# Qualitative Brain MRI at Term and Cognitive Outcomes at 9 Years After Very Preterm Birth

**WHAT'S KNOWN ON THIS SUBJECT:** Cross-sectional studies have demonstrated associations between the white matter injury and cognitive impairment in very preterm born children. Longitudinal studies confirmed the relationships between cerebral MRI at term and neurodevelopmental outcomes at up to 2 years old.

**WHAT THIS STUDY ADDS:** White matter injury (but not gray matter injury) on term MRI predicted cognitive impairments of very preterm born infants at 9 years old. Qualitative assessment of white matter signal intensities showed limited predictive values of cognitive impairments.


## abstract

**OBJECTIVE:** A prospective study was performed to assess the relationship between the appearance of cerebral MRI at term and the cognitive functioning at 9 years old in very preterm born infants.

**METHODS:** Seventy-six very preterm born infants (birth weight <1500 g or gestational age ≤32 weeks) obtained cerebral MRI at term-equivalent period, which was assessed by using established composite scores for the white and gray matter; cognitive outcomes at 9 years old were assessed in 60 subjects by using Wechsler Intelligence Scale for Children, Third Edition.

**RESULTS:** Mildly low scores on the different IQ indices (<85) were observed in 23.3% (verbal IQ), 41.7% (performance IQ), and 30.0% (full-scale IQ) of the cohort, whereas moderately low scores (<70) were noted in 3.3% (verbal IQ), 11.7% (performance IQ), and 11.7% (full-scale IQ); cerebral palsy was diagnosed in 10.0%, whereas special assistance at school was required in 56.7%. Abnormal white matter appearances predicted mildly low verbal, performance, and full-scale IQs; moderately low performance and full-scale IQs; cerebral palsy; and the requirement for special assistance at school. Abnormal white matter appearances predicted mild cognitive impairment even after the adjustment for known clinical risk factors. In contrast, abnormal gray matter appearances did not predict any of the outcome measures.

**CONCLUSIONS:** In a cohort of very preterm born infants, abnormal white matter appearance on term MRI showed consistent associations with cognitive impairments at 9 years old, further supporting the benefit of obtaining term MRI for very preterm born infants. *Pediatrics* 2012;129:e1138–e1147



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**KEY WORDS**

preterm infants, MRI, cognitive impairments, white matter injury, gray matter injury


**ABBREVIATIONS**

CI—confidence interval
DEHSI—diffuse excessive high signal intensity
FLAIR—fluid-attenuated inversion recovery
OR—odds ratio
PVL—periventricular leukomalacia

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The recent remarkable increase in the survival rate for very preterm born infants raised a concern on their long-term neurodevelopmental outcome.[1] The incidence of severe types of neurologic deficits, such as deafness, blindness, and cerebral palsy, have been declining in part because of the reduced incidence of severe cerebral injury, such as periventricular hemorrhagic infarction and periventricular leukomalacia (PVL).[2,3] In contrast, cognitive impairments are increasingly recognized as a prominent form of neurodevelopmental disorders in very preterm born infants.[4,5] The range of cognitive functioning of very preterm born infants at school age is various, yet significantly below that of term-born peers, with more than half of these children requiring special assistance at school.[6–9] To provide timely interventions, early prediction of neurodevelopmental impairments is essential.

Thus far, cerebral MRI has been used to identify structural brain abnormalities and related developmental impairments.[10] MRI studies of very preterm born children at school age demonstrated consistent associations between white matter volume reduction and cognitive impairments.[11–13] Recent studies have demonstrated the relationships between white matter abnormalities on term MRI and cognitive outcomes in very preterm born infants at 1 to 2 years old.[14–16] Additional studies with longer follow-up periods are still required, because neurodevelopmental assessments performed at early childhood period may not reflect cognitive functioning at school age and thereafter,[17–19] either because of the limited reliability of early assessment tools or because cognitive function itself may significantly alter under the influence of numerous intrinsic/extrinsic factors such as plasticity, compensation, reorganization of injured brain, environment, and education.

We conducted a prospective observational study in very preterm born infants hospitalized at a single tertiary center to test the hypothesis that abnormal MRI findings at term-equivalent age predict long-term cognitive impairments at 9 years old.

## METHODS

Ethical approval was obtained from the ethics committee of Nagano Children's Hospital. Informed parental consent was obtained for each participating infant.

### Study Population

The NICU of Nagano Children's Hospital is the only level III unit within the province of Nagano, which covers the population of ~2.5 million people including its neighbor provinces. Preterm infants with birth weight <1500 g and/or gestational age <34 weeks are enrolled into a domestic follow-up program for very preterm born infants at the time of discharge; we aim to obtain cerebral MRI between 38 and 42 weeks corrected age; neurodevelopmental outcomes are assessed at 18 and 36 months corrected age and 6 years chronological age by using individualized assessment tools.

