abnormality (none, mild, moderate, or severe). With increasing grade of white-matter abnormality, there was increasing ventricular size, decreasing white-matter volume, increasing intensity of white-matter signal on T_2-weighted imaging, and decreasing myelination in the posterior limb of the internal capsule. Also shown is axial T_2-weighted MRI at the level of the deep nuclear gray matter of infants with normal gray-matter scores (Panel C) and abnormal gray-matter scores (Panel D), demonstrating the simpler gyral patterns observed among infants with gray-matter abnormalities.

were completed by an ophthalmologist and an audiologist, respectively, or were recorded from recent hospital evaluations. A visual defect was defined by a requirement for corrective lenses, surgery, or both for strabismus or blindness. A hearing defect was defined as a sensorineural hearing loss of more than 30 db.

STATISTICAL ANALYSIS

The associations between white-matter and gray-matter abnormalities on MRI and adverse neurodevelopmental outcomes at two years of age were examined with the use of either one-way analysis of variance for continuously distributed variables or the Mantel–Haenszel chi-square test for dichotomous variables, with tests for linear trend. Odds ratios (and 95 percent confidence intervals) from chi-square analyses were reported as measures of the strength of associations between early risk factors and subsequent neurodevelopmental outcomes. Logistic-regression models were then used to assess the associations between the MRI measures and subsequent neurodevelopmental abnormalities, after adjusting for other factors, including

abnormalities on cranial ultrasonography (grade III or IV intraventricular hemorrhage, cystic periventricular leukomalacia, or both), a gestational age at birth of less than 28 weeks, intrauterine growth restriction, sex, the use of oxygen therapy at 36 weeks, patent ductus arteriosus, multiple birth, and postnatal use of corticosteroids. Finally, we compared the diagnostic accuracy of the MRI and ultrasonographic measures by computing the sensitivity and specificity indexes (and the 95 percent confidence intervals) from chi-square analysis tables. A P value of less than 0.05 was used to indicate statistical significance.

RESULTS

On MRI at term equivalent, 47 infants (28 percent) had no white-matter abnormalities, whereas 85 infants (51 percent) had mild white-matter abnormalities, 29 (17 percent) had moderate white-matter abnormalities, and 6 (4 percent) had severe white-matter abnormalities. In addition, 82 infants (49 percent) had gray-matter abnormalities. The severity of white-matter abnormalities was highly correlated with the presence of gray-matter abnormalities ($r=0.62$, $P<0.001$), with gray-matter abnormalities also being present in 43 of the 85 children with mild white-matter abnormalities (51 percent) and 34 of the 35 children with moderate or severe white-matter abnormalities (97 percent).

At two years of age, 164 children were assessed with the BSID-II; 1 child who was blind, and 2 children for whom only some data were available, were excluded. On the Mental Development Index, 87 (53 percent) had scores within 1 SD of the normalized mean (83 children) or more than 1 SD above the normalized mean (4 children), signifying above-average cognitive development. In addition, 50 children (30 percent) had a mild cognitive delay, and 27 (17 percent) had a severe cognitive delay. On the Psychomotor Development Index, 103 of the 164 children tested (63 percent) scored in the normal range (102 children) or the accelerated range (1 child), 44 children (27 percent) had mild psychomotor delay, and 17 (10 percent) had severe psychomotor delay. Of all 167 children, 17 children (10 percent) met the criteria for cerebral palsy (7 had mild, 4 moderate, and 6 severe cerebral palsy), 9 (5 percent) had a hearing defect (3 children had hearing aids), and 12 (7 percent) had a visual defect (1 child was blind). Among those with cerebral palsy, nine children showed severe psychomotor delay.

