pISSN 2384-1095
eISSN 2384-1109

iMRI 2020;24:30-37

https://doi.org/10.13104/imri.2020.24.1.30

iMRI
Investigative Magnetic Resonance Imaging

# MRI Findings to Predict Neurodevelopmental Outcomes in Preterm Infants Near Term-Equivalent Age

**Hyun Sook Hong[1], Sung Shin Kim[2], Ga Young Park[2]**

[1]Department of Radiology, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Korea
[2]Department of Pediatrics, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Korea

## Original Article

Received: October 16, 2019
Revised: November 25, 2019
Accepted: November 25, 2019

**Correspondence to:**
Hyun Sook Hong, M.D., Ph.D.
Department of Radiology, Soonchunhyang University Bucheon Hospital, 170 Jomaru-ro, Wonmi-gu, Bucheon-si, Gyeonggi-do 14584, Korea.
**Tel.** +82-32-621-5851
**Fax.** +82-32-621-5874
**E-mail:** hshong@schmc.ac.kr



**Purpose:** 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. It is controversial whether diffuse excessive high signal intensity (DEHSI) represents damage to the white matter or delayed myelination in preterm infants. This study investigated MRI findings for predicting the severity of neurodevelopmental outcomes and assessing whether preterm infants with DEHSI near term-equivalent age have abnormal neurodevelopmental outcomes.

**Materials and Methods:** Preterm infants (n = 64, gestational age at birth < 35 weeks) undergoing brain MRI near term-equivalent age and subsequent neurodevelopmental outcomes were evaluated between 18 and 24 months of age. The associations of MRI findings and the risk of severe cognitive delay, severe psychomotor delay, cerebral palsy (CP), and neurosensory impairment were analyzed. The associations of DEHSI with risks of severe cognitive delay, severe psychomotor delay, CP, and neurosensory impairment (hearing or visual impairment) were analyzed. Outcome data were evaluated by logistic regression and the Fisher's exact test.

**Results:** There were significant associations between abnormal white matter findings and delayed mental development, delayed psychomotor development, neurosensory impairment, and presence of CP. The presence of DEHSI was not correlated with delayed neurodevelopmental outcomes or presence of CP. In multivariate logistic regression analyses, cystic encephalomalacia, punctate lesion, loss of white matter volume and ventricular dilation were significantly associated with CP.

**Conclusion:** Abnormal MRI findings near term-equivalent age in preterm infants predict adverse neurodevelopmental outcomes. No significant association between DEHSI and adverse neurodevelopmental outcomes was demonstrated.

**Keywords:** Preterm; Periventricular leukomalacia; Punctate white matter lesion; Magnetic resonance imaging; Diffuse excessive high signal intensity (DEHSI); Brain

## INTRODUCTION

Advances in perinatal care have resulted in marked increases in survival rates of preterm infants. The premature brain is at increased risk of injury from many causes, resulting in adverse neurodevelopmental outcomes (1). The most premature infants at the time of birth are the most likely to be affected (2). Initially, there was an increase in the number of children with poor outcomes (3). The long-term consequences of very preterm birth are still unclear (4), and the proportion of children with disabilities is still high (5). Accurate identification of infants at greatest risk for subsequent neurodevelopmental disabilities and who may benefit from early intervention is important for the early prediction of motor sequelae and for targeting high-risk infants for appropriate rehabilitation.

A wide spectrum of lesions affect the brains of preterm infants, and recent applications of magnetic resonance imaging (MRI) have been relevant as a means of predicting neurodevelopmental outcomes in early life. MRI studies have revealed that the majority of very preterm infants have white matter abnormalities including signal abnormalities, loss of volume, cystic abnormalities, enlarged ventricles, thinning of the corpus callosum, delayed myelination, and enlarged extracerebral spaces (6-8). Overt white matter injury such as cystic periventricular leukomalacia (PVL) is a strong predictor of future impairments (9-12), but the incidence rates of PVL, periventricular hemorrhagic infarction (PHI), and major intraventricular hemorrhage (IVH) have decreased with improvements in neonatal intensive care (8, 13). In addition, cystic PVL does not explain all of the neurodevelopmental difficulties associated with preterm birth. Diffuse excessive high signal intensity (DEHSI) on MRI is a common finding, demonstrated in 75% of preterm infants at term-equivalent age (14, 15). DEHSI is linked to clinically significant patent ductus arteriosus (PDA), but not to other complications of preterm birth such as sepsis, necrotizing enterocolitis, or chronic lung disease (16). The neurodevelopmental implications of DEHSI are unclear. DEHSI has been suggested as a possible cause of cognitive abnormalities following preterm birth (9, 17-19), and may represent injury or death of late precursor oligodendrocytes (19, 20). On the other hand, it may represent delayed myelination and was reported not to be associated with poor neurological outcome (21, 22).

