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Diffuse excessive high signal intensity in low-risk preterm infants at term-equivalent age does not predict outcome at 1 year: a prospective study

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Abstract
Introduction The outcome of premature infants with only diffuse excessive high signal intensity (DEHSI) is not clear. We explored the relationship between DEHSI, white matter (WM) diffusion characteristics, perinatal characteristics, and neurobehavioral outcome at 1 year in a homogenous group of preterm infants without major brain abnormalities.
Methods Fifty-eight preterm infants, gestational age 29± 2.6 weeks, underwent an MRI at term-equivalent age (TEA). Griffiths Mental Developmental Scales, neurological assessment, and Parental Stress Index (PSI) were performed at 1 year corrected age. These measures were compared between preterm infants according to DEHSI classification (none, mild, moderate). Diffusion tensor imaging was used in major WM volumes of interest to objectively measure the degree of WM maturation.
Results No significant differences were detected in the perinatal risk characteristics, neurobehavioral outcome, and PSI at 1 year between infants with different DEHSI classifications. In infants with DEHSI, increased axial and radial diffusivities were detected in the optic radiations, centrum semiovale, and posterior limb of the internal capsule, indicating less advanced maturation of the WM. Significant correlations were detected between the time interval from birth to MRI and the WM microstructure in infants without DEHSI.
Conclusion DEHSI in premature infants is neither a predictive measure for short-term adverse neurobehavioral outcome nor related to perinatal risk characteristics. Extrauterine exposure time had a differential effect on WM maturational trajectories in infants with DEHSI compared to those without. We suggest DEHSI may represent an alteration in WM maturational characteristics. Further follow-up studies may verify later consequences of DEHSI in premature infants.

Keywords Prematurity · DEHSI · MRI · Developmental outcome · DTI

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Introduction

Prematurity is known to be associated with neurodevelopmental difficulties later in life, such as motor, cognitive, social, emotional, and behavioral problems [1, 2]. Prediction of the neurodevelopmental outcome of premature babies with white matter (WM) abnormalities is therefore of paramount

significance. In cases like periventricular leukomalacia (PVL), WM lesions represent damage that will likely cause neurodevelopmental abnormalities [3–6], and early intervention may improve outcome. Mild WM changes in specific locations may represent maturational variations, with no or only minimal consequences for developmental outcome. Yet, their significance for neurodevelopmental outcome remains controversial [6].

Diffuse excessive high signal intensity (DEHSI) is a frequent finding in preterm infants; Dyet et al. detected DEHSI in 80 % of their cohort of preterm infants born less than 30 weeks gestational age (GA) [7]. DEHSI is diagnosed at term-equivalent age (TEA) as regions of long T1 and T2 relaxation times within the WM, approaching those of the cerebrospinal fluid. Several studies examined the impact of DEHSI on neurodevelopmental outcome [7–14], reporting mixed results. However, many of these studies included infants with a wide range of brain abnormalities, making it hard to distinguish the impact of DEHSI alone on neurodevelopmental outcome from the effect of other brain abnormalities. Several studies using diffusion tensor imaging (DTI) in regions with DEHSI implied microstructural differences in WM areas with DEHSI [10, 11, 15–17, 18], but it is unclear whether these differences are related to later neurodevelopmental difficulties.

The current prospective study assessed the significance of "isolated" DEHSI in a preselected, homogenous group of preterm infants, comparing perinatal characteristics and neurodevelopmental outcome at 1 year corrected age between those with mild to moderate DEHSI and no other brain abnormalities and those without DEHSI. We further investigated WM DTI values in major WM fiber volumes of interest (VOIs) in preterm infants with different degrees of DEHSI and their correlation with outcome at 1 year corrected age.

Materials and methods

Participants Fifty-eight premature infants born at GA <34 weeks were included in the study. Inclusion criteria consisted of mild to moderate echogenicity identified on routine cranial ultrasound (cUS) performed within a week of birth in the neonatal intensive care unit (NICU). Echogenicity was assessed in relation to the echogenicity of the choroid plexus in the deep and periventricular WM in various regions as we recently described [19]. In the present study, echogenicity was used solely for inclusion criteria. The preterm infants who met the inclusion criteria underwent an MRI scan around TEA. We defined a TEA MRI scan as one obtained at postmenstrual age (PMA) of 36–42 weeks.

Exclusion criteria were significant findings on cUS such as greater than grade II intraventricular hemorrhage (according to the Volpe classification [20]), cystic periventricular leukomalacia, periventricular hemorrhagic infarction, and cerebral malformations; cerebellar malformation or cerebellar injury; genetic disorders; or any contraindication to MRI such as recent surgery or implants. Nine infants were excluded from the study due to structural abnormalities on TEA MRI. Two additional infants were excluded because their MRI scan was performed earlier than 36 weeks. Forty-six infants were included in the analysis.