With the exception of a higher rate of severe psychomotor delay for the children in the Melbourne cohort (16 percent vs. 5 percent in the Christchurch cohort; $P=0.02$), no significant differences were found between the cohorts in the mean Mental Development Index score, the mean Psychomotor Development Index score, or the mean rate of severe cognitive delay, cerebral palsy, or neurosensory disorders (see Supplementary Appendix 2). Further examination of the difference between cohorts in psychomotor delay revealed a tendency for more children to score just below the 2 SD cutoff in Melbourne than in Christchurch, despite the lack of any difference in the overall distribution of psychomotor scores across the two cohorts.

At follow-up, increasing severity of white-matter abnormalities on MRI at term equivalent was found to be associated with poorer performance on the cognitive and psychomotor scales of the BSID-II ($P<0.001$ for both scales), as well as with increased risks of severe cognitive delay ($P=0.008$), severe motor delay ($P<0.001$), cerebral palsy ($P<0.001$), and neurosensory impairment ($P=0.003$) (Table 2). Children with more severe white-matter abnormalities had a higher number of neurodevelopmental impairments than children with less severe or no abnormalities ($P<0.001$).

Preterm infants with gray-matter abnormalities at term equivalent also had poorer scores on the cognitive index ($P=0.02$) and the psychomotor index ($P=0.002$) of the BSID-II and had higher risks of severe cognitive delay ($P=0.02$), severe motor delay ($P=0.02$), and cerebral palsy ($P=0.02$) than infants without gray-matter abnormalities. The association with neurosensory impairment was not significant ($P=0.08$) (Table 3). Children with gray-matter abnormalities also had more neurodevelopmental impairments than children without gray-matter abnormalities ($P=0.004$).

A number of other risk factors during the neonatal period were also predictive of neurodevelopmental outcomes (Table 4). In addition to abnormalities on MRI, ultrasonographic evidence of grade III or IV intraventricular hemorrhage was a significant univariate predictor for severe cognitive delay, and the presence of cystic periventricular leukomalacia on cranial ultrasonography and postnatal use of corticosteroids predicted severe motor delay. The postnatal use of corticosteroids was also predictive of cerebral palsy. After adjustment for perinatal factors (including gestational age at birth of less than 28 weeks, small

Table 2. Neurodevelopmental Outcomes at a Corrected Age of Two Years.*

Outcome Measure	White-Matter Abnormality				P Value
	None (N=47)	Mild (N=85)	Moderate (N=29)	Severe (N=6)	
MDI score†	92.50±15.63	85.32±15.46	77.93±19.16	69.67±25.30	<0.001
Severe cognitive delay (%)	7‡	15	30	50	0.008
PDI score†	94.63±13.45	90.73±12.75	80.11±18.18	56.17±23.50	<0.001
Severe motor delay (%)	4	5	26	67	<0.001
Cerebral palsy (%)	2§	6	24	67	<0.001
Neurosensory impairment (%)	4	9	21	50	0.003
Any neurodevelopmental impairment (%)¶	15	26	48	67	<0.001
No. of impairments	0.22±0.47	0.40±0.71	1.15±1.20	2.33±1.97	<0.001

* Plus–minus values are means ±SD. Mental Development Index (MDI) scores ranged from 40 to 122; Psychomotor Development Index (PDI) scores ranged from 40 to 117. Higher scores indicate better test performance.
† The scores were based on 164 children, owing to the exclusion of 1 child who was blind and 2 children for whom only some data on the BSID-II were available.
‡ These three children with severe cognitive delay had family backgrounds of multiple severe psychosocial factors, including parental psychopathology, low maternal IQ, disruption of the family, and one or more placements in foster care.
§ This child with cerebral palsy had a family history of cerebral palsy.
¶ Any neurodevelopmental impairment was defined as the presence of any severe impairment at two years of age (MDI or PDI score less than 70, cerebral palsy, or neurosensory impairment).