This study investigated MRI findings for predicting the severity of neurodevelopmental outcomes in preterm infants and for assessing whether preterm infants with DEHSI near term-equivalent age have abnormal neurodevelopmental outcomes in early life.

## MATERIALS AND METHODS

This retrospective observational study was approved by our Institutional Review Board, and the requirement for informed consent was waived. However, written informed parental consent was obtained prior to brain MRI in all patients.

### Study Population

Between March 2014 and December 2017, 140 preterm infants born prior to 35 weeks of gestation were admitted NICU and scanned brain MRI at term-equivalent age. Subsequent neurodevelopmental outcomes were evaluated between 18 and 24 months of age by Bayley Scales of Infant Development II (BSID-II) (23). Three infants were excluded if they had evidence of congenital infections, metabolic disorders, or other conditions likely to affect their development independent of preterm birth (muscular dystrophy, n = 1; Silver-Russell syndrome, n = 1; metabolic disorder, n = 1). Seventy preterm infants during the same period who were not evaluated according to BSID-II or were lost to follow-up were excluded from the analyses. The exclusion group without neurodevelopmental assessment showed no differences in birth weight, GA at birth, or sex ratio compared to the study population. A final total 64 preterm infants born prior to 35 weeks of gestation were included in this study. No infants required mechanical ventilation at the time of MRI examination. Disabilities included neuromotor or neurosensory impairment (e.g., cerebral palsy [CP], sensorineural hearing loss requiring a hearing aid, blindness, surgery for strabismus) were reviewed. The associations between white matter abnormalities and being small for gestational age (GA), oxygen therapy at 36 weeks, PDA, and postnatal corticosteroid use were analyzed.

### MRI

MRI was performed with the Signa HDxt 1.5-T MR imaging scanner with 64 channel head coil (GE Healthcare, Milwaukee, WI, USA) using the following imaging sequence: axial fast spin-echo (FSE) T2-weighted imaging with a repetition time (TR)/echo time (TE) of 3500/102 ms; axial fluid-attenuated inversion recovery (FLAIR) with a TR/TE of 8000/120 ms, inverstion time (TI) of 2000 ms; axial

conventional SE T1WI with a TR/TE of 500/16 ms; axial diffusion-weighted echo-planar imaging (DWI EPI) with a TR/TE of 8000/97.8 ms, b value 1000; axial gradient-echo T2* imaging with a TR/TE of 450/15 ms, flip angle of 20°; coronal FSE T2 imaging with a TR/TE of 3500/102 ms; and sagittal SE T1 with a TR/TE of 500/9 ms. The infants were sedated for imaging with oral chloral hydrate (20-30 mg/kg), and pulse oximetry and electrocardiography were monitored throughout the procedure. Ear protection was used for each infant (Natus MiniMuffs; Natus Medical Inc., San Carlos, CA, USA). The MRI results were reviewed by a pediatric radiologist with 30 years of experience who was unaware of the infants' clinical course at the time of imaging review, and were reviewed a second time after a 2-week interval. The associations of MRI findings and the risk of severe cognitive delay, severe psychomotor delay, CP, and neurosensory impairment were analyzed. The associations of DEHSI with risks of severe cognitive delay, severe psychomotor delay, CP, and neurosensory impairment (hearing or visual impairment) were analyzed. The associations of white matter abnormalities with mental developmental score, psychomotor development score, presence of neurosensory impairment, and presence of CP were analyzed according to the scoring system of Woodward et al. (11). DEHSI is defined as higher than expected signal intensity in the white matter on T2-weighted imaging, not limited to areas where high signal intensity is normally seen, such as the "anterior caps" and "posterior arrowheads," and low signal intensity on T1-weighted and FLAIR images, with corresponding high signal intensity on apparent diffusion coefficient (ADC) maps (15). Punctate white matter lesions were defined as small areas of increased signal intensity on T1-weighted images and decreased signal intensity on T2-weighted images (21). Ventricular dilatation was defined more than 10 mm of largest atrial diameter.