Mean PMA at scanning was 37.5±1.5 weeks. Scans were performed on a 3-T GE Signa HDXT scanner (Milwaukee, WI, USA), using an eight-channel head coil. MR setup was performed according to the guidelines in Mathur et al. [21]. Briefly, infants were fed approximately half an hour before the procedure. During the scan, performed without sedation, infants were warmed and wrapped in a special cover and mattress. MRI noise was attenuated by using adapted neonatal ear muffs (NeoNatal Noise Guards, Newmatic Sound Systems), and a special microphone (Optoacoustics) was used to monitor any distress of the infant. For all subjects, blood oxygen saturation and pulse were monitored throughout the scan.

The MRI protocol included structural imaging: T1-weighted, T2-weighted, fluid attenuation inversion recovery (FLAIR), and gradient echo (GRE) imaging. In addition, DTI acquisition was performed with the following parameters: a set of axial GRE echo planar images covering the entire brain were prescribed using 33 diffusion gradient directions and b values of 0.700 s/mm^2.

WM signal assessment Regions with DEHSI were defined on T2-weighted MRI images as an increased signal intensity on T2, which extended beyond the regions of the crossroads [22, 23] toward the subcortical WM and appearance of multifocal intensities. Hypointensities in T1 were used for assessment of normal myelinization. A subset of the MRI images was scored independently by two senior pediatric neuroradiologists. The concordance between assessors was 95 %, kappa=0.783; $p<0.001$.

DEHSI was scored separately within four brain regions (frontal, posterior frontal, parietal, and occipital) and within the two hemispheres. All regions consisted of mainly deep WM, except for the posterior frontal region which also contained periventricular WM (see Fig. 1). We have previously described this methodology in detail [19]. The degree of DEHSI was defined as hyperintensity in the deep WM of the assessed brain region in relation to the hyperintense T2 signal of the "crossroads" in the periventricular WM [22] and as appearance of multifocal intensities (see Fig. 2). DEHSI was classified as follows: 0="none," no hyperintense signal was detected; 1="mild," slightly more hyperintensity detected but easily differentiated from the crossroads; and 2="moderate," diffuse homogenous hyperintense signal of the WM which is difficult to differentiate from the crossroads [19].

Regional DEHSI classifications were summed to give a total DEHSI score for each individual. The total DEHSI score (range 0–16) reflected the extent (number of areas with DEHSI), degree (0=normal, 1=mild, 2=moderate), and

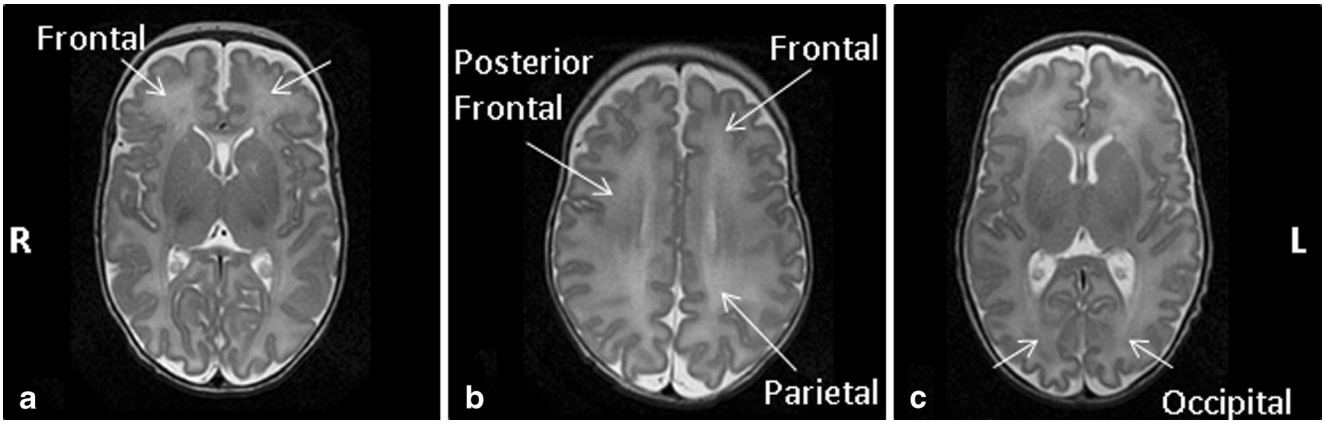

Fig. 1 Regional assessment of DEHSI on MRI: **a** frontal region, **b** posterior frontal and parietal regions, **c** occipital region. The DEHSI in these images was classified as mild

spatial distribution (unilateral or bilateral) of DEHSI. Subjects were subsequently classified into three groups using *k*-mean cluster analysis (k=10): no DEHSI (score=0), mild DEHSI (score=1–5), and moderate DEHSI (score=6–16).

DTI data analysis Using FMRIB Software Library (FSL) software (FMRIB, Oxford, UK, www.fmrib.ox.ac.uk/fsl) and the Johns Hopkins University (JHU) neonate space, DTI analysis was performed for major cerebral WM VOIs (corpus callosum [CC], posterior limb of the internal capsule [PLIC], optic radiations [OR], corona radiata (CR), cerebral peduncle [CP]) and the corticospinal tract (CST) [24]. In terms of anatomical locations, the CR VOI was located in the centrum semiovale (CSO) and the CST VOI was located in the corticospinal tracts at the level of the pontine WM.

