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ORIGINAL ARTICLE

Isolated mild white matter signal changes in preterm infants: a regional approach for comparison of cranial ultrasound and MRI findings

M Weinstein[1,2], D Ben Bashat[1,3,4], V Gross-Tsur[5], Y Leitner[3,6], I Berger[3,7], R Marom[3,7], R Geva[2], S Uliel[6] and L Ben-Sira[3,8]

OBJECTIVE: To compare echogenicity detected using cranial ultrasound (cUS) and diffuse excessive high signal intensity (DEHSI) detected using magnetic resonance imaging (MRI) by identical region-based scoring criteria in preterm infants. To explore the association between these white matter (WM) signal changes with early neurobehavior.
STUDY DESIGN: Forty-nine pre-selected premature infants with only echogenicity on a first routine cUS1 underwent MRI and a repeated cUS2 at term equivalent age. Echogenicity and DEHSI were graded in various brain areas and diffusivity values were calculated. Neurobehavior was assessed using the Rapid Neonatal Neurobehavioral Assessment Procedure.
RESULT: WM signal changes were significantly higher on cUS1 than cUS2; and higher in MRI than cUS2 in posterior regions. Infants with DEHSI demonstrated reduced tissue integrity. Imaging findings were not correlated with early neurobehavior.
CONCLUSION: Echogenicity and DEHSI likely represent the same phenomenon. Reduction of over-interpretation of WM signal changes may help define criteria for the judicious use of imaging in routine follow-up of premature infants.

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Keywords: echogenicity; DEHSI; cranial ultrasound; MRI; prematurity; DTI

INTRODUCTION

Cranial ultrasound (cUS) and magnetic resonance imaging (MRI) have been shown to have significant value for the prediction of outcome in preterm infants when substantial brain pathologies, such as intraventricular hemorrhage grade IV, cerebellar hemorrhages, periventricular leukomalacia and ventriculomegaly, are present.[1–3] However, when solitary diffuse white matter (WM) signal changes are detected, with no additional imaging findings, a dilemma exists regarding the radiological interpretation of normal and abnormal signal changes. Particular controversy surrounds the interpretation of mild WM signal changes, as the clinical significance of these signal changes is poorly understood.

Echogenicity detected using cUS and diffuse excessive high signal intensity (DEHSI) detected using MRI are common WM signal changes that are prevalent in preterm infants. Echogenicity is defined by 'brightness' more intense than the choroid plexus, whereas DEHSI is defined as higher signal intensity in WM than in normal unmyelinated WM on T2-weighted images. However, it is not clear whether echogenicity and DEHSI represent the same phenomenon. Understanding the relationship between these two frequent WM signal changes, defined by different modalities, may help us describe this phenomenon as it is not clear whether WM signal changes represent level of maturation or are part of a continuum of WM injury.[4]

Presence of periventricular echogenicities on cUS has been shown to correlate with DEHSI on MRI;[1] however, the absence of periventricular echogenicity did not predict normal WM signal intensity on MRI.[1,5] The discrepancy may be explained by the different modalities (magnetic field vs sonar waves) and differential access to the neonatal brain (in cUS via fontanelle, limiting the angle of view; in MRI no entry point, providing multi-spatial views). Ultrasound is considered to be 'user dependent', however, identification of DEHSI on MRI is also somewhat subjective.[6] Few studies directly compared echogenicity and DEHSI on a regional level using the same criteria.[1]

Microstructural properties underlying WM signal change in MRI can be assessed using diffusion tensor imaging (DTI). Previous studies have shown that DEHSI is associated with altered water diffusion, such as increased apparent diffusion coefficient and a decrease in fractional anisotropy (FA).[7–12] In the current study, we used DTI in order to understand the microstructural properties of the WM tissue with DEHSI and for validation of the radiological regional assessment of DEHSI.

Recent MRI studies of preterm infants did not detect an association between the presence of DEHSI and neurodevelopmental outcome at 18 and 24 months[9,12,13] and at 9 years;[14] although earlier studies reported lower overall development at 18 and 36 months in preterm infants with DEHSI.[15,16] However, most of these studies did not isolate WM signal changes, rather including preterm infants with additional brain abnormalities. Furthermore, most of these studied did not correlate WM signal changes with neurodevelopmental assessment in the neonatal stage.

