Imaging the preterm infant's brain
Leijser, L.M.

Chapter 8

Comparing brain white matter on sequential cranial
ultrasound and MRI in very preterm infants

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Abstract

Background and Aim:

Periventricular white matter (WM) echodensities, frequently seen in preterm infants, can be associated with suboptimal neurodevelopment. Major WM injury is well detected on cranial ultrasound (cUS). cUS seems less sensitive for diffuse or more subtle WM injury. Our aim was to assess the value of cUS and magnetic resonance imaging (MRI) for evaluating WM changes and the predictive value of cUS and/or MRI findings for neurodevelopmental outcome in very preterm infants with normal to severely abnormal WM on sequential high-quality cUS.

Patients and Methods:

Very preterm infants (< 32 weeks) who had sequential cUS and one MRI within the first 3 postnatal months were included. Periventricular WM on cUS and MRI was compared and correlated with neurodevelopmental outcome at 2 years corrected age.

Results:

Forty preterm infants were studied; outcome data were available in 32. WM changes on sequential cUS were predictive of WM changes on MRI. Severely abnormal WM on cUS/MRI was predictive of adverse outcome, and normal/mildly abnormal WM of favourable outcome. Moderately abnormal WM on cUS/MRI was associated with variable outcome. Additional MRI slightly increased the predictive value of cUS in severe WM changes.

Conclusions:

Sequential cUS in preterm infants is reliable for detecting WM changes and predicting favourable and severely abnormal outcome. Conventional and diffusion-weighted MRI sequences before term equivalent age in very preterm infants, suggested on cUS to have mild to moderately abnormal WM, do not seem to be warranted.

Introduction

Cranial ultrasound (cUS) is the preferred and most readily available tool to assess the neonatal brain (1). It is a safe and reliable technique for demonstrating the most frequently occurring forms of cerebral injury in preterm infants, assessing the evolution of lesions, and following brain development (1-7). Magnetic resonance imaging (MRI) demonstrates site and extent of cerebral lesions more precisely and shows maturational processes in detail (3-4,8-10).

In preterm infants, increased echogenicity in the periventricular white matter (WM), so-called periventricular flaring, may represent ischaemic and/or inflammatory damage. Flares are transient, persisting for a variable period of time, and can subsequently resolve or evolve into cystic lesions (2). When persisting for over one week and when the echogenicity exceeds that of the choroid plexus, flares are considered the first stage of periventricular leukomalacia (PVL) (2). Cystic forms of PVL are associated with neurological impairment and are well demonstrated by cUS (6,11-12). Milder flares, not evolving into cysts, are more frequently encountered in preterm infants and, if long-lasting, may also be associated with suboptimal or deviant neurological development, especially if there is change in ventricular size or shape (2,4-6,13-16). However, they may also represent normal maturational phenomena in the immature brain (9,17). Therefore, it is important to recognize pathological flares, especially those associated with neurological sequelae.

Diffuse WM injury has been described in MRI and pathology studies in newborn infants (4-5,10,12,18-24). Several studies have found a poor predictive value of cUS for detecting diffuse or more subtle WM injury (4-5,7,11-12,18,21,23). It has been suggested that MRI should be performed in all very preterm infants, particularly in those with only mild (non-cystic) or no WM changes on cUS (5,11-12,23). However, as MRI is more burdening to the newborn infant and more time-consuming and expensive than cUS, it is not a good tool for serial imaging of the neonatal brain, and it is important to know when MRI is warranted in sick, vulnerable preterm infants. In addition, if MRI is performed, it should be optimally timed in order to detect clinically significant lesions, assess brain maturation, and accurately predict outcome.

The aims of our study were to evaluate the predictive value of WM changes on sequential, high-quality cUS for those seen on MRI, to explore the additional value of MRI within the first 3 postnatal months for detecting WM changes, and to assess the predictive value of cUS and/or MRI findings for neurodevelopmental outcome in very preterm infants. This was done by comparing findings on sequential cUS examinations with MRI findings and by relating cUS and MRI findings to neurodevelopmental outcome at 2 years corrected age.

Patients and Methods

Patients

Very preterm infants born at a gestational age (GA) of < 32 weeks who were admitted to the tertiary neonatal intensive care unit of the Leiden University Medical Center, between May 2001 and April 2004 and underwent at least one MRI examination during the neonatal period, were included in the study. Exclusion criteria were neonatal meningitis, metabolic disorders, chromosomal disorders, congenital cardiac abnormalities and specific syndromes. In unstable infants with septicaemia, the MRI procedure was postponed until the infant was in a stable clinical condition. Medical records, neuro-imaging findings and follow-up data were reviewed.

After exclusion, data of 40 very preterm infants (31 male) were studied. Mean GA of the infants was 28.6 (range 25.1-31.9) weeks and mean birth weight 1203 (689-2062) grams. The mean number of cUS scans performed in each infant during admission was seven (3-16). MRI examinations were performed for various indications including very preterm birth, ventricular dilatation, (suspicion of) parenchymal injury and/or grade 2 echodensities on cUS.

Mean postnatal age and corrected GA at MRI were, respectively, 34.4 (4-111) days and 33.2 (27.3-45.1) weeks. Eight out of 40 infants were scanned at a very young postnatal age of less than 10 days and 32 out of 40 infants thereafter. In five infants, MRI was performed around term equivalent age (TEA) at a mean corrected GA of 39.4 (38.9-40.9) weeks.