Motion and eddy current corrections were performed using FSL software. The realignment and reslicing of the diffusion calculated maps were performed using affine transformation via the FSL linear image registration tool. A fractional anisotropy (FA) threshold of 0.2 was used for extracting the major WM skeleton in order to correct partial volume effects. Mean values of FA, mean diffusivity (MD), axial diffusivity (Da), and radial diffusivity (Dr) were averaged within each VOI.

Mean values of FA, MD, Da, and Dr were measured. Of the 46 infants who met the inclusion criteria, 41 infants had DTI data available; from the remaining five, no DTI data were available due to head movement artifacts.

Perinatal characteristics Medical information collected from the NICU included relevant maternal information, GA, birth weight, head circumference at birth, and gender.

Neurobehavioral assessment Outcome at 12 months (corrected age) was assessed by the Griffiths Mental Development Scales (GMDS) [25], performed by a qualified psychologist (MW). The GMDS provides an overall

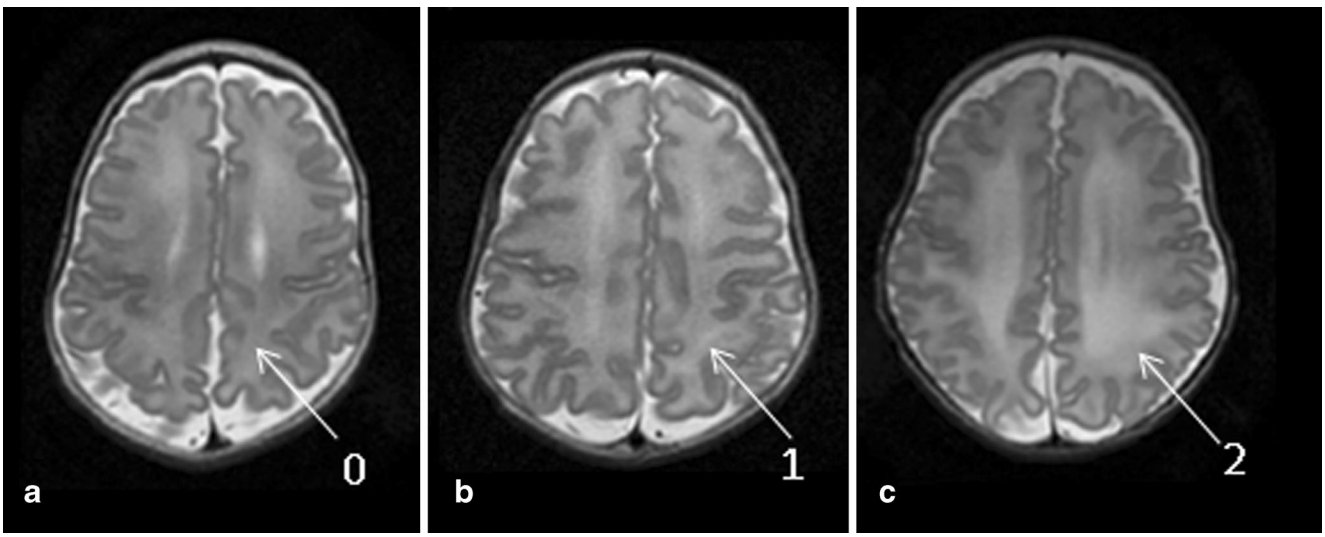

Fig. 2 Classification of DEHSI in the parietal region: **a** no DEHSI, **b** mild DEHSI, **c** moderate DEHSI

developmental quotient with subscales assessing six key skill areas (locomotor, personal-social, hearing and speech, hand-eye coordination, performance) and was scored according to corrected age. In addition, a neurological examination was performed by one of three experienced pediatric neurologists (YL, SU, KG). Parents completed the Parental Stress Index (PSI), a questionnaire which reflects parental coping [26].

Statistical analysis *K*-mean cluster analysis (k=10) was used to cluster the total DEHSI scores into three groups. One-way MANOVA was performed to investigate differences in perinatal variables, diffusion parameters, and neurobehavioral outcome measures between preterm infants according to DEHSI classification. The time interval from GA at birth until the GA at MRI scan was calculated. For comparison of the perinatal characteristics, GA at birth was used as a covariate. Bonferroni correction was used to account for multiple comparisons. Chi-square test was performed to investigate differences in noncontinuous variables between the various DEHSI groups. Pearson correlations were computed to test the relationship between total DEHSI score, diffusivity parameters in specific VOIs, and neurobehavioral outcome assessment. Pearson correlations were used to test the relationship between the time interval from birth to MRI and total DEHSI score. Correlations of the time interval from birth to MRI with diffusivity parameters of the VOIs were calculated in each DEHSI group. Additional analyses included correlations between DEHSI score in the right and left hemispheres with GMDS scores, and ANOVA was performed to examine differences in GMDS scores according to regional DEHSI classification. The level of significance for all statistical analyses was <0.05. All statistics were performed with SPSS version 17 (SPSS Inc., Chicago, IL).