This study aimed to explore the relationship between cUS and MRI findings by developing and proposing common criteria for regional assessment of WM signal changes, resulting in a radiological score for each infant. We used a common term 'WM

[1]Functional Brain Center, Wohl Institute for Advanced Imaging, Tel-Aviv Sourasky Medical Center (TASMC), Tel-Aviv, Israel; [2]Department of Psychology, Gonda Multidisciplinary Brain Research Center, Bar Ilan University, Ramat-Gan, Israel; [3]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [4]Sagol School of Neuroscience, Tel-Aviv University, Tel-Aviv, Israel; [5]Department of Pediatric Neurology, Shaare-Zedek Medical Center, Jerusalem, Israel; [6]Department of Pediatrics, Child Development Center, TASMC, Tel-Aviv, Israel; [7]Department of Neonatology, Lis Maternity Hospital, TASMC, Tel-Aviv, Israel and [8]Department of Radiology, TASMC, Tel-Aviv, Israel. Correspondence: Dr L Ben-Sira, Department of Radiology, TASMC, 6 Weizman Street, Tel-Aviv 64239, Israel.
E-mail: liatb@tlvmc.gov.il
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signal changes' for both US and MRI hyperintensities, in order to bridge the gap between imaging findings using different modalities. We prospectively studied, a pre-selected, homogeneous group of preterm infants with only WM signal changes and no additional brain imaging findings. Furthermore, we aimed to indirectly characterize microstructural changes underlying DEHSI using DTI in order to explore the precise neuronal basis and to examine the correlation with early neurobehavioral assessment at infancy.

METHODS

The Ministry of Health and the local institutional review board approved this study, and fully informed consent was obtained from parents.

Participants

Forty-nine premature infants participated in this study. Inclusion criteria were: preterm infants born at < 34 weeks' gestational age with minimal to moderate echogenicity as identified on routine cUS performed within a week of birth. Location of echogenicity was not a criterion. Exclusion criteria were: infants with abnormal imaging findings such as intraventricular hemorrhage or parenchymal hemorrhage, cortical or corpus-callosal and cerebellar malformations as identified on cUS or MRI. Eight subjects were excluded from the study: one due to a genetic disorder, five due to additional imaging findings such as intraventricular hemorrhage grade II and two due to cerebellar asymmetry.

cUS

cUS was performed on a VIVID-I US station as part of routine follow-up of all preterm infants in the neonatal intensive care unit. Two examinations were assessed in this study: cUS1, performed within a week from birth, and cUS2, performed near term equivalent age (TEA). The exams were performed with routine views through the anterior fontanelle and mastoid views for delineation of hemorrhage, WM echogenicity, intactness of midline structures and extra-axial fluids.

MRI setup

Preterm infants were scanned around TEA, 36–42 weeks' gestational age, on a 3T Signa HDXT GE scanner (3T System, General Electric SIGNA EXCITE, Milwaukee, WI, USA), using an eight-channel head coil. MRI setup was performed without sedation according to the guidelines by Mathur *et al*.[17] A senior neonatologist was present during all scans to monitor blood oxygen saturation and heart rate.

MR protocol

MR protocol included conventional imaging: Axial T1 weighted (repetition time (TR)/echo time (TE)= 620/8.8 ms, matrix of 512×512, field of view (FOV) = 180 mm and 3 mm slices with no gap), Axial T2 weighted (TR/TE = 8000/158 ms, matrix of 256×256, FOV = 180 mm and 3 mm slices with no gap); Axial T2 gradient echo imaging (TR/TE = 700/30 ms, matrix of 512×512, FOV = 180 mm and 3 mm slices with no gap), coronal T2 (TR/TE = 8000/137 ms, matrix of 256×256, FOV = 180 mm and 3 mm slices with no gap); and axial T2 fluid attenuation inversion recovery (TR/TE = 10002/160 ms, matrix of 256×256, FOV = 180 mm and 3 mm slices with no gap). DTI images were acquired along 33 non-collinear gradient directions with b values of 700 s mm^{-2}, and one that served as a reference with no applied diffusion gradient, TR/TE = 8000/88 ms, matrix of 64×64, FOV = 160 mm and 2.5 mm slices with no gap, in-plane resolution 2.0×2.0 mm and axial slices prescribed to cover the entire brain.