Of 1156 newborn infants who were hospitalized between August 1995 and March 2001, 380 infants met the entry criteria of the follow-up program. However, 236 subjects were transferred to local level I/II units before discharge, and mothers of 27 subjects moved back to their home provinces after giving birth in Nagano (giving birth at parents' home site is common in Japan[20]); these infants were followed-up at their local hospitals (Fig 1). The remaining 117 subjects were enrolled into the follow-up program, whose cognitive outcome at 6 years old have been reported elsewhere.[21] For the current study, we recruited 76 very preterm born infants (birth weight <1500 g and/or gestational age ≤32 weeks) from the follow-up program, excluding 14 infants with major chromosomal abnormality or multiple congenital malformation, 2 infants with gestational age >32 weeks and birth weight ≥1500 g, and 25 infants whose MRI was not obtained before 42 weeks corrected age (Fig 1).

### MRI Scans and Assessments

T1- and T2-weighted imaging and fluid-attenuated inversion recovery (FLAIR) imaging were obtained by using a 0.5-Tesla MRI system (Gyroscan NT5, Phillips, Best, Netherlands). The MRI methods used were T1-weighted imaging (repetition time, 384 milliseconds; echo time, 18 milliseconds), T2-weighted imaging (repetition time, 4000 milliseconds; echo time, 120 milliseconds), and FLAIR imaging (inversion time, 1800 milliseconds; repetition time, 6000 milliseconds; echo time, 140 milliseconds), with a slice thickness of 6 mm and an imaging matrix of 256 × 256 (Fig 2). Two investigators, blind to patient details, examined each scan independently; the evaluations of 1 investigator were used only for the assessment of interobserver variability[21]; all other results were based on the assessments of the other investigator.

We used an established scoring system for immature brain on T1- and T2-weighted imaging,[15,22] which consists of 5 and 3 subcategories for the white matter and gray matter, respectively. Each subcategory used a 3-point scale to give composite scores; abnormal findings in the white matter were then classified into no (score 5–6), mild (score 7–9), moderate (score 10–12), and severe (score 13–15) abnormality; no subject was ultimately assigned into severe abnormality in the current study population; abnormal findings in the gray matter were divided into 2 groups of normal (score 3–5) and abnormal (score 6–9). For the evaluation of the white matter, the presence of diffuse excessive high signal intensity (DEHSI)

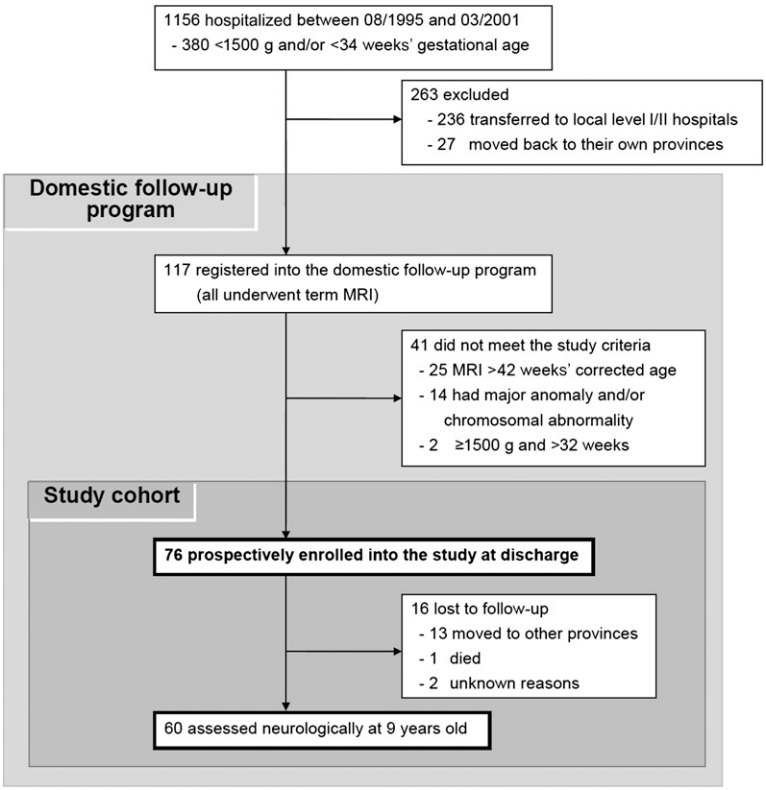


**FIGURE 1**

Flow of participants through the longitudinal study. During the study period, 380 infants met the criteria for the domestic follow-up program; however 263 subjects, who were either transferred to local hospitals before discharge or moved back to their parents' own provinces after discharge, were unavailable. Of 117 subjects who were enrolled to the follow-up program, 76 very preterm born infants without major congenital diseases were recruited for the prospective study.

on T2-weighted imaging and abnormal signal intensity on FLAIR imaging were also identified; FLAIR imaging was classified into 4 grades of normal, mildly abnormal (mild to moderate low-intensity), moderately abnormal (low-intensity equivalent to cerebrospinal fluid), and severely abnormal (widespread heterogeneous intensity; no subject was ultimately assigned into this grade; Fig 2 A and B).[21]

## Outcome Measures

At 9 years old (chronological age), the Wechsler Intelligence Scale for Children, Third Edition was performed to assess verbal, performance, and full-scale IQs by an experienced psychologist who was blind to the MRI data. At the same time, the presence of hypertonicity, hyperreflexia, dystonia, and spasticity was assessed to identify cerebral palsy by consultant neonatologists; parents were also asked whether their children required special assistance at school because of problems in social, emotional, and behavioral adaptation.