Results

Overall, 46 infants born at GA <34 weeks (mean GA=29.22± 2.6 weeks; 57 % male) underwent MRI at TEA and developmental assessment at 1 year corrected age.

The distribution of DEHSI

DEHSI was detected by TEA MRI in 31 (63 %) of the preterm infants. Ten (22 %) of them displayed DEHSI in one brain region, while the remainder exhibited DEHSI in multiple regions. The regional distribution of DEHSI was as follows: the frontal region was involved in 12 (26 %) infants, the posterior frontal region in 17 (37 %) infants, the parietal region in 22 (48 %) infants, and the occipital region in 12 (26 %) infants. DEHSI was not detected in 18 (39 %) infants.

The range of total DEHSI scores in our sample was 0–12 points. Mild DEHSI was found in 18 (39 %) and moderate DEHSI in 10 (22 %) subjects.

Perinatal characteristics related to DEHSI groups

Infants without DEHSI were born at earlier GA (28.11±2.70 vs. 30.64±1.91 weeks, p=0.049) with smaller head circumference (25.6±2.6 vs. 27.7±2.0 cm, p=0.029) and spent more days hospitalized in the NICU (70±31 vs. 39±17 days, p= 0.008) compared to infants with moderate DEHSI. When using GA as a covariate, there were no statistically significant differences in perinatal characteristics between DEHSI groups, except for head circumference at birth, as shown in Table 1.

Time interval between GA at birth and at MRI

A significant negative correlation was found between the time interval from birth to MRI and total DEHSI score (r=−0.38, p=0.01), indicating that the longer the extrauterine exposure (=time interval), the lower the total DEHSI score. The group difference in the time interval was close to significance (F(2,45)=2.84; p=0.067); preterm infants with no DEHSI had a longer time between birth and TEA MRI compared to preterm infants with moderate DEHSI (9.6±3.4 vs. 6.8± 2.8 weeks); see Table 1.

Diffusivity values in major WM fiber VOIs by DEHSI groups

In general, preterm infants with no DEHSI showed lower diffusivity values at TEA compared to preterm infants with mild and moderate DEHSI. There was a significant main effect of DEHSI classification on diffusivity values at the PLIC (MD: F(2,40)=8.624, p=0.001; Da: F(2,40)=4.190, p=0.023; Dr: F(2,40)=7.684, p=0.002), the CSO (FA: F(2,40)=6.090; p=0.005; MD: F(2,40)=8.947, p=0.001; Da: F(2,40)=7.270, p=0.002; Dr: F(2,40)=9.527, p= 0.0001), and the OR (FA: F(2,40)=3.518, p=0.040; MD: F(2,40)=4.039, p=0.026; Dr: F(2,40)=4.767, p=0.014). For mean diffusivity values according to DEHSI group, see Table 2. No significant differences in diffusivity parameters were detected between DEHSI groups in the CC, CP, and CST—at the level of the pontine WM. Bonferroni-corrected post hoc tests demonstrated significant differences in the diffusivity parameters between the no DEHSI group and the two DEHSI groups, but not between the mild and moderate DEHSI groups. For representative graphs, see Fig. 3.

Table 1 Perinatal characteristics in the NICU by DEHSI groups

Variable	Total	No DEHSI (n=18)	Mild DEHSI (n=20)	Moderate DEHSI (n=8)	p value
GA (weeks)	29.2±2.6	28.1±2.7	29.5±2.4	30.6±1.9	0.049*
Birth weight (g)	1,248±438	1,065±308	1,335±451	1,445±545	0.676
Head circ. at birth (cm)	27±2.7	25.6±2.6	27.8±2.5	27.7±2.0	0.023*
Male	26 (56.5 %)	11 (61 %)	12 (60 %)	3 (37.5 %)	0.489
GA at MRI (weeks)	37.5±1.5	37.7±1.6	37.5±1.6	37.3±1.3	0.748
Time interval (weeks)	8.4±3.3	9.6±3.4	7.9±2.9	6.8±2.8	0.069

Figures presented are mean ± standard deviation or number (%). Categorical variables were analyzed with chi-square test; continuous variables were analyzed with ANCOVA, adjusted for gestational age (GA)

Circ. circumference

*$p<0.05$

Maturation trajectories in major WM fiber VOIs by DEHSI group

In the no DEHSI group, significant correlations were detected between the time interval from birth to MRI and diffusivity parameters in the PLIC (MD: $r=-0.61$, $p=0.01$; Da: $r=-0.65$, $p=0.007$), CSO (FA: $r=0.64$, $p<0.007$; MD: $r=-0.68$, $p<0.004$; Da: $r=-0.64$, $p<0.008$; Dr: $r=-0.68$, $p<0.004$), and CST—at the level of the pontine WM (Da: $r=-0.55$, $p=0.026$). In the mild DEHSI group, the only significant correlation detected was between the time interval and FA in the CSO ($r=-0.77$, $p=0.001$). No correlations were detected in the moderate DEHSI group. In addition, no correlations were detected between the time interval and the other VOIs in any group. Figure 4 demonstrates the diffusivity values in the PLIC and CSO by DEHSI group, in relation to the time interval (extrauterine exposure)