WM echogenicity/DEHSI rating

Diffuse and focal echogenic regions were defined on the first cUS (cUS1) and at TEA (cUS2). Regions with DEHSI were defined on T1-, T2- and gradient echo T2-weighted MRI images. A common evaluative system was used to measure subtle WM signal changes in cUS and MRI. Scoring was based on the Inder *et al.*[18,19] MRI scoring system and the WM signal abnormalities section were further subdivided into regions based on cUS spatial geometry and a measure of extent of injury was added. Left and right hemisphere echogenicities were scored separately within the various regions (frontal, posterior frontal, parietal and occipital) correlating spatially to areas well defined on conventional coronal cUS. The frontal area was defined anterior to the frontal horns, the posterior frontal area was defined around the glomus/atrium (the thickest area of the choroid plexus, as defined by the intersection of the frontal, occipital and temporal horns). The parietal and occipital areas were defined posterior to the glomus with the parieto-occipital fissure dividing between the parietal (superior) and the occipital (inferior) regions. These regions were defined on MRI in all orientations (see Figure 1). The frontal area was defined from the frontal pole to the sensory–motor cortex; the posterior frontal was defined from the sensory–motor cortex until the pre-central gyrus. The parietal region was defined as the high posterior parietal region, posterior to the central gyrus. The occipital area was defined as the deep WM inferior to the parieto-occipital sulcus. The ratings of echogenicity were as follows: 0 = normal, 1 = mild, 2 = moderate–severe in relation to the echogenicity of the choroid plexus taking into account gestational age. Grade 0 = less echogenic than the choroid plexus and completely differentiated from it. Grade 1 = almost as echogenic as the choroid plexus but can still be differentiated. Grade 2 = no differentiation, so that the choroid plexus blends with the echogenicity of the WM. When there was heterogeneity within the WM echogenicity it was always scored as moderate–severe grade 2 (see Figure 2). The degree of DEHSI was defined as hyper-intensity in the deep WM of the assessed brain region in relation to the hyperintense T2 signal of the 'cross roads' in the periventricular WM and as appearance of multifocal intensities; whereas hypointensities in T1 were used for assessment of normal myelinization. The ratings of DEHSI were as follows: 0 = 'none' no hyperintense signal was measured, 1 = 'mild' slightly more hyperintense detected but easily differentiated from cross

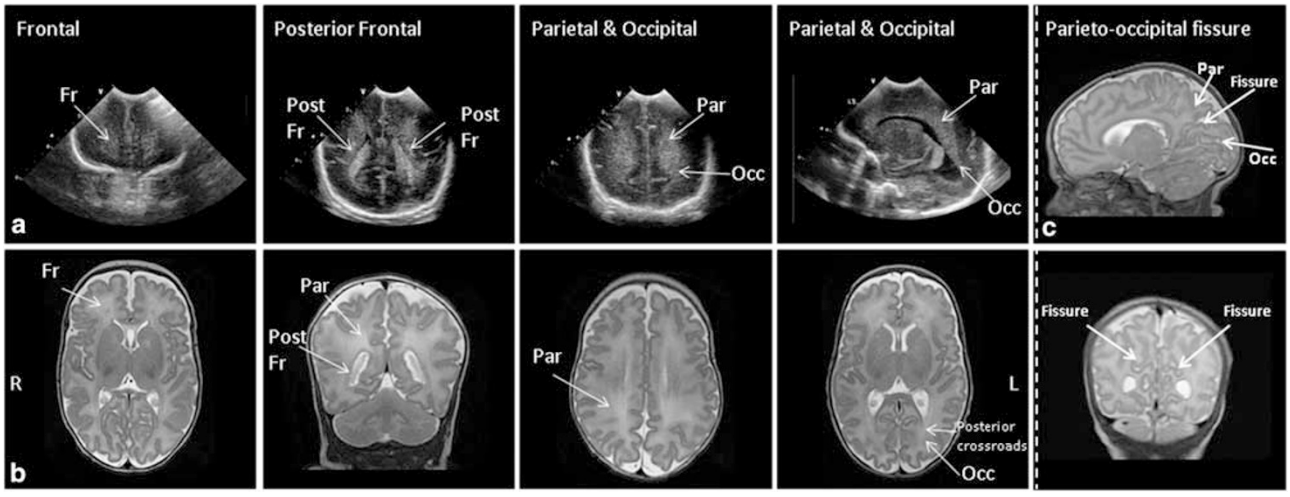

Figure 1. Regional assessment of echogenicity on cranial ultrasound (**a**) and diffuse excessive high signal intensity on magnetic resonance imaging (**b**). (**c**) Sagittal and coronal views of parieto-occipital fissure. Fr, frontal; L, left; Occ, occipital; Par, parletal; Post Fr, posterior frontal; R, right.