## Data Analysis

To assess the potential bias on the participants, background clinical variables were compared between the study cohort and their peers who were excluded because of the late timing of MRI scans by using analysis of variance, $\chi^2$ test, or Fisher exact test, as appropriate. The relationship between MRI findings was assessed by using Spearman rank correlation coefficient. For the purpose of additional analyses, MRI findings were dichotomized into normal or abnormal (mild to severe). The outcome measures were compared between subjects with or without abnormal MRI findings by using analysis of variance, $\chi^2$ test, or Fisher exact test, as appropriate. The predictive ability of abnormal MRI findings on the outcome measures, including mild (IQ $<85$) and moderate (IQ $<70$) cognitive impairments, was assessed by using logistic regression analysis (verbal IQ $<70$ was not used as a dependent variable because of only 2 corresponding subjects).[23] For dependent variables with incidence $>10$ (IQs $<85$ and requirement for special assistance at school), the predictive ability of MRI findings were assessed with adjustment for known clinical risk factors of cognitive impairments, such as gestational age $<28$ weeks and cystic PVL; birth weight, which showed marked collinearity with gestational age, and severe intraventricular hemorrhage, which corresponded to only 1 subject at 9 years old, were not entered into the multivariate model. We aimed to use additional cofactors from the clinical variables listed in the Table 1 on the basis of the results from univariate analysis; eventually no variable was included because of the lack of correlations between adverse outcomes and clinical variables other than the gestational age and cystic PVL.

# RESULTS

The 76 subjects within the study cohort had significantly greater birth weight, shorter duration on the positive pressure ventilation, and smaller incidence of intrauteral growth restriction compared with their 25 peers, whose MRI was acquired after 42 weeks' corrected age; no difference was observed for other background variables (Table 1).

## MRI Findings at Term

Interrater reliabilities for the category assignments of the white matter and gray matter were $\kappa = 0.80$ and $\kappa = 0.82$

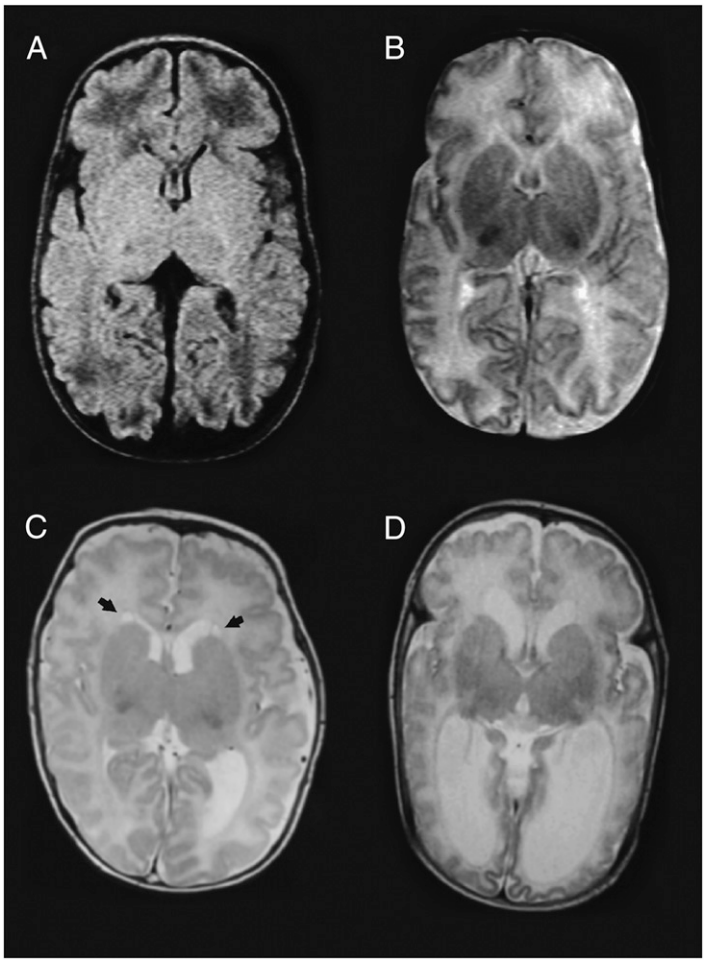


**FIGURE 2**

Representative MRI findings: A and B, Term MRI of an infant born at 28 weeks' gestation. The signal intensity of the white matter is excessively low on FLAIR imaging (A) and significantly increased on T2-weighted imaging (B). Except for mildly immature patterns of myelination of the posterior limb of the internal capsule and cortical folding, no abnormal cerebral architecture is noted. C, T2-weighted imaging of an infant born at 30 weeks' gestation demonstrates mild ventricular dilatation, bilateral periventricular cysts (arrows), and mild volume reduction of the gray and white matter. The architecture of the central gray and white matter is relatively preserved. D, T2-weighted imaging of an infant born at 25 weeks' gestation shows moderate dilatation of the lateral ventricles and moderate atrophy of the gray and white matter with an abnormal cortical folding pattern.

respectively. Agreement in the evaluation of DEHSI (T2-weighted imaging) and abnormal white matter signal intensity (FLAIR imaging) was also high ($\kappa = 0.65$ and $\kappa = 0.78$, respectively). Of 76 infants, abnormal high composite scores for the white matter and gray matter were observed in 24 (31.6%) and 16 (21.1%) infants, respectively, whereas DEHSI on T2-weighted imaging and abnormal white matter intensity on FLAIR imaging was noted in 13 (17.1%) and 58 (76.3%) infants, respectively. The presence of white matter abnormalities based on composite scores was positively correlated with the presence of gray matter abnormalities ($r = .60$, $P < .001$), DEHSI on T2-weighted imaging ($r = .34$, $P < .005$), and abnormal white matter signal intensity on FLAIR imaging ($r = .23$, $P < .05$).