Cranial ultrasound

Sequential cUS scans were performed routinely in all very preterm infants, from the day of birth until discharge or transfer to another hospital, and around TEA, according to a standard protocol. The transducer frequency was set at 7.5 MHz. For detection of cortical and/or subcortical abnormalities, higher frequencies up to 10.0 MHz were used, whereas deeper structures were assessed with lower frequencies down to 5.0 MHz. All images were saved on magneto-optical disks.

Of all included infants, the first cUS scan, the cUS scan performed closest to the day of the MRI examination and the last cUS scan before discharge were evaluated retrospectively by at least two experienced investigators (LML, research physician, IPdB, neonatologist, and GvWM, neonatologist) by consensus. The names of the infants were masked on the cUS scans, so the investigators were unaware of the MRI findings and outcome of the infants. Special attention was paid to the presence of echogenicity changes in the brain WM. For each area in the brain (frontal, parietal, occipital, and temporal) the presence and appearance of periventricular echodensities was recorded. The degree of echogenicity of the WM was scored according to the classification by van Wezel-Meijler et al. (9), which gives information on the intensity of periventricular echogenicity. A comment on homogeneity or inhomogeneity of the WM was added (10):

- Grade 0: Normal echogenicity of the periventricular WM (< choroid plexus)
- Grade 1: Moderately increased echogenicity of the periventricular WM, the affected region (or smaller areas within the affected region) being almost as bright or as bright as the choroid plexus. Separate notation: homogeneous, inhomogeneous
- Grade 2: Severely increased echogenicity, the affected region (or smaller areas within the affected region) being obviously brighter than the choroid plexus. Separate notation: homogeneous, inhomogeneous

PVL was scored according to the classification by de Vries et al. (2):
- Grade 1: Transient periventricular echodensities, persisting ≥ 7 days
- Grade 2: Transient periventricular echodensities, evolving into small, localized fronto-parietal cysts
- Grade 3: Transient periventricular echodensities, evolving into extensive periventricular cystic lesions
- Grade 4: Echodensities extending into the deep WM, evolving into extensive cystic lesions

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Peri- and intraventricular haemorrhages were classified according to Volpe (25). The presence of other abnormalities was recorded.

The cUS scans of each infant were scored based on WM changes, i.e. grade of echogenicity and/or PVL. Subsequently, the cUS scans were classified according to the most severe changes in the WM during admission. This was done to enable comparison of the cUS and MRI findings. Sequential cUS scans without echodensities or with homogeneous grade 1 echogenicity were classified as normal (9). cUS scans with inhomogeneous grade 1 echogenicity were classified as mildly abnormal, regardless of the total duration (9-10). Scans with grade 2 echogenicity, regardless of the total duration, and/ or localized, small cystic lesions (PVL grade 2) were classified as moderately abnormal, and those with multicystic PVL (PVL grades 3 and 4) and/or focal echodensities within the WM as severely abnormal (2,9-10).

MRI

MR images were obtained in 40 preterm infants according to a standard MR imaging protocol for newborn infants, using a 1.5 Tesla Philips MR system (Philips Medical Systems, Best, the Netherlands). This protocol comprised T_1-, T_2-, and diffusion-weighted images in the axial plane (slice thickness 4-5 mm, field of view 18-20 cm^2), and T_1-weighted images in the sagittal plane.

The infants were laid supine and snugly swaddled-up during the scanning procedure. Ear protection consisted of neonatal earmuffs (Natus MiniMuffs; Natus Medical Inc, San Carlos, CA, USA). The infant's head was immobilized with moulded foam, placed around the head. Temperature was maintained and heart rate and oxygen saturation were monitored throughout the procedure. A paediatrician experienced in resuscitation and MR procedures was present during the scanning.

All MRI examinations were assessed by consensus by two experienced investigators (GvWM, neonatologist, and LL, paediatric neuroradiologist). The names of the infants were masked on the MR images, so the investigators were unaware of the cUS findings and outcome of the infants. Special attention was paid to the signal intensity (SI) of brain WM. WM injury was scored according to Sie et al. (10). This scoring system was used to rate increasingly severe changes in the periventricular WM. Whenever characteristics of more than one MRI score were present, the highest score was used. MRI scores were

subdivided into different groups to enable comparison of MRI with cUS and to relate MRI to outcome. MRI examinations without WM changes (grade 1) were classified as normal, those with grade 2 and 3 changes (i.e. periventricular zone of changed SI, or ≤ 6 punctate WM lesions) as mildly abnormal, those with grade 4 changes (i.e. > 6 punctate WM lesions and/or small periventricular cysts and/or a few larger focal haemorrhages) as moderately abnormal, and those with grade 5 (i.e. extensive SI changes with haemorrhagic or (pre)cystic lesions in the periventricular WM, with, at most, focal subcortical extension) and grade 6 changes (i.e. diffuse SI changes with haemorrhagic or (pre)cystic lesions involving both the periventricular and subcortical WM) as severely abnormal. Presence of abnormalities other than WM changes was recorded. For MRI examinations performed around TEA (38-42 weeks' gestation), the presence of areas of diffuse and excessive high SI, diffusely distributed within the periventricular or subcortical WM (DEHSI) (19), was recorded on T_2-weighted MR images as a separate entity.