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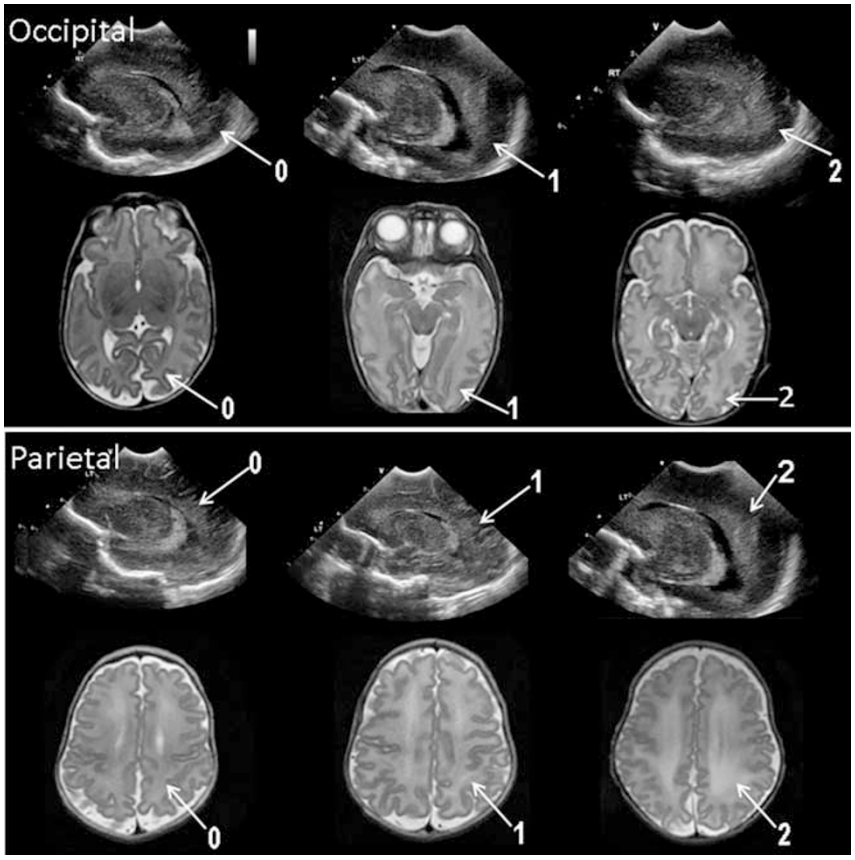

Figure 2. Severity grading of echogenicity in cranial ultrasound and diffuse excessive high signal intensity (DEHSI) in magnetic resonance imaging in parietal and occipital regions. 0, none; 1, mild; 2, moderate echogenicity/DEHSI.

roads, 2 = 'moderate' diffuse homogenous hyperintense signal of the WM, which is difficult to differentiate from cross roads (see Figure 2).

Total ratings of WM signal changes were determined by the extent of the WM injury (number of areas with echogenicity or DEHSI), the severity and the spatial distribution, using the same scale for both cUS and MRI.

At the beginning of the study, a subset (32%) of the cUS and MRI images were scored independently by two pediatric neuroradiologists with 20 and 15 years of experience, respectively. The concordance between assessors was 95%, kappa = 0.783; $P < 0.001$.

DTI data analysis

Two subjects were excluded from the DTI analysis due to movement artifacts. DTI analysis was performed using DTI Studio and ROI Editor (Johns Hopkins University, Maryland, USA).[20] Images were co-registered to the b_0 image and automated image registration algorithm was used to perform affine linear transformation.[21] Regions of interest (ROIs) were manually placed in the frontal, posterior frontal, parietal and occipital areas and were circular in shape, with a fixed size of 12 voxels, except for the ROI at the occipital region, which was 4 voxels (see Figure 3). Mean axial diffusivity (Da), radial diffusivity; MD, mean diffusivity and fractional anisotropy (FA) were calculated from the ROIs. A single investigator (with 5 years of pediatric imaging experience) made all of the WM outlines to maintain consistency and these were subsequently inspected and approved by a senior radiologist.

Neurobehavioral assessment

Behavioral outcome measures were assessed at TEA (36–40 weeks' gestational age) and at 44 weeks' gestational age, using the Rapid Neonatal Neurobehavioral Assessment Procedure (RNNAP), a clinical evaluation of the infant's neurobehavioral functioning, assessing the integrity and organization of the sensory–motor system.[22,23] This procedure evaluates early behavioral capabilities and dysfunction in areas often disrupted by central nervous system injury, such as attention, motor skills and auto-regulation and includes 17 behavioral subcategories. The RNNAP neonatal neurobehavioral assessment has concurrent and predictive validity in the neonatal intensive care unit population.[23] Infants' performance was rated as normal or abnormal based on clinical judgments in several categories including visual and auditory attention, sensory asymmetry, trunk, head/neck control, extremity movements/tone, motor asymmetry, state control, feeding and jitteriness. Assessments were performed by two experienced pediatric neurologists, blinded to imaging findings. Lower neurobehavioral functioning is reflected in an increased total score; normal score is 17.

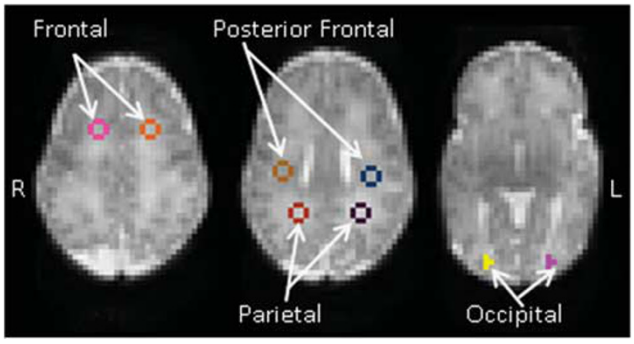

Figure 3. Location of regions of interest for measurement of diffusivity parameters.