### Neurodevelopmental Outcome

Patients were assessed for cognitive and psychomotor development using the BSID-II between 18 and 24 months of corrected age. Raw scores on the mental and psychomotor scales of BSID-II are converted to the Mental Development Index (MDI) and Psychomotor Development Index (PDI), with a mean of 100 and an SD of 15. Scores > 1 standard deviation (SD) or > 2 SD below the normative mean indicated mild and severe delays in development, respectively. The presence of CP and visual and hearing impairment were assessed. Visual defect was defined as the requirement for corrective lenses, surgery, or both for strabismus or blindness. Hearing defect was defined as sensorineural hearing loss exceeding 30 dB.

### Statistical Analyses

Data are reported as the mean ± SD for continuous variables and frequency (percentage) for categorical variables. Analyses were performed using the independent two-sample t-test for continuous variables and Fisher's exact test for categorical variables. The associations between white matter abnormalities on MRI and adverse neurodevelopmental outcomes near term-equivalent age were examined using either one-way analysis of variance (ANOVA) with Bonferroni's multiple comparison test for continuous variables or Fisher's exact test for categorical variables. Logistic regression analyses were performed to assess the associations between the MRI features and subsequent neurodevelopmental abnormalities. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for risk of CP according to specific MRI features were calculated. Statistical analyses were performed based on the two-tailed test, and $P < 0.05$ was taken to indicate significance. Analyses were performed using R software (3.4.3, The R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

The study population consisted of 33 male infants and 31 female infants. The mean GA of the infants at birth was $29^{+2} \pm 3^{+6}$ weeks, and the mean birth weight was 1292.5 ± 661.83 g. The mean postmenstrual age at MRI was $38^{+1}$ ± 2 weeks.

There were 16 (25.0%) cases of cystic encephalomalacia, 25 (39.07%) of punctate lesions, 31 (48.44%) with loss of white matter volume and ventriculomegaly, 50 (78.13%) with DEHSI, 9 (14.07%) with grade 3/4 germinal matrix hemorrhage (GMH), and 10 (15.63%) cases of cerebellar hemorrhage. There were significant associations between abnormal white matter findings and delayed mental developmental index score, delayed psychomotor index score, neurosensory impairment, and presence of CP ($P < 0.001$) (Table 1). There were no significant associations between abnormal white matter and presence of small for gestational age, oxygen therapy at 36 weeks, presence of PDA, or postnatal corticosteroid use (all Ps > 0.05). The incidence of DEHSI in infants was 78.13% (50/64). There were no significant differences in mental development

**Table 1. Associations between White Matter Abnormalities and Mental Developmental Scores, Presence of Neurosensory Impairment, and Cerebral Palsy**

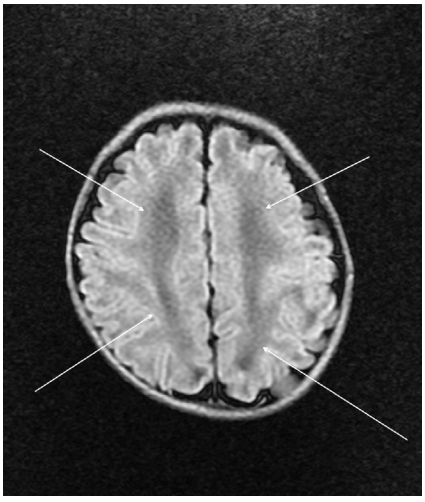
| Variable | White matter abnormality | | | | |
|---|---|---|---|---|---|
| | None (n = 25) | Mild (n = 21) | Moderate (n = 6) | Severe abnormality (n = 12) | P-value |
| Mental development index | 89.4 ± 13.63 | 78.7 ± 12.95 | 72.75 ± 24.6 | 56 ± 10.97 | < 0.001 |
| Psychomotor development index | 91.88 ± 15.77 | 71.05 ± 18.41 | 72.5 ± 20.27 | 54 ± 8.30 | < 0.001 |
| Neurosensory impairment | 2 (8) | 7 (33.3) | 3 (50) | 10 (83.3) | < 0.001 |
| Cerebral palsy | 9 (36) | 16 (76.2) | 6 (100) | 12 (100) | < 0.001 |

White-matter abnormality was graded according to the scoring system of Woodward et al. (11), 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. 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).
For MDI, the post hoc test showed significant differences between none vs severe (P < 0.001), and mild vs severe (P = 0.001).
For PDI, the post hoc test showed significant differences between none vs mild (P < 0.001), and none vs severe (P < 0.001).
MDI = Mental Development Index; PDI = Psychomotor Development Index
Data are reported as the mean ± SD for continuous variables and frequency (percentage) for categorical variables.
P-values were calculated by one-way ANOVA with Bonferroni's multiple comparison test for continuous variables and Fisher's exact test for categorical variables.
P < 0.05 was taken to indicate significance.