Neurodevelopmental outcome

Preterm infants born at a GA of < 32 weeks and admitted to the neonatal unit of the LUMC participated in a standardized follow-up program until the corrected age of 5 years. In a total of 32 out of 40 preterm infants (80%) with sequential cUS examinations and one or more MRI examinations outcome data were available. From eight out of 40 infants (20%), no outcome data at the corrected age of 24 months were available; two infants (5%) died during the neonatal period, one because of respiratory complications, and the other because of circulatory problems, and six infants were lost to follow-up. The infants were assessed by neonatologists with advanced training. For the purpose of this study, neurodevelopmental outcome data of the examination closest to the corrected age of 24 months were recorded. Mean corrected age at the follow-up examination was 23.2 (22.5-26.0) months. For most infants (n=24), Bayley Scales of Infant Development II scores for motor and mental development were available (26). A Mental or Psychomotor Developmental Index (MDI, PDI) of ≥ 85 was considered normal, a MDI or PDI between 70 and 84 as mildly abnormal, a MDI or PDI between 55 and 69 as moderately abnormal, and a MDI or PDI of < 55 as severely abnormal. Infants of whom Bayley II scores were not available, were assigned to one of the four outcome groups based on the available data from the outpatient clinic.

For this study, normal and mildly abnormal outcome were considered as favourable outcome and moderately and severely abnormal outcome as adverse outcome.

Data analysis

Statistical analyses were performed using SPSS software (version 12.0; SPSS inc., Chicago, Illinois, USA). cUS and MRI findings were compared. Predictive values of cUS findings for MRI findings and cUS and/or MRI findings for neurodevelopmental outcome were calculated. For the purpose of this study, normal and mildly abnormal neuro-imaging findings and normal and mildly abnormal outcome findings were considered together as one group.

Results

Cranial ultrasound (n=40)

In 37 out of 40 infants (93%), periventricular echodensities were seen on sequential cUS. The echodensities persisted for over 7 days and evolved into cystic lesions in 35%. In 22 out of 37 infants, the echodensities had an inhomogeneous appearance in one or more areas of the periventricular WM, while in the other infants, echodensities were consistently homogeneous. In three infants (8%), no echodensities were seen. Twenty-three infants (58%) had grade 1 (14 homogeneous, nine inhomogeneous) and one (3%) grade 2 (homogeneous) echogenicity, and seven infants (18%) had grade 2 and six (15%) grade 3 PVL. In 26 infants (65%), the WM was scored as normal to mildly abnormal, in eight (20%) as moderately abnormal, and in six (15%) as severely abnormal.

MRI (n=40)

In eight out of 40 infants (20%), no WM abnormalities were detected on MRI (grade 1). Eleven infants (28%) showed high SI areas in the periventricular WM (grade 2). In 16 infants (40%) punctate lesions were seen in the WM on both T_1- and T_2-weighted images; in seven infants (18%) six or less (grade 3) and in nine (23%) more than six (grade 4). Four infants (10%) had extensive SI changes in the periventricular WM with haemorrhagic and/or cystic lesions (grade 5) and one infant (3%) had diffuse SI changes

in the periventricular and subcortical WM with haemorrhagic and cystic lesions (grade 6).

In 26 infants (65%), the WM was scored as normal to mildly abnormal, in nine (23%) as moderately abnormal, and in five (13%) as severely abnormal on MRI. In all five infants who underwent MRI around TEA, DEHSI was seen in the frontal and occipital WM on T$_2$-weighted images.

Relation between cUS and MRI (n=35)

Twenty-four out of 35 infants had normal to mildly abnormal, six moderately abnormal, and five severely abnormal WM on both cUS and MRI. The relation between WM changes on cUS and those on MRI are depicted in Table 1. The predictive values of normal to mildly abnormal WM on cUS for normal to mildly abnormal WM on MRI were: sensitivity 0.92, specificity 0.86, positive predictive value (PPV) 0.92, and negative predictive value (NPV) 0.86; those of moderately abnormal WM on cUS for moderately abnormal WM on MRI, respectively, 0.75, 0.91, 0.67, and 0.94; and those of severely abnormal WM on cUS for severely abnormal WM on MRI, respectively, 0.83, 1.00, 1.00, and 0.97. So, sequential cUS predicted WM changes on neonatal MRI.

In 14 out of 23 infants with grade 1 echodensities on cUS, the echodensities had a homogeneous appearance, while in nine out of 23, they appeared inhomogeneous. In the 14 infants with homogeneous echodensities, MRI showed normal WM in four, a periventricular zone of changed SI in eight and punctate lesions in two. In the nine infants with inhomogeneous echodensities, MRI showed normal WM in one, a periventricular zone of changed SI in two, and punctate lesions in six. In the infant with homogeneous grade 2 echodensities, MRI showed punctate WM lesions.

In six out of seven infants with punctate WM lesions on MRI, cUS showed inhomogeneous echodensities in the periventricular WM. These were grade 1 echodensities in five infants and grade 2 echodensities in one infant.

In none of the infants, additional lesions were seen on sequential cUS after the MRI was performed, and the longest time-interval between the MRI and the last cUS examination that was scored was 10 days.

Examples of WM changes on cUS and MRI examinations of studied infants are presented in Figures 1-5.