Statistical analysis

Wilcoxon Signed-Rank test was performed to assess changes in ratings of echogenicity between cUS1 and cUS2 and differences in WM signal

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changes between cUS2 and MRI. Paired *t*-tests were used to compare FA and diffusivity values between right and left hemispheres. Multivariate GLM analysis was used to compare FA and diffusivity values (Da, Dr, MD) in preterm infants with and without WM abnormalities in the frontal, posterior frontal, parietal and occipital regions. Pearson correlations and partial correlations, corrected for GA, were used to test the relationship between WM signal changes, FA, diffusivity values and neurobehavioral scores at both time points.

RESULTS

Frequency and severity of regional echogenicity and DEHSI

On cUS1, echogenicity was highest in the posterior frontal areas (right/R = 85%, left/L = 87%) and less pronounced in the occipital (R = 39%, L = 41%), parietal areas (L = 68%, R = 68%) and frontal areas (R = 31%,L = 33%; Figure 4a). Most echogenicity was mild with some moderate echogenicity in cUS1 in the posterior frontal (moderate: R = 31%, L = 21%) and parietal regions (moderate: R = 18%, L = 10%). On cUS2, the incidence of echogenicity remained highest in the posterior frontal regions (R = 25%, L = 32%), the parietal regions (R = 15%, L = 13%) and in the frontal regions (R = 18%, L = 18%), whereas none was detected in the occipital regions (Figure 4b). Echogenicity decreased in all brain regions from the first to the second cUS. On MRI, the incidence of DEHSI was highest in the left parietal region (R = 35%, L = 53%), and was also apparent in the posterior frontal (R = 30%, L = 35%), frontal regions (R = 23%, L = 23%) and occipital regions (R = 33%, L = 35%; Figure 4c). Demographic data of the preterm infants is presented in Table 1.

Effect of the time of cUS assessment

A Wilcoxon signed-ranks test indicated that echogenicity was rated significantly higher in cUS1 than in cUS2 in the right posterior frontal ($Z = -4.917$, $P < 0.0001$), left posterior frontal ($Z = -5.035$, $P = 0.0001$), right parietal ($Z = -4.260$, $P = 0.0001$), left parietal ($Z = -4.327$, $P = 0.0001$), right occipital ($Z = -3.771$, $P = 0.0001$) and left occipital ($Z = -4.000$, $P = 0.0001$) brain regions. Echogenicity rating did not significantly differ by time of assessment in the right ($Z = -1.387$, $P = 0.166$) and left frontal ($Z = -1.604$, $P = 0.109$) brain regions.

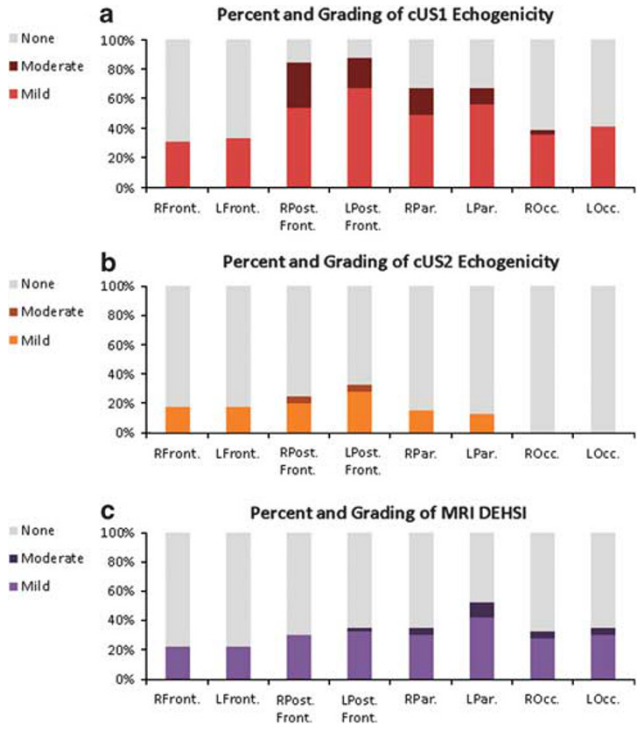

Figure 4. Frequencies and severity distribution of white matter signal changes in the left and right frontal, posterior frontal, parietal and occipital brain regions: (**a**) echogenicity in cranial ultrasound1 (cUS1), (**b**) echogenicity in cUS2, (**c**) diffuse excessive high signal intensity (DEHSI) in magnetic resonance imaging (MRI).