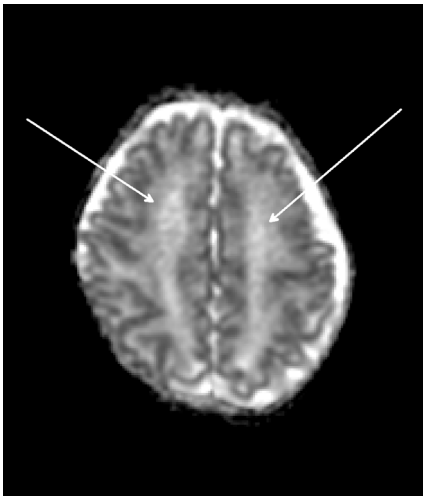
**Table 2. Associations between DEHSI and Mental Development Score, Psychomotor Development Score, Presence of Neurosensory Impairment, and Cerebral Palsy**

| Variable | DEHSI | | |
|---|---|---|---|
| | with (n = 50) | without (n = 14) | P-value |
| Mental development index score | 79.56 ± 18.21 | 80.67 ± 15.85 | 0.848 |
| Psychomotor development index score | 78.22 ± 21.57 | 77.18 ± 19.40 | 0.885 |
| Neurosensory impairment | 18 (36) | 4 (28.6) | 0.755 |
| Cerebral palsy | 35 (70) | 8 (57.1) | 0.520 |

DEHSI = diffuse excessive high signal intensity
Data are reported as the mean ± SD for continuous variables and frequency (percentage) for categorical variables.
P-values were calculated by independent two-samples t-test for continuous variables and Fisher's exact test for categorical variables.
P < 0.05 was taken to indicate significance.

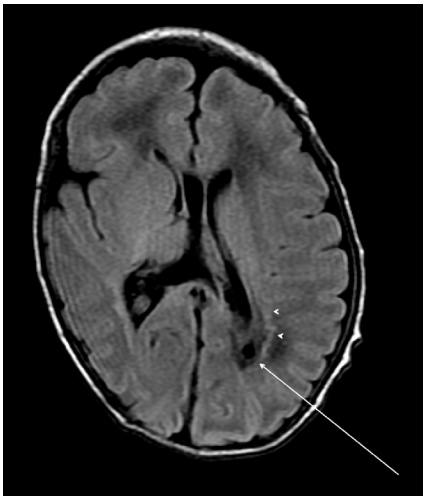


a



b

**Fig. 1.** Axial FLAIR (a) and (b) ADC map showing DEHSI at the level of the centrum semiovale. This male infant was born at 30+5 weeks with a birth weight of 1250 g. MRI was performed at gestational age of 36+2 weeks. He showed accelerated mental development index and psychomotor motor index.


a

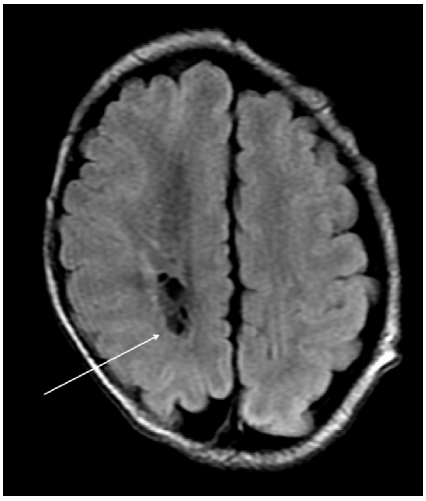

b

**Fig. 2.** (a, b) Cystic encephalomalacia (arrows) and punctate lesions (arrowheads) were seen in the parietal white matter. This male infant was born at 30+6 weeks with birth weight of 1620 g. MRI was performed at 38+2 weeks. He had PDA clipping. He showed delayed mental and psychomotor index at 2 years.