Table 2 Mean FA and diffusivity values in WM VOIs by DEHSI groups

Fiber tract	DEHSI group	N	FA (a.u.) Mean (std.)	MD ($\times10^{-3}$ mm^2/s) Mean (std.)	Da ($\times10^{-3}$ mm^2/s) Mean (std.)	Dr ($\times10^{-3}$ mm^2/s) Mean (std.)
CC	None	16	0.233 (0.02)	1.536 (0.12)	1.921 (0.14)	1.344 (0.11)
	Mild	15	0.241 (0.02)	1.564 (0.09)	1.970 (0.10)	1.360 (0.09)
	Moderate	10	0.229 (0.02)	1.592 (0.11)	1.984 (0.14)	1.395 (0.10)
PLIC	None	16	0.307 (0.04)	1.144 (0.06)[a]	1.540 (0.06)[a]	0.945 (0.07)[a]
	Mild	15	0.292 (0.04)	1.191 (0.05)	1.580 (0.05)	0.997 (0.06)
	Moderate	10	0.273 (0.02)	1.236 (0.06)	1.609 (0.07)	1.049 (0.07)
CP	None	16	0.270 (0.04)	1.145 (0.06)	1.482 (0.06)	0.976 (0.08)
	Mild	15	0.264 (0.03)	1.149 (0.08)	1.485 (0.10)	0.981 (0.08)
	Moderate	10	0.250 (0.02)	1.167 (0.07)	1.489 (0.09)	1.006 (0.07)
CR	None	16	0.204 (0.02)[a]	1.377 (0.10)[a, b]	1.663 (0.10)[a, b]	1.235 (0.10)[a, b]
	Mild	15	0.189 (0.02)	1.473 (0.08)	1.756 (0.09)	1.332 (0.08)
	Moderate	10	0.181 (0.01)	1.524 (0.09)	1.810 (0.10)	1.381 (0.08)
OR	None	16	0.226 (0.02)[a]	1.569 (0.13)[a]	1.952 (0.16)	1.378 (0.11)[a]
	Mild	15	0.215 (0.02)	1.582 (0.11)	1.948 (0.12)	1.398 (0.11)
	Moderate	10	0.203 (0.01)	1.698 (0.12)	2.076 (0.16)	1.509 (0.10)
CST	None	16	0.200 (0.03)	1.210 (0.08)	1.469 (0.11)	1.080 (0.08)
	Mild	15	0.192 (0.02)	1.242 (0.08)	1.490 (0.09)	1.119 (0.08)
	Moderate	10	0.191 (0.02)	1.267 (0.11)	1.527 (0.15)	1.136 (0.09)

CC corpus callosum, *PLIC* posterior limb of internal capsule, *CP* cerebral peduncle, *CR* corona radiata, *OR* optic radiations, *CST* corticospinal tract, *FA* fractional anisotropy, *MD* mean diffusivity, *Da* axial diffusivity, *Dr* radial diffusivity, *a.u.* arbitrary units, *std.* standard deviation

[a] Significant differences between infants with no DEHSI and moderate DEHSI

[b] Significant differences between infants with no DEHSI and mild DEHSI

$p<0.05$, corrected for multiple comparisons using Bonferroni

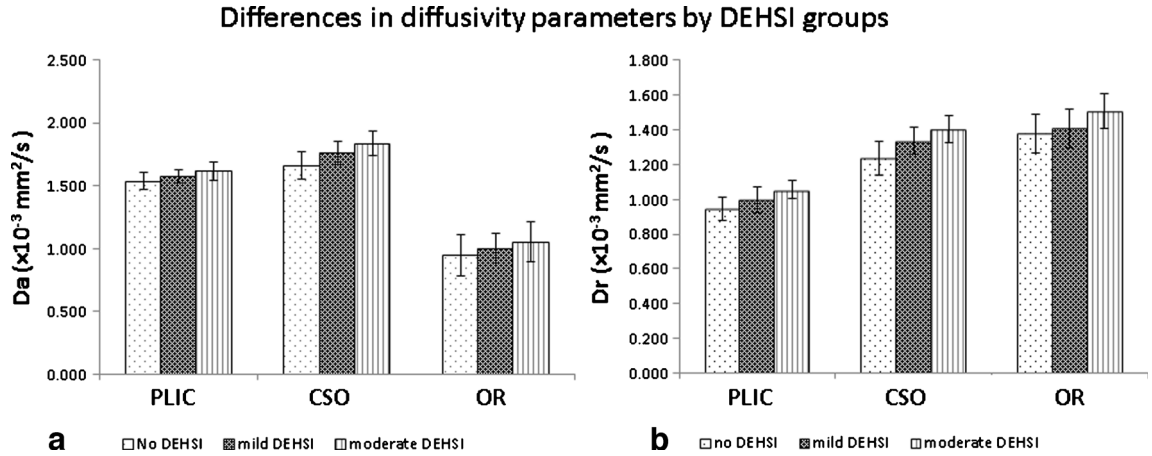

Fig. 3 Differences in diffusivity parameters between DEHSI groups in the posterior limb of the internal capsule (PLIC), centrum semiovale, and optic radiations (OR): **a** axial diffusivity (Da), **b** radial diffusivity (Dr)