Table 3. Cerebral Gray-Matter Abnormalities on MRI at Term Equivalent and Neurodevelopmental Outcomes at a Corrected Age of Two Years.*

Outcome Measure	Normal Gray Matter (N=85)	Abnormal Gray Matter (N=82)	P Value
MDI score	88.75±15.94	82.11±18.30	0.02
Severe cognitive delay (%)	10	24	0.02
PDI score	92.70±13.68	84.79±17.99	0.002
Severe psychomotor delay (%)	5	16	0.02
Cerebral palsy (%)	5	16	0.02
Neurosensory impairment (%)	7	16	0.08
Any neurodevelopmental impairment (%)	21	35	0.04
No. of impairments	0.33±0.59	0.76±1.17	0.004

* Plus–minus values are means ±SD. Mental Development Index (MDI) scores ranged from 40 to 122; Psychomotor Development Index (PDI) scores ranged from 40 to 117. Higher scores indicate better test performance.

size for gestational age, male sex, the need for oxygen therapy at 36 weeks, the presence of patent ductus arteriosus, multiple birth, postnatal use of corticosteroids, and abnormalities on cranial ultrasonography), the associations between moderate-to-severe white-matter abnormalities on MRI and subsequent risks of severe motor delay (odds ratio, 9.79; 95 percent confidence interval, 2.56 to 37.47) and cerebral palsy (odds ratio, 8.39; 95 percent confidence interval, 2.28 to 30.89) remained significant, whereas the association with neurosensory impairment did not (odds ratio, 3.27; 95 percent confidence interval, 0.97 to 11.01; P=0.06) (Table 4). In comparison, the ultrasonographic findings of grade III or IV intraventricular hemorrhage, periventricular leukomalacia, or both, as well as gray-matter abnormalities on MRI, were no longer significant predictors of subsequent neu-

Table 4. Associations between Perinatal and Radiologic Factors and Neurodevelopmental Outcomes at a Corrected Age of Two Years.*

Measure	No. of Infants	Severe Cognitive Delay	Severe Motor Delay	Cerebral Palsy	Neurosensory Impairment
		odds ratio (95 percent confidence interval)			
Clinical factor					
Gestational age at birth <28 wk	95	1.70 (0.72–4.06)	2.01 (0.67–5.99)	2.70 (0.84–8.65)	2.32 (0.79–6.76)
Birth weight <1000 g	87	0.97 (0.43–2.22)	1.34 (0.48–3.70)	0.61 (0.22–1.70)	1.03 (0.39–2.67)
Small size for gestational age†	10	0.53 (0.06–4.33)	0.89 (0.84–0.94)	0.93 (0.11–7.83)	0.87 (0.82–0.93)
Male sex	88	1.43 (0.62–3.31)	1.37 (0.50–3.80)	2.33 (0.79–6.96)	1.27 (0.48–3.33)
Multiple birth	60	0.54 (0.21–1.36)	0.68 (0.23–2.02)	0.68 (0.23–2.03)	0.28 (0.08–1.01)
Oxygen therapy at 36 wk	58	0.63 (0.25–1.61)	1.12 (0.38–3.25)	1.50 (0.53–4.25)	0.75 (0.25–2.24)
Patent ductus arteriosus	86	0.72 (0.32–1.66)	0.64 (0.23–1.76)	0.82 (0.30–2.24)	0.83 (0.32–2.16)
Postnatal corticosteroid use	11	3.23 (0.88–11.92)	6.15 (1.59–23.82)	10.00 (2.66–37.62)	3.28 (0.79–13.63)
Cranial ultrasonographic finding					
IVH (grade III or IV)	9	4.59 (1.15–18.39)	2.66 (0.51–14.01)	2.72 (0.52–14.31)	4.44 (1.01–19.48)
Cystic PVL	3	2.60 (0.23–29.69)	19.47 (1.67–227.53)	19.87 (1.70–232.18)	4.06 (0.35–46.99)
IVH (grade III or IV) or cystic PVL	13	3.23 (0.88–11.92)	3.72 (0.89–15.67)	3.80 (0.91–15.99)	3.28 (0.79–13.63)
MRI finding					
Any white-matter abnormality	120	3.57 (1.02–12.53)	3.13 (0.69–14.28)	6.92 (0.89–53.80)	3.63 (0.80–16.39)
Moderate-to-severe white-matter abnormality	35	3.56 (1.45–8.70)	10.33 (3.46–30.83)	9.55 (3.22–28.30)	4.19 (1.55–11.33)
Gray-matter abnormality	82	3.00 (1.20–7.13)	3.83 (1.19–12.31)	3.77 (1.17–12.09)	2.45 (0.88–6.79)
Adjusted MRI finding‡					
Any white-matter abnormality	120	3.04 (0.81–11.43)	2.62 (0.51–13.41)	5.14 (0.60–43.91)	6.62 (0.80–54.76)
Moderate-to-severe white-matter abnormality	35	2.41 (0.86–6.75)	9.79 (2.56–37.47)	8.39 (2.28–30.89)	3.27 (0.97–11.01)
Gray-matter abnormality	82	2.47 (0.95–6.43)	3.10 (0.88–10.88)	3.17 (0.89–11.31)	2.12 (0.66–6.84)