## Neurodevelopmental Outcomes

At age 9 years, 16 subjects were lost to follow-up because of family relocation to other provinces ($n = 13$), mortality by an accident ($n = 1$), or lost contact ($n = 2$; follow-up rate, 78.9%). Moderately low verbal, performance, and full-scale IQs <70 were recorded in 2, 7, and 7 subjects, respectively, whereas mildly low IQs <85 were noted in 14, 25, and 18 subjects, respectively. Cerebral palsy was diagnosed in 6 subjects; parents of 34 subjects reported the requirement for special assistance at school.

## Term MRI Findings and Neurodevelopmental Outcomes

Subjects with abnormal white matter appearances based on the composite assessment had lower verbal ($P < .005$), performance ($P < .001$) and full-scale ($P < .001$) IQs, a higher incidence of cerebral palsy ($P < .05$), and a greater rate of subjects who require special assistance at school ($P < .005$) compared with their peers with normal findings (Table 2). Neither abnormal gray matter appearances nor DEHSI on T2-weighted imaging were associated with any of the outcome measures (Tables 3 and 4). Subjects with abnormal white matter intensities on FLAIR imaging had lower verbal and full-scale IQs (both $P < .05$) compared with their peers with normal findings (Table 5).

The presence of white matter injury defined by the composite assessment predicted mildly low verbal (odds ratio [OR] 6.3, 95% confidence interval [CI] 1.7–23.9), performance (OR 7.1, 95% CI 2.2–22.8), and full-scale (OR 8.3, 95% CI 2.4–29.1) IQs, moderately low performance (OR 12.7, 95% CI 1.4–114.0) and full-scale (OR 12.7, 95% CI 1.4–114.0) IQs, incidence of cerebral palsy (OR 10.0, 95% CI 1.1–92.1), and the requirement for special assistance at school (OR 7.0, 95% CI 2.0–24.6) (Tables 6 and 7; see online Supplemental Table 8 for the predictive value of each element from the composite assessment). After the effect was adjusted for gestational age and cystic PVL, significant

**TABLE 1** Patients' Characteristics

| | Study Cohort ($n$ = 76) | Exclusion Due to Late MRI ($n$ = 25) | $P$ |
|---|---|---|---|
| Clinical variables | | | |
| Birth wt, g[a] | 1118 ± 262 (560–1747) | 884 ± 273 (483–1580) | <.001 |
| Gestational age, wk[a] | 28.6 ± 2.5 (23.7–34.6) | 27.5 ± 2.1 (23.4–32.6) | |
| Female gender | 30 (39) | 13 (52) | |
| Multiple birth | 22 (29) | 11 (44) | |
| Intrauterine growth restriction <2 SD below the average for gestational age | 8 (11) | 10 (40) | <.005 |
| Antenatal steroids | 29 (38) | 9 (36) | |
| Days on positive pressure ventilation[a] | 39.2 ± 40.1 (0–274) | 67.8 ± 39.6 (4–186) | <.001 |
| Chronic lung disease with oxygen requirement on day 28- or 36-wk corrected age | 26 (34) | 14 (56) | |
| Symptomatic patent ductus arteriosus | 23 (30) | 8 (32) | |
| Necrotizing enterocolitis with requirement for surgical intervention | 2 (3) | 0 (0) | |
| Intraventricular hemorrhage, grade III/IV based on Papile classification | 2 (3) | 0 (0) | |
| Cystic periventricular leukomalacia | 11 (14) | 3 (12) | |

Values are shown as the number of corresponding subjects (%). $P$ values are from $\chi^2$ test, Fisher exact test or analysis of variance.

[a] Mean ± SD (range).

**TABLE 2** Neurodevelopmental Outcome at 9 Years in Subjects With or Without Abnormal MRI Findings: Composite Assessment of White Matter

| | Normal ($n$ = 37) | Abnormal ($n$ = 23) | $P$ |
|---|---|---|---|
| IQ | | | |
| Verbal | 100.8 ± 12.9 | 88.7 ± 17.0 | <.005 |
| Performance | 93.5 ± 12.4 | 78.6 ± 17.5 | <.001 |
| Full scale | 97.0 ± 11.2 | 82.3 ± 16.6 | <.001 |
| Incidence of cerebral palsy (%) | 1 (3) | 5 (22) | <.05 |
| Requirement for special assistance at school (%) | 15 (41) | 19 (83) | <.005 |

Values are shown as the number of corresponding subjects (%) or mean ± SD. $P$ values are from $\chi^2$ test Fisher exact test, or analysis of variance.