Neurobehavioral assessment at 1 year corrected age

Two children were lost to follow-up. The majority of children had normal neurological examination at 1 year corrected age (see Table 3). Mild hypotonicity was identified in 24 (52 %) children, and other neurological abnormalities were infrequent (see Table 3). Mean total GMDS score in all subjects was within the normal range, 92.93±7.59 (GMDS normative score is 100±15).

In the locomotor and personal-social subscales, the majority of infants showed scores above 85, demonstrating normative performance in these categories: 15 % of the infants showed scores under 85 (<1 SD) on the locomotor scale, and 2 % scored below 1 SD on the personal-social scale. A larger proportion of children manifested scores lower than 1 SD in the hearing and language scales (39 %), the hand-eye coordination scale (37 %), and the performance subscale (67 %).

Association between DEHSI and neurobehavioral assessment at 1 year corrected age

No significant differences were detected in the outcome measures (neurological outcome or GMDS scores) assessed at 1 year corrected age between the three DEHSI classification groups as shown in Table 3. Total DEHSI score did not correlate with the total Griffiths score (r=0.157; p=0.297) or with any of the GMDS subscales. Furthermore, children who showed mild delay (more than 1 SD below the normative mean) did not have significantly different total DEHSI score than those with normal scores.

Correlations between DEHSI score in the right and left hemispheres and developmental outcome at 1 year did not detect any significant associations. There were no significant differences in GMDS scores by regional DEHSI scores, except for the parietal region where DEHSI was associated with higher score on the Griffiths motor scale [99.3 vs. 91.5] (F(1,42)=5.675, p=0.022).

Parental Stress Index

The mean total score was 63.41±15.37, range 38–97. A score of above 90 indicates clinically significant levels of stress [27]. There were no significant differences in PSI scores between the DEHSI groups (p=0.378).

Discussion

WM abnormalities detected by MRI in preterm neonates are correlated with neurodevelopmental outcome [28]; therefore, knowledge of WM characteristics is important for targeting those children requiring early intervention and for parental counseling. Our prospective study undertook to evaluate the 1 year neurobehavioral outcome of a group of preterm infants, selected by the absence of major structural lesions based on their perinatal cUS examinations. While infants with and without DEHSI showed mild neurodevelopmental difficulties, we did not detect differences between infants with mild/moderate DEHSI or without DEHSI in either the primary perinatal (NICU) characteristics or the neurological and neurobehavioral outcome at 1 year corrected age. In addition, the location and degree of DEHSI were not related to outcome. The neurodevelopmental difficulties found can be attributed to prematurity as previously described by others [2, 29].

Contrary to expectation, preterm infants without DEHSI at TEA were born at an earlier GA than preterm infants with moderate DEHSI. We could not find, in the present data, any perinatal factor explaining this finding. This trend was previously reported but not discussed by Jeon et al. [10] and by Kidokoro et al. [11]. Kidokoro et al. showed that DEHSI grade 0 and grade 1 were found at earlier GA [11]. We addressed this