Table 1. Relation between white matter changes on sequential cUS and on neonatal MRI within the first 3 postnatal months
(n, number of infants)

cUS findings (n=40)	MRI findings		
	Normal/mildly abnormal (n=26)	Moderately abnormal (n=9)	Severely abnormal (n=5)
Normal/mildly abnormal (n=26)	24	2	
Moderately abnormal (n=8)	2	6	
Severely abnormal (n=6)		1	5

Figure 1. Coronal (a) and parasagittal (b) cUS scan of a preterm infant (gestational age 25.1 weeks) at a corrected gestational age of 32.0 weeks (postnatal age 48 days) showing normal appearing brain white matter (classified as normal white matter). Note the symmetrical, subtle echodensities in the frontal white matter that are considered a normal finding in this age group (arrow; reference 9), and the symmetrical echodensities in the area of the basal ganglia (asterisks; reference 36). Transverse T_1- (c) and T_2- (d) weighted MR image at the level of the basal ganglia of the same infant, performed on the same day as the cUS scans, also showing normal appearing brain white matter (classified as normal white matter). Note the normal maturational phenomena of the white matter, especially prominent on the T_2-weighted MR image, showing bands of alternating signal intensity within the white matter (arrows; reference 19). This infant had a normal outcome at 2 years corrected age.
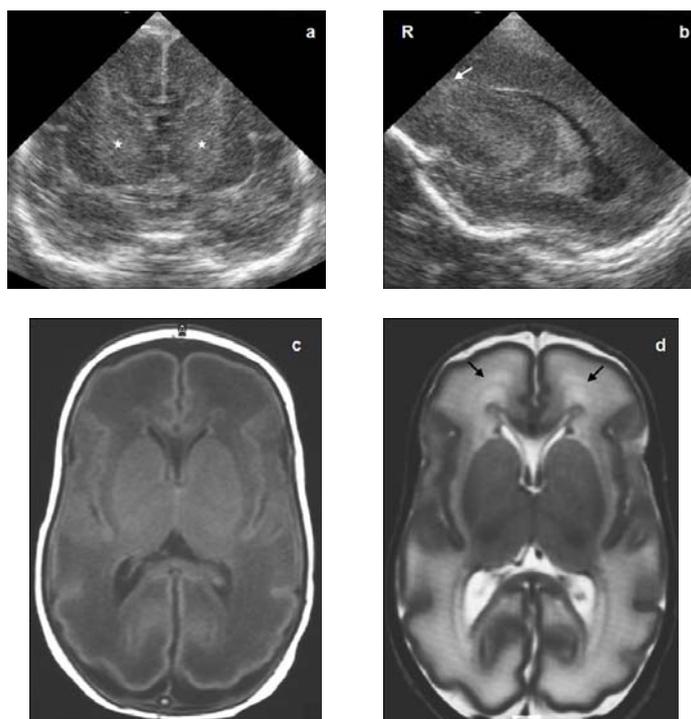
Figure 2. Parasagittal cUS scans (a and b) of a preterm infant (gestational age 28.0 weeks) at a corrected gestational age of 32.4 weeks (postnatal age 31 days) showing mildly increased echogenicity (less than the echogenicity of the choroid plexus) in the parietal white matter (arrows; classified as normal white matter). cUS also demonstrated a right-sided intraventricular haemorrhage grade 2 (not shown here). Transverse T_1- (c) and T_2- (d) weighted MR image at high ventricular level of the same infant, performed 3 days after the cUS scans (postnatal age 34 days), showing punctate haemorrhages (< 6) in the periventricular white matter on the right (arrows; classified as mildly abnormal white matter), an intraventricular haemorrhage on the right, and a very small germinal matrix haemorrhage on the left. This infant had a mildly abnormal outcome at 2 years corrected age.
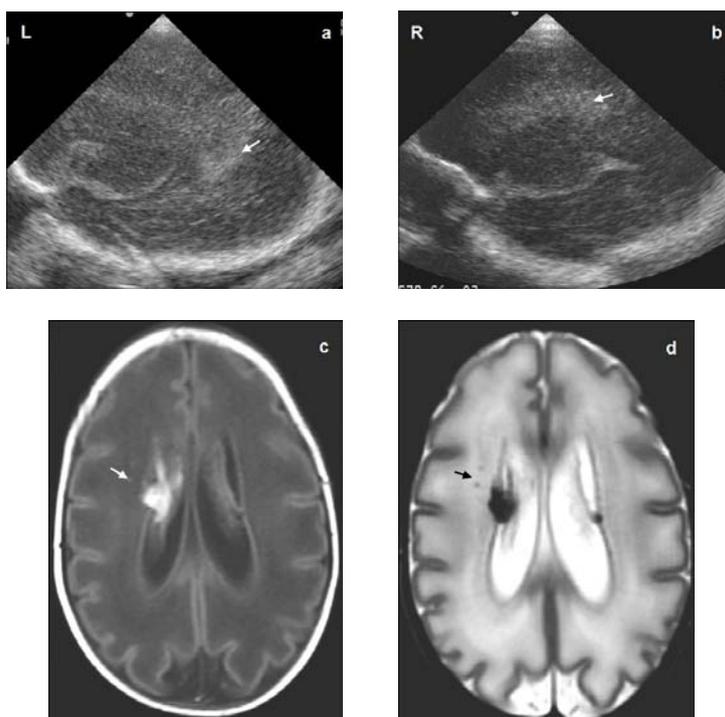
Figure 3. Coronal (a) and parasagittal (b and c) cUS scans of a preterm infant (gestational age 28.1 weeks) at a corrected gestational age of 31.0 weeks (postnatal age 20 days) showing an intraventricular haemorrhage (long arrow) with periventricular intraparenchymal echodensity on the left (medium arrow), rather localized inhomogeneously increased echogenicity in the parietal white matter on the left (short arrow; classified as severely abnormal white matter), and mildly increased echogenicity in the