Effect of the modality of assessment at TEA

A Wilcoxon signed-ranks test indicated that WM signal changes (echogenicity or DEHSI) were rated significantly higher in MRI than in cUS2 in the right parietal ($Z = -2.134$, $P = 0.033$) and left parietal ($Z = -4.291$, $P < 0.0001$), right occipital ($Z = -3.419$, $P = 0.001$) and left occipital ($Z = -3.557$, $P = 0.0001$) brain regions. There were no significant differences in WM signal change ratings according to the mode of assessment in the right frontal ($Z = -0.632$, $P = 0.527$), left frontal ($Z = -0.707$, $P = 0.480$), right posterior frontal ($Z = 0.000$, $P = 1.0$) and left posterior frontal ($Z = 0.000$, $P = 1.0$) regions.

Differences in FA and diffusivity values

Paired *t*-tests showed no significant difference in FA and diffusivity values between the right and left hemispheres ($P > 0.05$), so the mean value was calculated from the bilateral measurements to give values of Da, Dr, MD ($\times 10^{-3}$ mm^2 s^{-1}) and FA for each region (Table 2). Preterm infants were subsequently divided into two groups, separately for each brain region: (1) preterm infants with mild–moderate DEHSI and (2) preterm infants with absence of DEHSI in each brain region. In preterm infants with DEHSI, significantly higher Dr was detected in all brain regions compared with those without DEHSI: frontal (normal WM signal: $n = 30$, DEHSI: $n = 8$), $F(1,37) = 4.441$, $P < 0.05$; posterior frontal (normal: $n = 24$, DEHSI: $n = 14$), $F(1,37) = 5.33$, $P < 0.05$; parietal (normal: $n = 18$, DEHSI: $n = 20$), $F(1,37) = 7.18$, $P < 0.05$ and occipital (normal: $n = 25$, DEHSI: $n = 13$), $F(1,37) = 7.74$, $P < 0.05$. In addition, significantly higher MD was detected in the posterior frontal region $F(1,37) = 4.63$, $P < 0.05$; parietal region $F(1,37) = 7.59$, $P < 0.05$ and occipital region $F(1,37) = 8.296$, $P < 0.05$ in DEHSI compared with infants with no DEHSI. Significantly higher Da was detected in the parietal $F(1,37) = 7.68$, $P < 0.05$ and occipital $F(1,37) = 8.296$, $P < 0.05$ regions. No significant differences in FA were found. Mean FA and diffusivity values in each brain region for each group are presented in Table 2.

Neurobehavioral outcome at infancy

The mean RNNAP scores at term (20.26 ± 2.4, range 17–25) and at 1 month corrected age (20.33 ± 2.4, range 17–25) did not differ significantly. Almost half (46.1%) of preterm infants had a nearly normal score in RNNAP assessment at term (⩽19), i.e., performed optimally in most tested neurobehavioral subcategories. The remaining 53.9% had some degree of RNNAP abnormality, presenting dysfunction in three or more subcategories. At 44 weeks, 47.2% had a nearly normal score in RNNAP assessment; the remaining 52.8% had some degree of RNNAP abnormality.

Table 1. Demographic data

Clinical factors	*Data*
GA at birth (wk)	29.03 ± 2.7[a]
Birth weight (g)	1275.1 ± 480.6[a]
GA at MRI (wk)	37 ± 1.6[a]
IUGR	2 (5.1)
No. of male infants	25 (62.5)
No. of singletons	14 (35)

Abbreviations: GA, gestational age; IUGR, intrauterine growth restriction; MRI, magnetic resonance imaging; wk, week.
[a]Mean ± standard deviation. Numbers in parentheses are percentages.

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Table 2. Differences in diffusivity parameters between preterm infants with and without DEHSI

Area	*Diffusivity parameters*	*Normal*	*DEHSI*	*F*	p
Frontal	Da	0.179 ± 0.01	0.189 ± 0.02	3.16	0.084
	Dr	0.151 ± 0.02	0.164 ± 0.02	4.441	*0.042
	FA	0.121 ± 0.03	0.101 ± 0.02	2.65	0.112
	MD	0.160 ± 0.02	0.173 ± 0.02	4.13	0.050
Posterior Frontal	Da	0.161 ± 0.01	0.167 ± 0.01	2.45	0.126
	Dr	0.123 ± 0.01	0.132 ± 0.01	5.33	*0.027
	FA	0.194 ± 0.04	0.169 ± 0.03	4.03	0.052
	MD	0.135 ± 0.01	0.144 ± 0.01	4.63	*0.038
Posterior Parietal	Da	0.186 ± 0.02	0.198 ± 0.01	7.68	*0.009
	Dr	0.155 ± 0.02	0.169 ± 0.01	7.18	*0.011
	FA	0.124 ± 0.03	0.107 ± 0.02	3.79	0.059
	MD	0.165 ± 0.02	0.179 ± 0.01	7.59	*0.009
Posterior Occipital	Da	0.152 ± 0.01	0.167 ± 0.03	6.697	*0.014
	Dr	0.131 ± 0.01	0.141 ± 0.01	7.74	*0.009
	FA	0.110 ± 0.02	0.117 ± 0.06	0.23	0.637
	MD	0.138 ± 0.01	0.150 ± 0.02	8.296	*0.007