**TABLE 3** Neurodevelopmental Outcome at 9 Years in Subjects With or Without Abnormal MRI Findings: Composite Assessment of Gray Matter

| | Normal ($n$ = 46) | DEHSI ($n$ = 14) |
|---|---|---|
| IQ | | |
| Verbal | 96.4 ± 15.4 | 95.1 ± 17.0 |
| Performance | 88.3 ± 16.0 | 86.1 ± 17.3 |
| Full scale | 91.8 ± 15.0 | 90.1 ± 16.4 |
| Incidence of cerebral palsy (%) | 4 (9) | 2 (14) |
| Requirement for special assistance at school (%) | 26 (57) | 8 (57) |

Values are shown as the number of corresponding subjects (%) or mean ± SD.

predictive ability of abnormal white matter appearances was still identified on mildly low verbal (OR 6.2, 95% CI 1.5–25.1), performance (OR 6.0, 95% CI 1.7–20.9), and full-scale (OR 6.3, 95% CI 1.7–23.4) IQs, as well as the requirement for special assistance at school (OR 5.9, 95% CI 1.6–22.2; Table 6). The presence of abnormal gray matter appearance identified by the composite assessment and DEHSI on T2-weighted imaging did not predict any of the outcome measures. Abnormal white matter intensities on FLAIR imaging predicted verbal IQ (OR 10.4, 95% CI 1.1–98.7) only after adjustment for gestational age and cystic PVL.

## DISCUSSION

In a cohort of very preterm born infants, we have demonstrated consistent associations between abnormal white matter appearances on term MRI and cognitive impairments, incidence of cerebral palsy, and requirement for special assistance at school at 9 years old. In contrast, abnormal gray matter appearances did not predict cognitive outcomes. Our current findings supported the benefit of obtaining cerebral MRI at term after very preterm birth to identify a subset of infants who may require additional follow-up supports.

### Abnormal White Matter Appearance and Cognitive Outcome

#### *Composite Assessment of White Matter and Outcome*

The impact of white matter injury in very preterm born children has thus far been emphasized in conjunction with later visual perceptual impairment; impaired ability to process and comprehend the visual input has been linked with lower performance IQ.[13,24–26] Our current findings suggest that the white matter injury in very preterm born infants may also be responsible for the impairment in language processing tasks. In addition to the associations with the incidence of cognitive impairment and cerebral palsy, abnormal white matter appearances were associated with the requirement for special assistance at school; this is not surprising given the relationship between a child's cognitive ability and adaptation to school after very preterm birth.[4,27] Early diagnosis of cognitive impairment is still challenging;[17–19] however, term MRI may help screen a group of very preterm born infants at increased risks of cognitive impairment. Future studies need to test

**TABLE 4** Neurodevelopmental Outcome at 9 Years in Subjects With or Without Abnormal MRI Findings: Qualitative Assessment of White Matter Signal Intensities on T2-Weighted Imaging

| | Normal ($n$ = 50) | DEHSI ($n$ = 10) |
|---|---|---|
| IQ | | |
| Verbal | 96.8 ± 16.2 | 92.5 ± 12.4 |
| Performance | 88.3 ± 15.6 | 85.2 ± 19.5 |
| Full scale | 92.1 ± 15.0 | 88.0 ± 16.4 |
| Incidence of cerebral palsy (%) | 5 (10) | 1 (10) |
| Requirement for special assistance at school (%) | 27 (54) | 7 (70) |

Values are shown as the number of corresponding subjects (%) or mean ± SD.

**TABLE 5** Neurodevelopmental Outcome at 9 Years in Subjects With or Without Abnormal MRI Findings: Qualitative Assessment of White Matter Signal Intensities on FLAIR Imaging

| | Normal ($n$ = 16) | Abnormal ($n$ = 44) | $P$ |
|---|---|---|---|
| IQ | | | |
| Verbal | 104.6 ± 16.2 | 93.1 ± 14.4 | <.05 |
| Performance | 93.4 ± 12.2 | 85.7 ± 17.0 | |
| Full scale | 99.4 ± 13.2 | 88.5 ± 14.9 | <.05 |
| Incidence of cerebral palsy (%) | 1 (6) | 5 (11) | |
| Requirement for special assistance at school (%) | 7 (44) | 27 (61) | |

Values are shown as the number of corresponding subjects (%) or mean ± SD. $P$ values are from $\chi^2$ test, Fisher exact test, or analysis of variance.

the hypothesis by using domain-specific assessment tools of cognitive functioning.

### *Pattern of White Matter Injury in the Study Cohort*

Because the survival rate of very preterm born infants at Nagano Children's Hospital was reasonably fair (survival rates of infants born at 23–24 [68%] and 25–26 [79%] weeks' gestation between 1995 and 2001 were comparable to average rates for Japanese level III units in 2005[28]), background characteristics, such as low rates of antenatal steroid and inborn admission, may negatively influence the quality of survival. However, in our study population, extensive white matter injury was rare; even in the subjects with cystic PVL (our cohort had a relatively high incidence of cystic PVL), most lesions were small and focal and were rarely accompanied by marked white matter atrophy. The small incidence of severe intraventricular hemorrhage may contribute to white matter sparing; subjects with extensive white matter injury might be excluded from the cohort because of selection biases; however, moderate to severe white matter injury was also rare for subjects who were excluded from the cohort because of the late timing of MRI scans. In addition to the clinical backgrounds, the threshold of the injury-score assignment in our institution might be higher compared with the original classification,[15] because interinstitutional variations of qualitative MRI assessments are common.[21,29,30] However, given the high interrater agreement of the MRI assessment, there would be only limited influence of bias on the current data interpretation.