**Table 3. Logistic Regression Analyses of Risk of Developing CP According to MR Features**

| Variable | CP | | | |
|---|---|---|---|---|
| | Univariate | | Multivariate | |
| | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Cystic encephalomalacia | 25.797 (1.343-495.548) | 0.031 | 0.102 (0.004-2.482) | 0.041 |
| Punctate lesion | 10.93 (2.72-74.05) | 0.003 | 0.19 (0.034-0.833) | 0.029 |
| Loss of WM volume | 19.68 (4.83-134.95) | < 0.001 | 0.171 ( 0.036-0.824) | 0.028 |
| Ventricular dilation | 19.68 (4.83-134.95) | < 0.001 | 0.171 (0.036-0.824) | 0.028 |
| DEHSI | 1.75 (0.50-5.94) | 0.368 | | |
| IVH | 1.62 (0.95-2.83) | 0.989 | | |
| Cerebellar hemorrhage | 1.17 (0.29-5.91) | 0.837 | | |

CI = confidence interval; DEHSI = diffuse excessive high signal intensity; IVH = intraventricular hemorrhage; IVH = germinal matrix hemorrhage 3/4; OR = odds ratio; WM = white matter

P < 0.05 was taken to indicate significance.

index score or psychomotor development index score between children with and without DEHSI (all Ps > 0.05) (Table 2, Fig. 1). The presence of DEHSI was not associated with the presence of neurosensory impairment or CP (Table 2). Demographic data, associated clinical factors were no significant difference between patients with and without DEHSI (all Ps > 0.05). Among abnormal white matter lesions, cystic encephalomalacia (OR: 25.797; 95% CI: 1.343-495.548) and punctate lesions (OR: 10.93; 95% CI: 2.72-74.05) (Fig. 2), loss of white matter volume (OR: 19.68; 95% CI: 4.83-134.95), and ventricular dilation (OR: 19.68; 95% CI: 4.83-134.95) were significant predictors of CP. In multivariate logistic regression analyses, cystic encephalomalacia, punctate lesions, loss of white matter volume, and ventricular dilation were significantly associated with CP and delayed development according to BSID-II (Tables 3, 4). At about 2 years of age, 28/64 (43.8%) of infants had neurosensory impairment (visual, n = 7 [10.9%]; hearing, n = 6 [8.1%]; CP, n = 10 [15.6%]; combined defect, n = 6 [9.4%]).

## DISCUSSION

Preterm infants are at high risk of neurodevelopmental delay (5, 10, 24). A large proportion of premature infants show minor cognitive problems later in life (10). MRI at 14-15 years of age detect many more abnormalities in

**Table 4.** Logistic Regression Analyses for Delayed Development on Bayley Scale According to MR Features

| Variable | Bayley scale | | | |
|---|---|---|---|---|
| | Univariate | | Multivariate | |
| | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Cystic encephalomalacia | 11.90 (2.03-227.67) | 0.023 | 0.256 (0.0.4-1.918) | 0.085 |
| Punctate lesion | 1.42 (0.47-4.40) | 0.532 | 1.432 (0.377-5.434) | 0.198 |
| Loss of WM volume | 6.65 (2.09-24.44) | 0.002 | 0.236 (0.060-0.933) | 0.039 |
| Ventricular dilation | 6.65 (2.09-24.44) | 0.002 | 0.236 (0.060-0.933) | 0.039 |
| DEHSI | 1.25 (0.34-4.58) | 0.732 | | |
| IVH | 6 (0.93-117.71) | 0.109 | | |
| Cerebellar hemorrhage | 1.47 (0.33-7.83) | 0.621 | | |

CI = confidence interval; DEHSI = diffuse excessive high signal intensity; IVH = intraventricular hemorrhage; IVH = germinal matrix hemorrhage 3/4; OR = odds ratio; WM = white matter

$P < 0.05$ was taken to indicate significance.

individuals who are born very preterm compared to their full-term counterparts (5). These infants show significantly less developed executive functioning, smaller receptive and expressive language lexicons, and weaker motor skills than full-term infants (25). Early identification of preterm infants at high risk for neurodevelopmental difficulties would allow the early treatment and amelioration of these difficulties to maximize the child's outcome (26). Several studies have reported that neonatal MRI around term can be used to predict CP with high sensitivity and specificity (4, 27-29). The results of this study indicated that MRI findings can help to predict adverse neurodevelopmental outcomes in preterm infants, although longer term follow-up of these children is needed.