parietal white matter on the right (short arrow; classified as normal white matter). Transverse T_1- (d) and T_2- (e) weighted MR image at the level of the centrum semiovale of the same infant, performed 1 day before the cUS scans (postnatal age 19 days), showing bilateral signal intensity changes in the parieto-occipital white matter on the T_2-weighted MR image (e, long arrows), possibly a normal finding at this age, and several small cystic lesions and punctate haemorrhagic lesions (> 6) in the parietal white matter on the left on the T_1- (d) and T_2- (e) weighted MR image (short arrows; classified as severely abnormal white matter). These abnormalities were also seen at a lower level and extended into the ipsilateral basal ganglia and internal capsule. This infant had a severely abnormal outcome at 2 years corrected age.
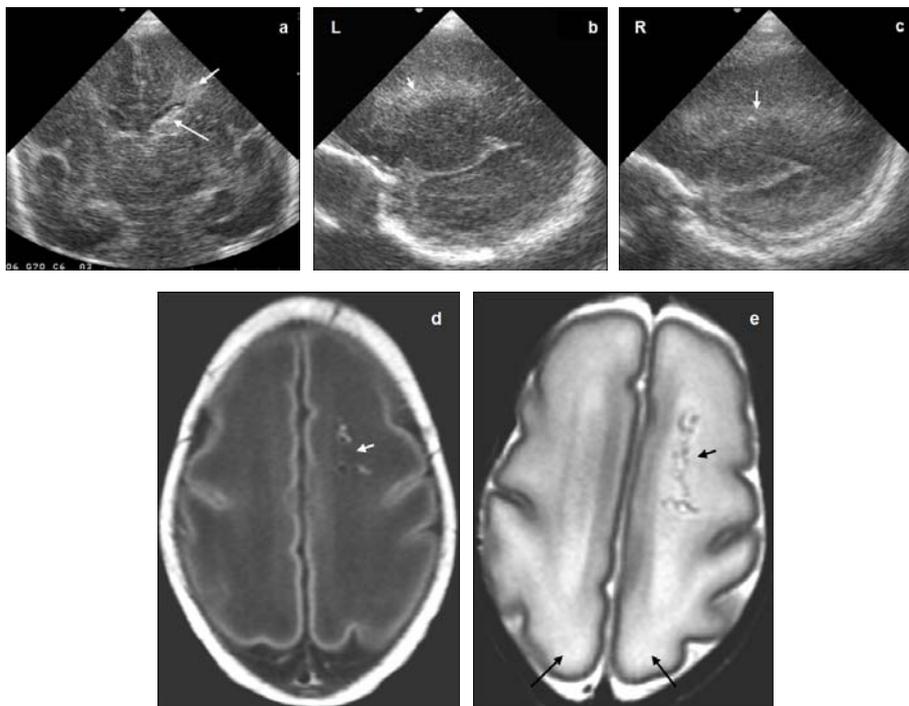
Figure 4. Coronal (a) and parasagittal (b and c) cUS scans of a preterm infant (gestational age 29.1 weeks) at a corrected gestational age of 33.0 weeks (postnatal age 27 days) showing inhomogeneously increased echogenicity in the parietal white matter on both sides (arrows; classified as moderately abnormal white matter). Note the symmetrical echodensities in the area of the basal ganglia (reference 36). Parasagittal T_1-weighted MR image (d) through the right lateral ventricle and basal ganglia region and transverse T_2-weighted MR image (e) at the level of the centrum semiovale of the same infant, performed 2 days after the cUS scans (postnatal age 29 days), showing multiple haemorrhagic lesions (> 6) in the white matter, being punctate on the right (short arrows) and also more extensive on the left (long arrow; classified as moderately abnormal white matter). This infant had a moderately abnormal outcome at 2 years corrected age.
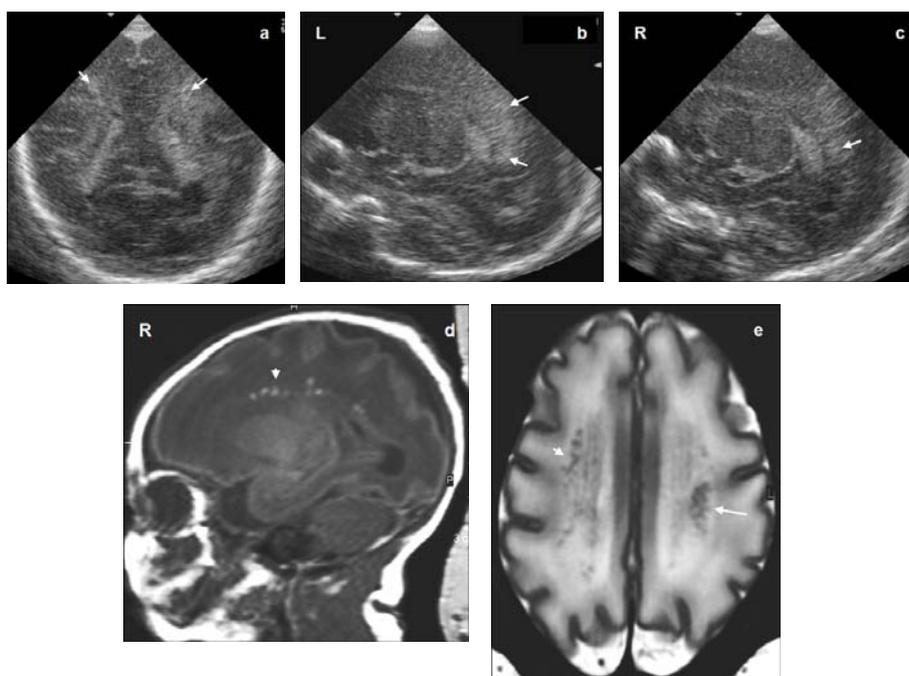
Figure 5. Coronal (a) and parasagittal (b) cUS scan of a preterm infant (gestational age 26.3 weeks) around term equivalent age (corrected gestational age 42.0 weeks, postnatal age 105 days) showing a widened interhemispheric fissure (arrow) and normal appearing brain white matter (classified as normal white matter). Transverse T_2- (c) and diffusion-weighted (d) MR image at high ventricular level of the same infant, performed on the same day as the cUS scans, showing a widened interhemispheric fissure in the frontal region (long arrow). Also showing diffuse and excessive high signal intensity in the frontal and parieto-occipital white matter on the T_2-weighted image (c, short arrows), and high signal in the frontal and parieto-occipital white matter on the diffusion-weighted image (d, short arrows). This infant had a mildly abnormal outcome at 2 years corrected age.
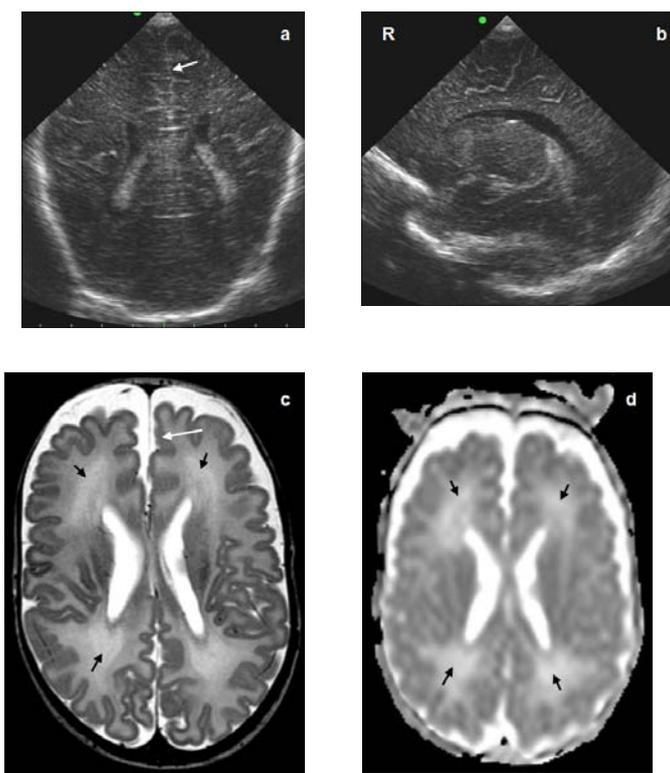
Neurodevelopmental outcome (n=32)