### *Abnormal White Matter Signal Intensity and Outcome*

In our previous study in a cohort of moderately preterm born infants, the presence of DEHSI on term T2-weighted imaging (observed in 17% of the subjects) was associated with low full-scale IQs, whereas abnormal white matter intensities on FLAIR imaging (63%) was association with unfavorable performance and full-scale IQs at 6 years old; abnormal findings on FLAIR imaging were mainly associated with mild cognitive impairments, whereas DEHSI appeared to be specific to relatively more severe impairments.[21] In our current study, which prospectively followed up a part of the previous cohort with more strict entry criteria in gestational age and timing of MRI scans, associations with performance IQ were not observed for these abnormal signal intensities; instead, a modest correlation was observed between abnormal intensities on FLAIR (but not T2-weighted) imaging and verbal IQ. It is unclear why abnormal findings on term FLAIR imaging was associated with different IQ domains at different developmental stages. Standard cognitive batteries may be insensitive to subtle verbal impairments at earlier ages, and the difference might be caused by chance given the limited associations between abnormal signal intensities and cognitive outcomes. Regardless of the explanation, the evaluation of term MRI based solely on the white matter signal intensity may not provide precise estimation of long-term outcomes; the composite assessment should be prioritized to other MRI markers.

## Abnormal Gray Matter Appearance and Outcome

In very preterm born children, reduced cortical gray matter volume has also been associated with poor cognitive outcome at school age.[11,31,32] In our current study, abnormal gray matter appearances at term were associated with the presence of white matter injury but not with any of the outcome measures at 9 years old. Previous studies observed a stronger correlation of cognitive outcomes with white matter injury compared with gray matter injury,[15,33] which is consistent with our current findings. Cortical gray matter lesions may contribute less to the later cognitive functioning; neurologic functioning associated with gray matter injury might be affected more by repairing process, plasticity, and extrinsic factors such as education and