Abbreviations: Da, axial diffusivity ($\times 10^{-3}$ mm^2 s^{-1}); DEHSI, diffuse excessive high signal intensity; Dr, radial diffusivity ($\times 10^{-3}$ mm^2 s^{-1}); FA, fractional anisotropy (arbitrary units); MD, mean diffusivity ($\times 10^{-3}$ mm^2 s^{-1})
*$p < 0.05$.

Correlations of WM signal changes and diffusivity values with behavior at infancy

No significant correlations were detected between total echogenicity on cUS1 and cUS2, DEHSI on MRI and neurodevelopmental examination at term (RNNAP1) or at 1 month corrected age (RNNAP2), both with and without adjustment for GA.

Furthermore, no correlations were detected between FA and diffusivity values (Da, Dr, MD, FA) in the different brain regions and neurodevelopmental examination at term (RNNAP1) or at 1 month corrected age (RNNAP2), both with and without adjustment for GA.

DISCUSSION

In this study, we addressed the dilemma of diffuse WM signal changes in preterm infants in the absence of additional abnormalities, regarding both the radiological interpretation and their clinical significance. We developed common criteria for regional assessment of echogenicity detected using cUS and DEHSI detected using MRI, in order to try and define whether they represent a common phenomenon. Neither regional WM abnormalities detected in the two imaging modalities nor local diffusivity values were associated with early neurobehavioral assessment in the neonatal stage.

This regional approach helped us define the WM signal changes in coronal cUS based vs multiple axis-MRI. At TEA, high concordance was found in the distribution and severity of WM signal changes on cUS and MRI in the frontal and posterior frontal areas; whereas in the posterior brain areas MRI detected significantly more WM signal changes. The fact that no significant differences were detected between echogenicity and DEHSI in the frontal and posterior frontal areas, which are well visualized by both modalities, suggest that these two WM signal changes represent the same phenomenon and therefore may share a similar neuronal basis, which is currently poorly understood. We postulate that the significant differences detected in the posterior brain areas originate from technical limitations of cUS to visualize these areas. It may thus be useful for pediatric radiologists to be aware of a risk for making a type-II error using cUS, when a posterior lesion is suspected.

When considering the timing of the cUS examination, echogenicity was both more frequent and more severe on cUS1 (performed within 7 days of birth) compared with cUS2 (performed around TEA). The higher frequency of echogenicity in cUS1, detected in all brain regions, indicates, as documented in previous studies,[24,25] that much echogenicity is transient. Specifically, in the occipital region, 40% of the preterm infants displayed echogenicity in cUS1, whereas none in cUS2. This may be related not only to the transiency of the phenomenon but also to technical factors including smaller fontanelle and difficulty in obtaining an acute angle that enables visualization of the more posterior regions with age. Regarding severity of echogenicity, in cUS1, a large proportion of the echogenicity in the posterior frontal and parietal regions was moderate, whereas at TEA most was mild, strengthening the transiency of this phenomenon. Whether DEHSI is a transient phenomenon remains to be answered, if so, it may imply that it is part of a developmental change, such as maturation, and does not reflect WM injury.

We further used DTI to assess WM integrity in the same regions where conventional MRI detected DEHSI. We found higher Dr and MD values in all brain regions in preterm infants with DEHSI compared with those without DEHSI. In addition, higher Da was detected in the parietal region and lower FA in the posterior frontal region. These findings indicate lower WM maturation level in preterm infants with DEHSI. Our results of altered Dr evident in all brain regions in preterm infants with DEHSI are consistent with previously published reports.[7,10] Increased apparent diffusion coefficient values were detected in preterm infants with DEHSI compared with those with normal-appearing WM or controls[8,11–13,26] with some studies reporting the most marked apparent diffusion coefficient increases in the posterior WM.[11,12] It was suggested that posterior WM was affected more than other regions, because of the presence of more late-progenitor oligodendrocytes at a critical period when many injurious processes occur.[11]

