



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

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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, inversion 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 \pm 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 $38^{+1} \pm 2$ 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 P s > 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				P-value
	None (n = 25)	Mild (n = 21)	Moderate (n = 6)	Severe abnormality (n = 12)	
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		P-value
	with (n = 50)	without (n = 14)	
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.

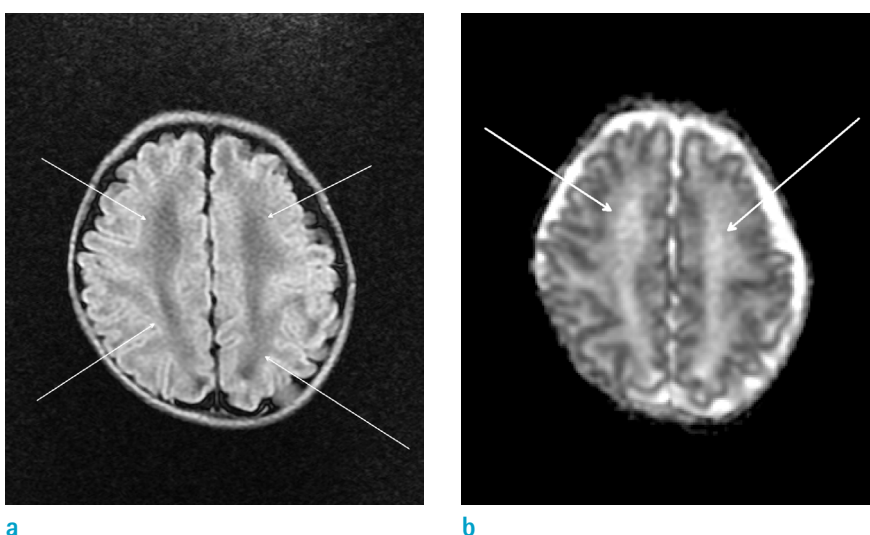


Fig. 1. Axial FLAIR (a) and (b) ADC map showing DEHSI at the level of the centrum semiovale. This male infant was born at 30+5 weeks with a birth weight of 1250 g. MRI was performed at gestational age of 36+2 weeks. He showed accelerated mental development index and psychomotor development index.

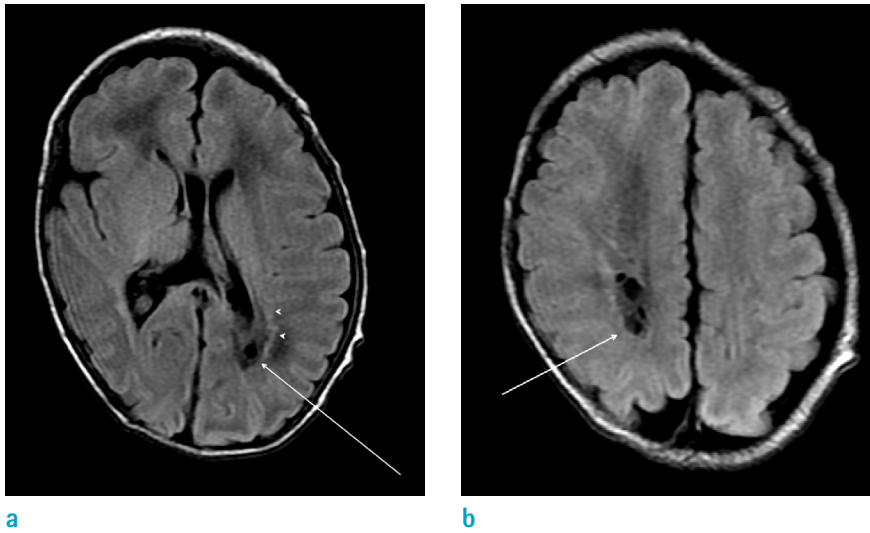


Fig. 2. (a, b) Cystic encephalomalacia (arrows) and punctate lesions (arrowheads) were seen in the parietal white matter. This male infant was born at 30+6 weeks with birth weight of 1620 g. MRI was performed at 38+2 weeks. He had PDA clipping. He showed delayed mental and psychomotor index at 2 years.

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 (0.04-1.918)	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.

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