Twenty out of 32 infants (63%) were classified as normal to mildly abnormal, five (16%) as moderately abnormal, and seven (22%) as severely abnormal.

Relation between cUS and outcome (n=32)

The relation between cUS findings and neurodevelopmental outcome is shown in Table 2. The predictive values of normal to mildly abnormal and severely abnormal cUS findings for, respectively, normal to mildly abnormal (favourable) and severely abnormal outcome are shown in Table 3. Moderately abnormal cUS findings were associated with variable outcome. So, normal to mildly abnormal WM on cUS was predictive of normal to mildly abnormal outcome and severely abnormal WM on cUS of severely abnormal outcome, while moderately abnormal WM on cUS had low predictive values for moderately abnormal outcome.

Table 2. Relation between cUS findings and neurodevelopmental outcome at 2 years corrected age
(n, number of infants)

cUS findings (n=32)	Outcome		
	Normal/mildly abnormal (n=20)	Moderately abnormal (n=5)	Severely abnormal (n=7)
Normal/mildly abnormal (n=21)	17	2	2
Moderately abnormal (n=7)	3	2	2
Severely abnormal (n=4)		1	3

Table 3. Predictive values of normal to mildly abnormal and severely abnormal cUS and/or MRI findings for, respectively, normal to mildly abnormal and severely abnormal neurodevelopmental outcome at 2 years corrected age
(n, number of infants; NPV, negative predictive value; PPV, positive predictive value)

Neuro-imaging findings		Predictive values for outcome			
		Sensitivity	Specificity	PPV	NPV
cUS findings (n=32)	Normal/mildly abnormal	0.81	0.73	0.85	0.67
	Severely abnormal	0.75	0.86	0.43	0.96
MRI findings (n=32)	Normal/mildly abnormal	0.80	0.67	0.80	0.67
	Severely abnormal	1.00	0.86	0.43	1.00
cUS and MRI findings (n=28)	Normal/mildly abnormal	0.79	0.78	0.88	0.64
	Severely abnormal	1.00	0.84	0.43	1.00

Relation between MRI and outcome (n=32)

The relation between MRI findings and neurodevelopmental outcome is shown in Table 4. Like for the cUS findings, the predictive values of MRI findings for outcome are shown in Table 3. Comparable predictive values for outcome were found for the MRI findings as for the cUS findings, although severely abnormal WM on MRI was highly predictive of severely abnormal outcome.

In six out of 32 infants, MRI was performed before the postnatal age of 10 days and in 26 out of 32 after 10 days. No differences were found in predictive values of MRI findings for outcome between the two subgroups.

There was no tendency for more severe WM changes (grades 4-6) occurring more often on MRI scans performed after 10 days than before 10 days.

None of the infants developed adverse events after the MRI examination that could be of importance for outcome.