* IVH denotes intraventricular hemorrhage, and PVL periventricular leukomalacia.
† Small size for gestational age was defined as a birth weight more than 2 SD below the mean for gestational age and sex.
‡ Covariate factors included in the logistic-regression models were abnormalities on cranial ultrasonography (grade III or IV IVH or cystic PVL) and perinatal factors including gestational age at birth of less than 28 weeks, small size for gestational age, male sex, the need for oxygen therapy at 36 weeks, the presence of patent ductus arteriosus, multiple birth, and the postnatal use of corticosteroids.

rodevelopmental risk after adjustment for moderate-to-severe white-matter abnormalities on MRI at term equivalent.

The presence of any white-matter abnormalities and the presence of moderate-to-severe white-matter abnormalities on MRI were more sensitive than were ultrasonographic findings of intraventricular hemorrhage or periventricular leukomalacia in identifying children who had subsequent severe neurodevelopmental impairments (Table 5). Although the findings on MRI were less specific than the abnormalities on ultrasonography, the use of moderate-to-severe abnormality to define "abnormal" resulted in reasonable specificity (82 to 89 percent): most children with a normal or mildly abnormal result on MRI were free of severe impairments at two years of age.

DISCUSSION

We found significant associations between the qualitative measures of cerebral white-matter and gray-matter abnormalities on MRI at term equivalent and the subsequent risks of adverse neurodevelopmental outcomes at two years of age among very preterm infants. The presence of moderate-to-severe white-matter abnormalities was predictive of severe psychomotor delay and cerebral palsy,

Table 5. Sensitivity and Specificity of Findings on MRI and Cranial Ultrasonography in Predicting Severe Neurodevelopmental Impairment at a Corrected Age of Two Years.*

Outcome	Moderate-to-Severe White-Matter Abnormalities (N=35)		Any White-Matter Abnormalities (N=120)		Abnormalities on Cranial Ultrasonography† (N=13)	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
	percent					
Severe cognitive delay						
Value	41	84	89	31	15	95
95% CI	23–61	76–89	70–97	23–39	4–35	89–98
Severe motor delay						
Value	65	85	88	30	18	95
95% CI	39–85	78–90	62–98	22–38	5–44	89–97
Cerebral palsy						
Value	65	84	94	31	18	95
95% CI	39–85	76–89	69–100	24–39	5–44	89–97
Neurosensory impairment						
Value	82	82	89	30	16	95
95% CI	48–97	75–88	65–98	23–38	4–40	89–97
Any neurodevelopmental impairment						
Value	38	89	84	34	11	95
95% CI	25–51	80–94	71–92	25–44	4–23	89–98

* CI denotes confidence interval.
† Abnormalities on cranial ultrasonography were defined as grade III or IV intraventricular hemorrhage or periventricular leukomalacia.

independently of abnormalities on cranial ultrasonography and of other perinatal factors.