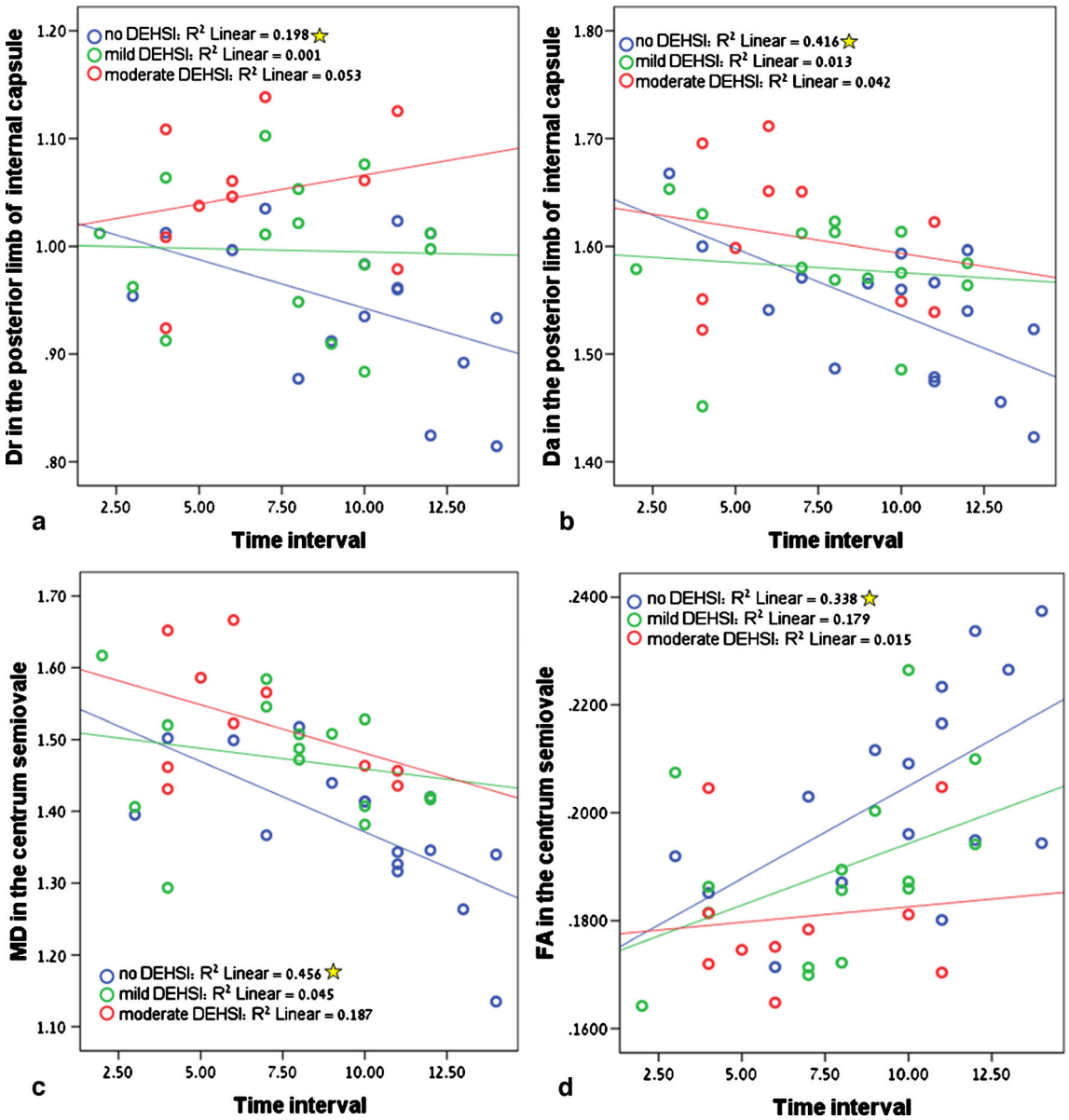

Fig. 4 Scatter plots of diffusivity parameters and FA with time interval according to DEHSI classification. Note that in the no DEHSI group, the longer the exposure to the extrauterine environment, the more mature the WM in the centrum semiovale (CSO VOI) and in the posterior limb of the internal capsule (PLIC VOI): **a** Dr in the PLIC VOI, **b** Da in the PLIC VOI, **c** MD in the CSO, **d** FA in the CSO VOI

counterintuitive finding by looking at the time interval from birth to the TEA MRI scan in relation to the degree of DEHSI and found a negative correlation between the time interval and degree of DEHSI, indicating that the longer the exposure to the extrauterine environment, the less overall DEHSI was detected.

In normal development, maturational stages are reflected by microstructural changes, such as changes in water content and membrane density that are measured by an overall decrease in MD, Dr, and Da from birth to childhood, with the Dr showing a higher rate of decline [30], resulting in an increase in FA with age [31]. In our study, we used DTI in order to objectively validate the subjective radiological assessment of DEHSI by measuring diffusivity parameters in WM VOIs of the preterm infants. Looking at the DEHSI group as a whole, some WM VOIs (PLIC, CSO, and OR) demonstrated higher diffusivity values and lower FA, compatible with reduced or delayed WM maturation, while others (CP and CST at the level of the pontine WM) were not different between those with or without DEHSI at TEA. In the group without DEHSI at TEA, diffusion parameters reflected progressively more mature WM with longer extrauterine exposure time, whereas in the groups with mild-moderate DEHSI at term, the association between extrauterine exposure and more mature WM diffusion parameters was not detected (see Fig. 4). These observations support the hypothesis of delayed or altered