Table 4. Relation between MRI findings and neurodevelopmental outcome at 2 years corrected age
(n, number of infants)

MRI findings (n=32)	Outcome		
	Normal/mildly abnormal (n=20)	Moderately abnormal (n=5)	Severely abnormal (n=7)
Normal/mildly abnormal (n=20)	16	2	2
Moderately abnormal (n=9)	4	3	2
Severely abnormal (n=3)			3

Relation between cUS combined with MRI and outcome (n=28)

From 19 infants with normal to mildly abnormal, all six infants with moderately abnormal and three infants with severely abnormal WM on both cUS and MRI, outcome data were available. The relation between cUS and MRI findings and neurodevelopmental outcome is shown in Table 5. Like for the cUS and MRI findings separately, the predictive values of the combined cUS and MRI findings for outcome are shown in Table 3. Comparable predictive values for outcome were found for the combined cUS and MRI findings as for the cUS findings alone, although severely abnormal WM on cUS and MRI was highly predictive of severely abnormal outcome. Thus, MRI performed within

the first 3 postnatal months slightly increased the predictive value of cUS for severely abnormal outcome.

Table 5. Relation between cUS and MRI findings and neurodevelopmental outcome at 2 years corrected age
(n, number of infants)

cUS and MRI findings (n=28)	Outcome		
	Normal/mildly abnormal (n=17)	Moderately abnormal (n=4)	Severely abnormal (n=7)
Normal/mildly abnormal (n=19)	15	2	2
Moderately abnormal (n=6)	2	2	2
Severely abnormal (n=3)			3

Relation between DEHSI and cUS and outcome findings (n=5)

In all five infants in whom MRI was performed around TEA, DEHSI was present in the frontal and occipital WM. DEHSI on MRI was associated with variable other neuro-imaging findings; one infant had normal WM on cUS and MRI, one mildly abnormal WM and two moderately abnormal WM, and one mildly abnormal WM on cUS and normal WM on MRI. Four of the five infants (80.0%) with DEHSI did not have a normal outcome at 2 years corrected age.

Discussion

This study retrospectively assessed cUS and brain MRI findings within the first 3 postnatal months in very preterm infants, focusing on the periventricular WM. cUS and MRI findings were compared and related to neurodevelopmental outcome. Sequential cUS was predictive of WM changes on neonatal MRI. Our findings are partially consistent with several cUS, pathology, and MRI correlation studies in preterm infants, showing that cUS is a reliable tool for demonstrating major forms of WM lesions, including cystic PVL and parenchymal infarction (2-5,7,10-12,21), but a poorer predictor of diffuse and more subtle WM lesions, such as punctate WM lesions (4-5,7,10-12,18,21,23). In nearly all infants with punctate WM lesions on MRI, cUS showed inhomogeneous grade

1 echodensities in the periventricular WM. We therefore hypothesize that inhomogeneous grade 1 echodensities are the cUS correlate of punctate WM lesions. This is different from previous studies showing that in preterm infants with punctate WM lesions on MRI, no corresponding lesions are detected on cUS (10-11,21) and can be explained by our performance of frequent cUS examinations throughout the neonatal period until TEA. For this study, we did not only assess the cUS performed close to the MRI examination, but assessed three cUS examinations and used the cUS with the most severe WM changes for comparison with MRI.

In the 14 infants with homogeneous grade 1 echodensities, MRI showed normal WM or a periventricular zone of changed SI in all but two infants, while in the nine infants with inhomogeneous grade 1 echodensities, MRI showed punctate lesions in six. In the infant with homogeneous grade 2 echodensities, MRI showed punctate WM lesions. These findings suggest that inhomogeneous echodensities are associated with more severe WM changes on MRI than homogeneous echodensities, which is consistent with a previous study (10).

In all five infants with MRI around TEA, DEHSI was present in the WM. DEHSI is found in up to 80% of preterm infants around TEA and may persist for several weeks (4,19,27). It is associated with cerebral atrophy, WM lesions and significantly increased diffusivity, suggesting that it represents diffuse WM injury (19,22,24,27). Infants with DEHSI have a less optimal neurodevelopment than those with normal appearing WM around TEA (27-28), indicating that DEHSI can be of clinical importance and may be related to the high incidence of neurodevelopmental impairment in preterm infants (29). So far, no cUS correlate has been established for DEHSI. In our infants with DEHSI, WM changes on cUS were variable. Neurodevelopmental outcome of these infants tended to be suboptimal, which may not only be attributable to DEHSI but also to other (WM) abnormalities. From this small group of infants, no conclusions can be drawn about the relation between DEHSI and certain WM changes on cUS and neurodevelopmental outcome.

We found severely abnormal WM on cUS to be predictive of adverse neurodevelopmental outcome at 2 years corrected age, while normal or only mildly abnormal WM was predictive of favourable outcome. If the WM was moderately abnormal on cUS, outcome was variable. These results are partially consistent with those from previous

studies, indicating that severely abnormal WM on cUS generally predicts adverse outcome (3,6-7,30). However, in infants with normal WM, cUS has been suggested to be a poor predictor of neurodevelopmental outcome, attributed to the lower sensitivity of cUS for detecting diffuse and more subtle WM injury (4-5,11-12,18,21,23). Differences between those and our studies include the cUS classification of WM changes; we did not consider the total duration of periventricular echodensities but focused on their degree and homogeneity, comparing the echogenicity of the WM to that of the choroid plexus, and relating outcome to the most severe WM changes during admission. Only homogeneous grade 1 echodensities were considered a normal finding. Grade 2 echodensities were classified as moderately abnormal. Also the frequency and continuation of, and the interval between cUS examinations may differ between studies. We continued cUS throughout the neonatal period until TEA, while others performed cUS less frequently and/or only during the early neonatal period (23).