As in previous studies,[22-24] neurodevelopmental impairment was common among preterm infants in this cohort by two years of age. The most common impairment was severe cognitive delay; nearly one in five children scored six months or more below their corrected age level. In addition, approximately 10 percent of children had severe psychomotor delay and a similar percentage received a diagnosis of cerebral palsy. Finally, 11 percent had neurosensory impairment (visual, hearing, or both). These high rates of neurodevelopmental impairment underscore the importance of the early identification of infants who are at greatest neurodevelopmental risk.

As in our study, prior studies have demonstrated associations between the presence of white-matter and gray-matter abnormalities on MRI at term equivalent and subsequent risks of neurobehavioral abnormalities,[17,25] cerebral palsy,[26-28] impaired working memory,[14] and global developmental delay.[15,29] However, these studies have been limited by the use of small or selected samples or both, the assessment of a narrow range of outcomes, and the combination of different outcomes that are likely to have different causes and correlates on MRI. Furthermore, it has been unclear to what extent information yielded by MRI during the neonatal period improves on other available clinical information for risk prediction.

We found that white-matter abnormalities, especially those that are moderate and severe, were useful markers for the elevated risk of severe cognitive delay, severe psychomotor delay, cerebral palsy, and neurosensory impairment. Gray-matter abnormalities, assessed qualitatively, were also associated with an increased risk of severe cognitive delay, psychomotor delay, and cerebral palsy, but to a lesser extent than white-matter abnormalities. These findings confirm the relevance of early structural neurologic abnormalities for subsequent neurodevelopmental risk across multiple domains spanning neurologic, cognitive, and motor functioning.

A number of other factors during the neonatal

period that are recognized to predict subsequent neurodevelopmental outcomes were also predictive of subsequent severe impairment in our cohort. These factors included the postnatal use of dexamethasone and the ultrasonographic findings of grade III or IV intraventricular hemorrhage and cystic periventricular leukomalacia.[30-32] However, these factors were infrequent in our cohort, accounting for only a small proportion of the children with severe impairment at two years of age. Furthermore, when MRI and other measures were taken into account, postnatal exposure to corticosteroids remained a significant predictor of subsequent motor impairment (psychomotor delay or cerebral palsy), but the presence of grade III or IV intraventricular hemorrhage or cystic periventricular leukomalacia was no longer a significant predictor of outcome (data not shown). In contrast, abnormalities on qualitative MRI at term equivalent were more strongly associated with neurodevelopmental impairment than were findings on cranial ultrasonography and other measurements performed during the neonatal period. The MRI findings also predicted impairment independently of those measures.

The potential for MRI performed during the neonatal period to improve the prediction of adverse neurodevelopmental outcomes in preterm infants was further supported by analyses showing a high sensitivity of moderate-to-severe abnormalities on MRI for these outcomes. However, it is important to note that a substantial proportion of children with moderate-to-severe white-matter abnormalities were free of severe impairment at two years of age. Although a longer-term follow-up of these children is needed, this finding underscores the fact that worrisome MRI findings may not necessarily result in severe neurodevelopmental problems. It also highlights the potential importance of other factors, both genetic and environmental, in influencing neurodevelopmental outcomes.

The strengths of our study include its prospective design, the high rate of retention of subjects, and the assessment of a diverse range of outcomes by observers who were unaware of the MRI findings. However, the limitations of this study should also be noted. First, despite a relatively large sample size, the low rate of hearing impairment precluded a separate analysis of hearing and visual problems. Second, the low rates of some factors during the neonatal period may have limited the statistical power of the study to assess their contributions to the outcomes. Third, given that early delays in development may not correspond with subsequent impairment,[33] further follow-up including neuropsychological, motor, educational, and behavioral assessments will be important to better understand the clinical implications of our MRI findings.

Nonetheless, our findings suggest that the identification of early cerebral abnormalities with the use of MRI should offer a valuable complement to other neonatal and psychosocial risk factors in improving the identification of preterm infants at high risk for subsequent neurodevelopmental impairment.

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