Table 3 Clinical, neurological, and developmental characteristics at 1 year

Variable	Total	No DEHSI (n=18)	Mild DEHSI (n=20)	Moderate DEHSI (n=8)	p value
Head circumference (cm)	45.55±1.65	45.13±1.16	46.09±1.19	44.98±2.37	0.126
Weight (kg)	9.30±1.03	9.26±1.03	9.32±0.87	9.29±1.50	0.992
Hypotonia	24 (52 %)	8 (44 %)	13 (65 %)	3 (37.5 %)	0.260
Hypertonia	0	0	0	0	NA
Symmetry abnormality	1 (2 %)	0	1	0	NA
DTR	3 (6.5 %)	1 (5.5 %)	2 (10 %)	0	0.379
Hemiparesis	0	0	0	0	NA
Diplegia/quadriplegia	0	0	0	0	NA
Spasticity	0	0	0	0	NA
Pyramidal signs	1 (2 %)	0	1	0	0.343
Extrapyramidal signs	0	0	0	0	NA
Significant clumsiness	0	0	0	0	NA
Ataxia	0	0	0	0	NA
Dysmetria	0	0	0	0	NA
GMDS locomotor	95.38±11.33	90.19±9.64	99.23±11.23	96.29±12.03	0.054
GMDS personal-social	107.76±11.42	107.31±12.81	107.28±12.18	110.14±5.11	0.840
GMDS language and hearing	89.7±11.56	89.81±11.10	89.12±13.14	91.14±8.86	0.926
GMDS hand-eye coordination	88.45±12.08	90.13±9.60	87.90±13.99	86.21±12.57	0.754
GMDS performance	83.27±8.92	80.38±6.90	84.59±9.09	86.14±11.76	0.246
GMDS DQ	92.93±7.59	91.56±6.56	93.63±8.73	94.03±6.83	0.669

Figures presented are mean ± standard deviation or number (%). Normative GMDS scores are 100±15

GMDS Griffith Mental Developmental Scales, *DQ* developmental quotient, *DTR* deep tendon reflexes

WM maturation trajectory in infants with DEHSI at least in the specified areas. Counsell et al. [17] have previously reported similar data of elevated Dr in the PLIC, splenium, CSO, frontal, periventricular, and occipital WM in preterm infants with DEHSI.

In preterm infants who had neonatal brain ultrasounds without major structural lesions, Gimenez and colleagues [32] noted higher values for FA at TEA when compared with term controls in areas corresponding to fiber tracts of the neurosensory pathways of vision and hearing that mature more rapidly in preterm infants owing to early experience. A recent study reported that FA in the optic radiations at TEA was related to both PMA at birth and PMA at scan and revealed an effect of the period of premature extrauterine life which was additional to the degree of prematurity [33]. Our finding of more mature WM associated with longer exposure to the extrauterine environment in infants without DEHSI at TEA, but not in those with DEHSI, suggests a differential maturational trajectory of the WM between both groups, which may result from the longer exposure to the extrauterine environment in preterm infants without DEHSI at TEA.

In our study, as found in recent studies [9–12, 34], no direct association was documented between DEHSI and neurobehavioral outcome. However, some of these previous studies were hampered by a retrospective design using heterogeneous clinical samples, including infants with other WM lesions [10, 12, 34]. Other studies performed MRI earlier or after TEA [10, 12], which could change the prevalence of DEHSI, known to be an age-dependent radiological phenomenon (see Fig. 3 in [12]). The current study overcame some of these obstacles by using a prospective design and by recruiting a homogenous group of preterm infants with only mild or moderate white matter echogenicity and no major brain abnormalities. Despite the relatively small sample size, this highly selective group allows for the "isolation" of the impact of DEHSI on later neurodevelopment and thereby strengthens the findings of previous studies that did not find an association between DEHSI and adverse early outcome [10–12].

No significant differences in parental stress were found between the DEHSI groups. This may be attributed to the fact that parental stress was assessed when the infant was 1 year of age and not during hospitalization in the NICU when stress levels were probably elevated.

Limitations of our study include the small study group. Due to ethical constraints, we did not perform serial perinatal MRI, which could have provided information regarding the timing of the appearance of DEHSI and its evolution during the first weeks of extrauterine life with regard to prognosis. An

additional limitation was that neurobehavioral follow-up was restricted to 1 year corrected age, limiting our ability to detect more subtle neurocognitive difficulties, although it does rule out major handicaps.

The present study does not provide a direct answer to the question of what DEHSI is, but our DTI analysis indicates it is related to altered WM integrity and to altered maturational trajectory. We have shown that DTI parameters were correlated with extrauterine exposure time in those without DEHSI, reflecting altered WM maturation, but this consistent correlation with time was not found in the group with DEHSI at TEA. These results confirm that DEHSI is a real phenomenon, reflected by alterations at the microstructural level. While we cannot rule out an early injury to the oligodendrocytic or astrocytic lineage as a possible etiology of this altered maturation, the fact that DEHSI was not related to perinatal neurological risk factors or to abnormal neurobehavioral outcome at 1 year suggests a maturational "delay" rather than permanent WM injury. Other investigators have also shown that DEHSI does not predict abnormal neurodevelopment at 1 year of age and at older ages (10–12, 35), suggesting that WM maturation during the first year compensates, at least at the clinical level, for this delayed or altered maturation. Further neurocognitive evaluations at school age are warranted, however, to appreciate learning disabilities that would not be apparent in a toddler.

These findings should reassure parents when "isolated" DEHSI is detected at TEA MRI, but larger studies using serial MRI and DTI with regard both to the nature and progression of DEHSI and its prognostic implications are still needed.

Ethical standards and patient consent We declare that all human and animal studies have been approved by the Institutional Review Board of the Ministry of Health and the Hospital Ethics Committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all participants gave informed consent prior to inclusion in this study.

Conflict of interest We declare that we have no conflict of interest.

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