We focused on early neurodevelopmental performance, contrary to other studies that assessed outcome in later developmental stages, as it may be a sensitive time to detect brain-behavior correlates before compensatory mechanisms and environmental effects have a role. We intentionally included only preterm infants with normal–moderate WM signal changes and no other imaging findings. This pre-selection of participants enabled us to specifically focus on the population where the dilemma regarding the clinical significance of the imaging findings is the greatest. Using cUS, Pisani *et al*.[27] demonstrated that infants with transient echogenicity on cUS showed normal neurodevelopmental outcome at 1 year of age, whereas 87.8% of preterm infants with persistent echogenicity demonstrated impaired outcome. Another study reported that periventricular echodensities did not predict unfavorable outcome at 2 years corrected age.[1] MRI studies that investigated the association between DEHSI and developmental outcome in preterm infants yielded inconsistent results.[9,12,16] Some recent studies that focused on later developmental stages did not detect an association between the presence of DEHSI and neurodevelopmental outcome at 18 and 24 months[9,12,13] and at 9 years.[14] The varying results may be explained by the different inclusion criteria. Infants studied displayed significant brain abnormalities in addition to DEHSI that might have had a direct or indirect effect on their outcome.[7,8,13,16,28,29] Our results indicate that the presence of mild–moderate echogenicity or DEHSI in preterm infants near TEA was not correlated with early neurodevelopmental outcomes in infancy, strengthening recent suggestions that the presence of DEHSI at TEA in preterm infants should not be regarded as a sole prognostic marker for adverse neuro-developmental outcome.

Although preterm infants in this study had only mild WM signal changes, as detected by both imaging modalities, a large proportion showed abnormal neurobehavioral performance at

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TEA and at 44 weeks. Yet WM signal changes, as well as regional DTI values, failed to predict which infants would display neurological abnormalities. This may be due to the use of regional DTI instead of estimating specific WM tracts. Indeed, several DTI studies demonstrated an association between WM integrity of several major WM tracts such as the corpus callosum and posterior limb of the internal capsule with neurodevelopmental outcome in preterm infants.[30–32] Our study differs from these studies as we extracted FA and diffusivity values from regional ROIs, in order to investigate the microstructure underlying DEHSI and in accordance with the method and findings reported in previous studies.[7,9,11–13,26] One possibility is that WM abnormalities in specific WM fiber tracts, rather than DEHSI, may underlie some of the neurobehavioral abnormalities seen in our cohort and should be explored.

We compared our diffusion parameter values to those reported in previous studies.[9,11,26] Although the locations of the ROIs in each study were not identical, we found a similar range of FA and diffusivity values.[9,11,26] Currently, no DTI norms have been published for preterm infants. Establishing typical diffusion reference values in several WM regions will enable application of DTI for clinical use.

In our special setting, where cUS and MRI are performed by the same group, we achieved a high inter rater reliability both on cUS and on conventional MRI, which may be a result of our systematic region-based observation and the interpretation by two very experienced neuroradiologists. Although it has been argued that visual appearances of echogenicity on cUS and DEHSI on conventional MRI are highly subjective.[6] Diffusivity values measured at the same brain areas differed between preterm infants with and without DEHSI, additionally supporting the reliability of the radiological scoring on MRI.

A limitation of this prospective study is the relatively small number of preterm infants. However, our cohort was fairly homogeneous, comprising only preterm infants with normal–moderate WM signal changes without other imaging findings, enabling us to determine the unique co-variation of both imaging methods and the impact of the detected changes. An additional limitation is that only very early neurodevelopment was assessed; we recommend a long-term follow-up to study possible effects of echogenicity and DEHSI on later developmental stages.

The birth of a premature baby is an upsetting event for both the parents and the extended family.[33] The caregivers often rely on imaging exams to shed light on the future developmental consequences of their baby and thus often over emphasize imaging findings that may have little impact on future neurodevelopment. This may lead to elevated parental stress every time a cUS or MRI is performed, which may itself have an adverse effect on behavioral outcome.[34] Differentiation should be made between isolated findings like echogenicity and DEHSI, which although very common seem to have little significance on outcome, and severe findings such as hemorrhage and cerebellar injury, which are known to be linked to adverse neurodevelopmental outcome.[2,19] Our findings that regional imaging signal changes do not correlate with early outcome, in addition to recent studies,[9,12,13,29] may drive the development of further methods to screen out more efficiently those in need of a high-risk follow-up care as compared with a routine premie follow-up.

In conclusion, we suggest that echogenicity detected using cUS and DEHSI detected using MRI represent the same phenomenon in preterm infants. However, the region-based comparison of the two modalities demonstrated that MRI has significantly higher sensitivity in detection of posterior WM signal changes compared with cUS. We suggest that future studies will make use of these criteria in order to relate to the WM signal changes in a more comprehensive manner and not on a modality-specific level, as this approach may direct us to better suited treatment. Recognition of the transiency of echogenicity in preterm infants and of the lack of predictive value associated with DEHSI may reduce over-interpretation of echogenicity, thus reducing both costs of repeated examinations and surplus anxiety to parents.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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