There were significant associations between white matter abnormalities on MRI near term-equivalent age and subsequent risks of adverse neurodevelopmental outcomes. In this study, children with more severe white matter abnormalities had a greater number of neurodevelopmental impairments than children with less severe or no abnormalities. In multivariate logistic regression analyses, cystic encephalomalacia, punctate lesions, loss of white matter volume, and ventricular dilation were significantly associated with CP. T1 hyperintense punctate lesions detected on MRI pathologically corresponded to cellular reactions of glial cells and macrophages, as well as formation of microcalcifications (30-32). They were often adjacent to regions of cystic change, consistent with necrotic changes without cyst formation. Due to shrinkage of the necrotic lesions, the broad findings of T1 hyperintense lesions as well as cystic lesions led to ventriculomegaly and irregularity (33).

DEHSI in the white matter is the most common MRI finding in the brains of preterm infants at term-equivalent age. There has been some debate regarding the neurodevelopmental significance of DEHSI since it was first described by Maalouf et al. (15). There have been no histopathological reports regarding DEHSI, and there was some controversy regarding whether DEHSI reflects damage or altered development of late precursor oligodendrocytes (16, 34, 35) or is simply a transient, normal developmental process the resolution of which is delayed following preterm birth (21, 22). In this study, the presence of DEHSI was not associated with delayed neurodevelopmental outcomes and the presence of neurosensory impairment or CP (2, 21). DEHSI may be indicative of delayed myelination in preterm infants. In contrast to other studies (2, 21), probably due to small number of enrolled patients, there were no significant associations between neurodevelopmental delay and risk factors including postnatal use of dexamethasone, presence of PDA, small for GA, oxygen therapy at 36 weeks, grade III or IV GMH, and cerebellar hemorrhage (1, 11). This study had some limitations. First, it was a single-center retrospective study with a relatively small number of patients. Second, the follow-up period was relatively short. Hack et al. (36) reported that normal outcome at 2 years of age with BSID-II did not guarantee normal outcome at 8 years of age. Follow-up studies with complex assessment of development are needed in these premature infants.

In conclusion, abnormal MRI findings near term-equivalent age in preterm infants predict adverse neurodevelopmental outcomes. DEHSI was the most

commonly observed MRI finding and was not associated with developmental delay in early life.

**Acknowledgments**

We are grateful to Ji Eun Moon, Ph.D., senior statistician of Department of Biostatistics, Soonchunhyang University Bucheon Hospital, for the statistical analysis.

This work was supported in part by the Soonchunhyang University Research Fund.