**TABLE 6** Predictive Ability of MRI Findings on Neurodevelopmental Outcomes at 9 Years

| | *n* | Verbal IQ <85 (*n* = 14) | | Performance IQ <85(*n* = 25) | | Full-scale IQ <85 (*n* = 18) | | Performance IQ <70 (*n* = 7) | | Full-scale IQ <70 (*n* = 7) | | Cerebral Palsy (*n* = 6) | | Special Assistance (*n* = 34) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OR | (95% CI) | OR | (95% CI) | OR | (95% CI) | OR | (95% CI) | OR | (95% CI) | OR | (95% CI) | OR | (95% CI) |
| Univariate analysis | | | | | | | | | | | | | | | |
| Clinical variables | | | | | | | | | | | | | | | |
| Birth wt <1000 g | 19 | 0.5 | (0.1–2.1) | 1.9 | (0.6–5.8) | 1.1 | (0.3–3.6) | 0.9 | (0.2–4.8) | 0.3 | (0.0–2.9) | 1.1 | (0.2–6.5) | 0.8 | (0.3–2.4) |
| Gestational age <28 wk | 23 | 2.8 | (0.8–9.4) | 2.7 | (0.9–7.9) | 5.6 | (1.7–18.7)** | 4.9 | (0.9–27.6) | 2.4 | (0.5–11.8) | 1.7 | (0.3–9.2) | 2.4 | (0.8–7.2) |
| Female gender | 24 | 0.3 | (0.1–1.3) | 1.0 | (0.4–2.9) | 1.3 | (0.4–4.0) | 0.6 | (0.1–3.2) | | [a] | 3.4 | (0.6–20.3) | 0.6 | (0.2–1.8) |
| Multiple birth | 18 | 2.1 | (0.6–7.4) | 0.4 | (0.1–1.4) | 0.9 | (0.3–2.9) | 0.9 | (0.2–5.3) | 1.9 | (0.4–9.5) | 0.4 | (0.1–4.0) | 0.7 | (0.2–2.1) |
| Intrauterine growth restriction | 6 | 0.6 | (0.1–5.9) | 1.5 | (0.3–7.9) | 1.2 | (0.2–7.2) | | [a] | 1.6 | (0.2–16.1) | | [a] | 0.7 | (0.1–4.0) |
| Antenatal steroids | 23 | 0.9 | (0.3–3.0) | 0.5 | (0.2–1.4) | 0.7 | (0.2–2.3) | | [a] | 0.2 | (0.0–2.1) | | [a] | 0.6 | (0.2–1.6) |
| Chronic lung disease | 21 | 1.6 | (0.5–5.3) | 0.8 | (0.3–2.4) | 1.8 | (0.6-5.6) | 0.3 | (0.0–2.5) | 0.7 | (0.1–4.1) | 0.3 | (0.0–3.1) | 1.0 | (0.4–3.0) |
| Symptomatic patent ductus arteriosus | 17 | 1.6 | (0.4–5.6) | 1.0 | (0.3–3.0) | 1.4 | (0.4–4.7) | 0.4 | (0.0–3.5) | 1.0 | (0.2–5.8) | 2.9 | (0.5–15.8) | 1.1 | (0.4–3.5) |
| Necrotizing enterocolitis | 1 | | [a] | | [a] | | [a] | | [a] | | [a] | | [a] | | [a] |
| Intraventricular hemorrhage (grade III or IV) | 1 | | [a] | | [a] | | [a] | | [a] | | [a] | | [a] | | [a] |
| Cystic PVL | 10 | 0.8 | (0.2–4.3) | 7.8 | (1.5–40.7)* | 2.8 | (0.7–11.4) | 4.9 | (0.9–26.9) | 2.3 | (0.4–13.7) | 2.9 | (0.5–18.4) | 9.0 | (1.1–76.4)* |
| Abnormal MRI findings | | | | | | | | | | | | | | | |
| Composite assessment | | | | | | | | | | | | | | | |
| White matter | 23 | 6.3 | (1.7–23.9)** | 7.1 | (2.2–22.8)*** | 8.3 | (2.4–29.1)*** | 12.7 | (1.4–114.0)* | 12.7 | (1.4–114.0)* | 10.0 | (1.1–92.1)* | 7.0 | (2.0–24.6)*** |
| Gray matter | 14 | 0.9 | (0.2–3.7) | 1.6 | (0.5–5.2) | 0.9 | (0.3–3.4) | 0.5 | (0.7–4.7) | 1.4 | (0.2–8.0) | 1.8 | (0.3–10.7) | 1.0 | (0.3–3.4) |
| White matter signal intensity | | | | | | | | | | | | | | | |
| DEHSI on T2–weighted imaging | 10 | 1.5 | (0.3–6.9) | 0.9 | (0.2–3.7) | 1.7 | (0.4–7.0) | 0.8 | (0.1–7.6) | 0.8 | (0.1–7.6) | 1.0 | (0.1–9.6) | 2.0 | (0.5–8.6) |
| FLAIR imaging | 44 | 6.3 | (0.8–52.7) | 1.8 | (0.6–6.2) | 4.0 | (0.8–19.9) | | [a] | | [a] | 1.9 | (0.2–17.9) | 2.0 | (0.6–6.5) |
| Multivariate analysis | | | | | | | | | | | | | | | |
| Adjusted for abnormal MRI findings | | | | | | | | | | | | | | | |
| Composite assessment | | | | | | | | | | | | | | | |
| White matter | 23 | 6.2 | (1.5–25.1)* | 6.0 | (1.7–20.9)** | 6.3 | (1.7–23.4)** | | [b] | | [b] | | [b] | 5.9 | (1.6–22.2)** |
| Gray matter | 14 | 0.7 | (0.2–3.3) | 1.3 | (0.4–4.9) | 0.6 | (0.2–2.8) | | [b] | | [b] | | [b] | 0.8 | (0.2–3.1) |
| White matter signal intensity | | | | | | | | | | | | | | | |
| DEHSI on T2–weighted imaging | 10 | 1.5 | (0.3–7.1) | 0.6 | (0.1–2.8) | 1.3 | (0.3–6.2) | | [b] | | [b] | | [b] | 1.5 | (0.3–7.3) |
| FLAIR imaging | 44 | 10.4 | (1.1–98.7)* | 1.4 | (0.4–5.1) | 5.6 | (0.9–34.6) | | [b] | | [b] | | [b] | 1.6 | (0.5–5.7) |

Values are shown as the number of corresponding subjects or mean (95% CI). *P* values (*$P < .05$, **$P < .01$, and ***$P < .005$) are from logistic regression analysis. Analysis was not conducted for verbal IQ <70 because of insufficient corresponding subjects.

[a] Analysis was not conducted because of the complete separation of subjects.

[b] Analysis was not performed because of insufficient corresponding subjects.

**TABLE 7** Sensitivity, Specificity, and Positive Likelihood Ratio of Composite Assessment on MRI in Predicting Cognitive Impairment at 9 Years Old