Several studies have suggested that milder echodensities, if long-lasting, may be associated with suboptimal or deviant neurological development (2,4-6,13-16). Although inhomogeneous echodensities seem to be associated with more severe WM changes on MRI (10), these studies did not make a distinction in appearance of echodensities. Of the 11 infants with homogeneous grade 1 echodensities for whom outcome data were available, 10 were normal or mildly abnormal (seven normal, three mildly abnormal) and only one was severely abnormal at 2 years. This latter infant showed bilateral intraventricular haemorhages grade 3 with post-haemorrhagic ventricular dilatation on neonatal cUS and MRI, which probably explains his severely abnormal outcome. We therefore hypothesize that homogeneous grade 1 echodensities represent normal maturational phenomena in the immature brain, especially if occurring in the frontal or parietal WM (9,17).

Like cUS, severely abnormal WM on MRI within the first 3 postnatal months was highly predictive of adverse outcome, while normal or only mildly abnormal WM predicted a favourable outcome in almost all cases. Moderately abnormal WM on MRI was associated with variable outcome. Previous studies have shown a good correlation between WM changes as detected on MRI and outcome (3,30-31). In our study, moderately abnormal WM on MRI was associated with more variable outcome than in other studies. This may be related to the timing and the variance in timing of the MRI examinations. During

the study-period, MRI in preterm infants was still done before discharge or transfer to another hospital, so mostly before TEA. Nowadays, it is preferably performed around TEA. DEHSI, possibly associated with less favourable outcome, is mostly not seen before TEA (27). MR imaging performed before TEA is probably less predictive of neurodevelopmental outcome than MRI performed around TEA. Normal or only mildly abnormal WM on cUS and/or MRI was not conclusive of a favourable outcome; two infants were moderately and two severely abnormal at 2 years. This is consistent with previous studies (3,6-7,30) and may partially be related to the fact that we did not take other abnormalities into account when assessing the predictive value of cUS and MRI for outcome, and/or to the fact that brain growth and/or maturation may be globally delayed in very preterm infants, even without overt WM lesions (32-34). Both infants with normal or mildly abnormal cUS/MRI but moderately abnormal outcome had an intraventricular haemorrhage grade 2 on one side, in one infant combined with echogenicity increase in the basal ganglia; of the two infants with severely abnormal outcome, one had bilateral intraventricular haemorrhages grade 3 with severe post-haemorrhagic ventricular dilatation, while the other did not have other cerebral lesions on cUS or MRI.

Because MRI is more burdening than cUS and cannot be easily repeated, it is important to know when MRI has additional value for detecting cerebral lesions and predicting outcome. MRI did not detect mild WM lesions better than cUS. In infants with severely abnormal WM, MRI performed within the first 3 postnatal months predicted outcome more accurately. However, MRI within the first 3 postnatal months, alone or in combination with sequential cUS, had no additional value for predicting outcome in infants with moderately abnormal WM, a group in which outcome is variable and therefore difficult to predict. In addition, in all infants in whom other cerebral lesions that might have prognostic importance, such as severe intraventricular haemorrhage, were detected on MRI, these were also detected on cUS. Based on our study, we think that routine MRI within the first 3 months is not warranted in very preterm infants, suggested to have mild or moderately abnormal WM on cUS.

We appreciate several limitations of our study. Firstly, we only scored the degree of WM changes on cUS and not the timing (4,14) and total duration of echodensities (15). Because in all our cases, echodensities persisted for at least seven days, and no significant differences were observed in the duration of echodensities between the different groups of WM changes, we feel that this will not have influenced our findings considerably. Secondly, we evaluated the most severe cUS findings and the MRI findings obtained at different ages, and not cUS and MRI findings obtained on the same day. This may limit the reliability of the MRI and its predictive value for neurodevelopmental outcome. Thirdly, we only obtained neuro-imaging data around TEA in a few infants and were therefore not able to assess brain growth and maturation properly. In only five infants, MRI was performed around TEA, which is probably the most optimal time for MR imaging in preterm infants (3-4,19,27,30-31). There was a substantial variability in postnatal age at MRI scanning. This may have influenced our results; it is possible that some abnormalities (such as SI changes) are best seen on early diffusion-weighted scans, while others (such as cystic lesions) need time to develop and are therefore better or only recognized on scans performed at older age. However, no differences in predictive values of MRI findings for outcome were found between the infants scanned at a very young postnatal age (< 10 days) and those scanned later (≥ 10 days). And there was no tendency of severe lesions occurring more often in the infants scanned at older age (≥ 10 days) than in the infants scanned at very young age (< 10 days). Another possible limitation is that our study was retrospective and performed in a relatively small number of infants. Because of the small number of infants, we did not assess a possible relation between the site and shape of the WM changes and outcome (15,35). However, comparable data have been obtained in a prospective study in preterm infants (12). Finally, not in all infants Bayley II scores or neurodevelopmental outcome data at 2 years were available and outcome was assessed at a relatively young age, so, developmental problems may still occur in these infants. A larger, prospective study with longer-term follow-up is needed to analyze the relation between neuro-imaging findings and neurodevelopmental outcome in more detail.

In conclusion, this study shows that in very preterm infants, sequential, high-quality cUS throughout the neonatal period is a reliable tool for detecting WM changes. Homogeneous grade 1 echodensities on cUS probably represent normal (maturational)

phenomena in the preterm brain and inhomogeneous grade 1 echodensities possibly reflect punctate WM lesions. cUS is predictive of favourable and severely abnormal outcome at 2 years corrected age. MRI within the first 3 postnatal months is only of clinical importance for outcome prediction in infants with severe WM changes on cUS. So, conventional and diffusion-weighted MRI sequences before TEA in very preterm infants, suggested on cUS to have mild to moderately abnormal WM, do not seem to be warranted and a combination of sequential cUS and a MRI around TEA probably provides more valuable information and is more predictive of neurodevelopmental outcome.

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