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

1. Inder TE, Warfield SK, Wang H, Huppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. Pediatrics 2005;115:286-294
2. Hoekstra RE, Ferrara TB, Couser RJ, Payne NR, Connett JE. Survival and long-term neurodevelopmental outcome of extremely premature infants born at 23-26 weeks' gestational age at a tertiary center. Pediatrics 2004;113:e1-6
3. Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. Pediatrics 2005;115:997-1003
4. Stewart AL, Rifkin L, Amess PN, et al. Brain structure and neurocognitive and behavioural function in adolescents who were born very preterm. Lancet 1999;353:1653-1657
5. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008;371:261-269
6. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. N Engl J Med 2000;343:378-384
7. Horsch S, Hallberg B, Leifsdottir K, et al. Brain abnormalities in extremely low gestational age infants: a Swedish population based MRI study. Acta Paediatr 2007;96:979-984
8. Horbar JD, Badger GJ, Carpenter JH, et al. Trends in mortality and morbidity for very low birth weight infants, 1991-1999. Pediatrics 2002;110:143-151
9. Dyet LE, Kennea N, Counsell SJ, et al. Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. Pediatrics 2006;118:536-548
10. Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. J Pediatr 2003;143:171-179
11. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med 2006;355:685-694
12. Hart AR, Whitby EW, Griffiths PD, Smith MF. Magnetic resonance imaging and developmental outcome following preterm birth: review of current evidence. Dev Med Child Neurol 2008;50:655-663
13. Marlow N, Wolke D, Bracewell MA, Samara M; EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005;352:9-19
14. Taylor HG, Klein N, Minich NM, Hack M. Middle-school-age outcomes in children with very low birthweight. Child Dev 2000;71:1495-1511
15. Maalouf EF, Duggan PJ, Rutherford MA, et al. Magnetic resonance imaging of the brain in a cohort of extremely preterm infants. J Pediatr 1999;135:351-357
16. Skiold B, Horsch S, Hallberg B, et al. White matter changes in extremely preterm infants, a population-based diffusion tensor imaging study. Acta Paediatr 2010;99:842-849
17. Inder TE, Anderson NJ, Spencer C, Wells S, Volpe JJ. White matter injury in the premature infant: a comparison between serial cranial sonographic and MR findings at term. AJNR Am J Neuroradiol 2003;24:805-809
18. Volpe JJ. Cerebral white matter injury of the premature infant-more common than you think. Pediatrics 2003;112:176-180
19. Back SA, Riddle A, McClure MM. Maturation-dependent vulnerability of perinatal white matter in premature birth. Stroke 2007;38:724-730
20. Gilles FH, Gomez IG. Developmental neuropathology of the second half of gestation. Early Hum Dev 2005;81:245-253
21. Hart A, Whitby E, Wilkinson S, Alladi S, Paley M, Smith M. Neuro-developmental outcome at 18 months in premature infants with diffuse excessive high signal intensity on MR imaging of the brain. Pediatr Radiol 2011;41:1284-1292
22. Jeon TY, Kim JH, Yoo SY, et al. Neurodevelopmental outcomes in preterm infants: comparison of infants with and without diffuse excessive high signal intensity on MR images at near-term-equivalent age. Radiology 2012;263:518-526
23. Park HW, Cho BH. Korean Bayley scales of infant development: interpretation manual. 2nd ed. Seoul: Kidspop Publishing Co., 2006
24. Stephens BE, Vohr BR. Neurodevelopmental outcome of the

premature infant. Pediatr Clin North Am 2009;56:631-646
25. Evensen KA, Skranes J, Brubakk AM, Vik T. Predictive value of early motor evaluation in preterm very low birth weight and term small for gestational age children. Early Hum Dev 2009;85:511-518
26. Aylward GP. Cognitive and neuropsychological outcomes: more than IQ scores. Ment Retard Dev Disabil Res Rev 2002;8:234-240
27. Mirmiran M, Barnes PD, Keller K, et al. Neonatal brain magnetic resonance imaging before discharge is better than serial cranial ultrasound in predicting cerebral palsy in very low birth weight preterm infants. Pediatrics 2004;114:992-998
28. Roelants-van Rijn AM, Groenendaal F, Beek FJ, Eken P, van Haastert IC, de Vries LS. Parenchymal brain injury in the preterm infant: comparison of cranial ultrasound, MRI and neurodevelopmental outcome. Neuropediatrics 2001;32:80-89
29. Valkama AM, Paakko EL, Vainionpaa LK, Lanning FP, Ilkko EA, Koivisto ME. Magnetic resonance imaging at term and neuromotor outcome in preterm infants. Acta Paediatr 2000;89:348-355
30. Schouman-Claeys E, Henry-Feugeas MC, Roset F, et al. Periventricular leukomalacia: correlation between MR imaging and autopsy findings during the first 2 months of life. Radiology 1993;189:59-64
31. Garel C, Delezoide AL, Elmaleh-Berges M, et al. Contribution of fetal MR imaging in the evaluation of cerebral ischemic lesions. AJNR Am J Neuroradiol 2004;25:1563-1568
32. Roelants-van Rijn AM, Nikkels PG, Groenendaal F, et al. Neonatal diffusion-weighted MR imaging: relation with histopathology or follow-up MR examination. Neuropediatrics 2001;32:286-294
33. Volpe JJ. Neurology of the newborn. 4th ed. Philadelphia, PA: WB Saunders, 2001
34. Counsell SJ, Shen Y, Boardman JP, et al. Axial and radial diffusivity in preterm infants who have diffuse white matter changes on magnetic resonance imaging at term-equivalent age. Pediatrics 2006;117:376-386
35. Hagmann CF, De Vita E, Bainbridge A, et al. T2 at MR imaging is an objective quantitative measure of cerebral white matter signal intensity abnormality in preterm infants at term-equivalent age. Radiology 2009;252:209-217
36. Hack M, Taylor HG, Drotar D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. Pediatrics 2005;116:333-341