| | | Abnormal Findings on Composite Assessment | | | | | | Abnormal White Matter Signal Intensity | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | White Matter | | | Gray Matter | | | DEHSI on T2-Weighted Imaging | | | FLAIR Imaging | | |
| | | Sens (%) | Spec (%) | LR+ | Sens (%) | Spec (%) | LR+ | Sens (%) | Spec(%) | LR+ | Sens (%) | Spec (%) | LR+ |
| Cognitive impairment | | | | | | | | | | | | | |
| Verbal IQ <85 | Value | 71 | 72 | 2.5 | 21 | 76 | 0.9 | 21 | 85 | 1.4 | 93 | 33 | 1.4 |
| | 95% CI | 45–88 | 57–83 | 1.4–4.5 | 8–48 | 62–86 | 0.3–2.8 | 8–48 | 72–92 | 0.4–4.7 | 69–99 | 21–47 | 1.1–1.8 |
| Performance IQ <85 | Value | 64 | 80 | 3.2 | 28 | 80 | 1.4 | 16 | 83 | 0.9 | 80 | 31 | 1.2 |
| | 95% CI | 45–80 | 64–90 | 1.6–6.6 | 14–48 | 64–90 | 0.6–3.5 | 6–35 | 67–92 | 0.3–3.0 | 61–91 | 19–48 | 0.9–1.6 |
| Full-scale IQ <85 | Value | 72 | 76 | 3.0 | 22 | 76 | 0.9 | 22 | 86 | 1.6 | 89 | 33 | 1.3 |
| | 95% CI | 49–88 | 61–87 | 1.6–5.6 | 9–45 | 61–87 | 0.3–2.6 | 9–45 | 72–93 | 0.5–4.9 | 67–97 | 21–48 | 1.0–1.7 |
| Verbal IQ <70 | Value | 100 | 64 | 2.8 | 50 | 78 | 2.2 | 0 | 83 | 0 | 100 | 28 | 1.4 |
| | 95% CI | 34–100 | 51–75 | 2.0–3.9 | 9–91 | 65–86 | 0.5–9.7 | 0–66 | 71–90 | NA | 34–100 | 18–40 | 1.2–1.6 |
| Performance IQ <70 | Value | 86 | 68 | 2.7 | 14 | 75 | 0.6 | 14 | 83 | 0.8 | 100 | 30 | 1.4 |
| | 95% CI | 49–97 | 54–79 | 1.6–4.4 | 3–51 | 62–85 | 0.1–3.8 | 3–51 | 71–91 | 0.1–5.7 | 65–100 | 20–44 | 1.2–1.7 |
| Full-scale IQ <70 | Value | 86 | 68 | 2.7 | 29 | 77 | 1.3 | 14 | 83 | 0.8 | 100 | 30 | 1.4 |
| | 95% CI | 49–97 | 54–79 | 1.6–4.4 | 8–64 | 64–87 | 0.4–4.5 | 3–51 | 71–91 | 0.1–5.7 | 65–100 | 20–44 | 1.2–1.7 |
| Cerebral palsy | Value | 83 | 67 | 2.5 | 33 | 78 | 1.5 | 17 | 83 | 1.0 | 83 | 28 | 1.2 |
| | 95% CI | 44–97 | 53–78 | 1.5–4.2 | 10–70 | 65–87 | 0.4–5.2 | 3–56 | 71–91 | 0.2–6.6 | 44–97 | 18–41 | 0.8–1.7 |
| Special assistance | Value | 56 | 85 | 3.6 | 24 | 77 | 1.0 | 21 | 88 | 17 | 79 | 35 | 12 |
| | 95% CI | 39–71 | 66–94 | 1.4–9.4 | 12–40 | 58–89 | 0.4–2.6 | 10–37 | 71–96 | 0.5–6.2 | 63–90 | 19–54 | 0.9–1.7 |

LR+, likelihood ratio for a positive finding; NA, not applicable: CI not calculated because of the null sensitivity; Sens, sensitivity; Spec, specificity.

family environment compared with white matter injury.

Thus far, gray matter injury has been predominantly linked with cerebral injury for term-born infants, whereas white matter injury has been recognized as a prominent injury form for very preterm born infants.[2] However, recent studies highlighted that white matter injury and gray matter injury may coexist in both preterm and term subjects.[32,34,35] Studies in preterm infants suggest an association between gray matter abnormalities and moderate to severe (but not mild) white matter abnormalities[15,22]; the lack of correlations between gray matter injury and cognitive outcomes in our cohort may be in part caused by the difficulty in identifying subtle gray matter injury at term because of insufficient cortical gray matter volume.

### Strengths and Limitations

To our knowledge, this is the first longitudinal study to compare term MRI findings with neurodevelopmental outcomes at middle school age. However, given the dramatic alteration of higher cognitive functions after school age, additional studies with longer follow-up periods are necessary. The follow-up rate of our study would be acceptable for the period of 9 years; the cohort size was medium; however, it was still too small to incorporate sufficient number of clinical variables within the multivariate model; several important cofactors, such as maternal educational level and socioeconomic status, were unavailable.

MRI was obtained by using a relatively low magnetic field, which provided brain images with lower resolutions and thicker slices compared with those obtained by modern scanners. Our current study used qualitative assessment of term MRI as an established predictor of neurodevelopmental outcomes at 2 to 4 years old[15,16,36]; the evaluation of MRI might be slightly different from other institutions; assessments using quantitative MRI, such as apparent diffusion coefficient and fractional anisotropy, may provide additional diagnostic value. We used Wechsler Intelligence Scale for Children, Third Edition as the cognitive battery, which has also been standardized for Japanese children; we were unable to assess the motor function.

Selection biases, including background characteristics of the unit and patients' clinical conditions, were not completely eliminated; indeed, the infants with intrauteral growth restriction were more likely to undergo MRI after 42 weeks corrected age; of the 16 infants who were lost to follow-up, only 1 and 2 infants showed abnormal white matter and gray matter abnormalities, respectively, based on the composite assessment. These limitations should be considered when interpreting our findings.

## CONCLUSIONS

Our findings build on previous reports observing that very preterm born children are more likely to suffer a range of neurodevelopmental impairments compared with their peers. Consistent relationships between white matter injury at term and altered cognitive functioning at 9 years old were observed. Because ultrasound scans are insensitive to most MRI findings,[15,37]

early MRI may help identify a group of very preterm born infants with an increased risk of later cognitive impairment. Such information may provide an important key to improve follow-up strategies and to allow better risk stratification for future clinical trials which enroll very preterm born infants.


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