Imaging the preterm infant's brain

Leijser, L.M.

Chapter 9

Does sequential cranial ultrasound predict white matter injury on MRI in very preterm infants?

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Abstract

Background and Aim:

Cranial ultrasound (cUS) seems not a good tool to detect diffuse white matter (WM) injury. Our aim was to prospectively assess the reliability of a classification system for detecting WM injury in very preterm infants on frequent, sequential high-quality cUS throughout the neonatal period, using a magnetic resonance imaging (MRI) classification system as reference standard.

Patients and Methods:

In 110 very preterm infants (gestational age < 32 weeks), sequential cUS during admission (median 8, range 4-22), and cUS and MRI around term equivalent age (TEA) were performed. cUS during admission were assessed for WM changes, and contemporaneous cUS and MRI around TEA additionally for abnormality of lateral ventricles. Sequential cUS up to TEA and MRI were classified as normal/mildly abnormal, moderately abnormal or severely abnormal, based on a combination of findings of the WM and lateral ventricles. Predictive values of the cUS classification for the MRI classification were calculated.

Results:

cUS were classified as normal/mildly abnormal, moderately abnormal and severely abnormal in respectively 14%, 73% and 13%, and MRI in respectively 25%, 57% and 18% of infants. The positive predictive value of the cUS classification for the MRI classification was high for severely abnormal cUS (0.79) but lower for normal/mildly abnormal (0.50) and moderately abnormal (0.65) cUS.

Conclusions:

When using the classification system, sequential neonatal cUS up to TEA detects severely abnormal WM in very preterm infants, but is less reliable for detecting mildly and moderately abnormal WM. MRI around TEA is needed to reliably detect WM injury in very preterm infants with normal to moderately abnormal WM.

Introduction

Diffuse white matter (WM) injury is frequently encountered in very preterm infants (1-15). On magnetic resonance imaging (MRI) it is reflected by signal changes in the WM (2-11,13). Concerns have been raised that cranial ultrasound (cUS) is not a good tool to detect diffuse WM injury as the abnormalities may be subtle (2-10). Preterm infants with diffuse WM injury are at risk for motor and mental impairment (3-5,11,13). Several authors have therefore suggested a standard MRI examination in all infants born very prematurely (gestational age (GA) < 32 weeks) (6-9).

In preterm infants, WM injury has been associated with reduced WM and deep (i.e. basal ganglia and thalami) and cortical grey matter volumes and increased cerebrospinal fluid volumes around term equivalent age (TEA) (16-18). However, previous cUS studies on WM injury in very preterm infants have only assessed changes within the WM, but did not assess associated changes such as ventricular dilatation (3-4,6-8). Most studies assessed either cUS or MRI, but none included frequent, sequential cUS throughout the neonatal period.

In this prospective study we assess the reliability of a classification system for WM injury in very preterm infants, based on a combination of findings of the WM and lateral ventricles on frequent, sequential high-quality cUS throughout the neonatal period, using a MRI classification system as reference standard.

Materials and Methods

Patients

Very preterm infants (GA < 32 weeks), admitted to the tertiary neonatal intensive care unit of the Leiden University Medical Center between May 2006 and October 2007, were eligible for a prospective neuro-imaging study, assessing WM injury by cUS and MRI. The study was approved by the Medical Ethics Committee and informed consent was obtained from the parents. Exclusion criteria were congenital anomalies of the central nervous system, severe other congenital anomalies, chromosomal and metabolic disorders, and neonatal meningitis.

Cranial ultrasound

Image acquisition

Sequential cUS scans were performed by a team of experienced examiners (LML, SJS, GvWM), using an Aloka α10 scanner (Biomedic Nederland B.V., Almere, the Netherlands) and according to our standard protocol: scanning with a transducer frequency of 7.5 MHz within 24 hours of birth, at least weekly from the day of birth or admission until discharge or transfer to another hospital, and again on the day of the MRI examination around TEA (19-20).

Visual assessment

WM. On the sequential cUS scans performed during admission (i.e. adm-cUS), special attention was paid to the WM. Periventricular echodensities (PVE) were defined and classified according to van Wezel-Meijler et al. (21), relating the echogenicity of the WM to that of the choroid plexus, and their appearance (homogenous or inhomogeneous) was noted (Figures 1, 2 and 3) (2). Subtle, symmetrical echogenic areas in the frontal WM or adjacent and parallel to the atrium of the lateral ventricles were considered normal phenomena and not scored as PVE (21-22).

Figure 1. Coronal (a) and sagittal (b) cUS of preterm infant (gestational age 27.9 weeks), scanned at postmenstrual age 31.1 weeks, showing normal echogenicity of periventricular white matter (Adm-cUS white matter score: normal/mildly abnormal). Also showing grade 1 intraventricular haemorrhage.

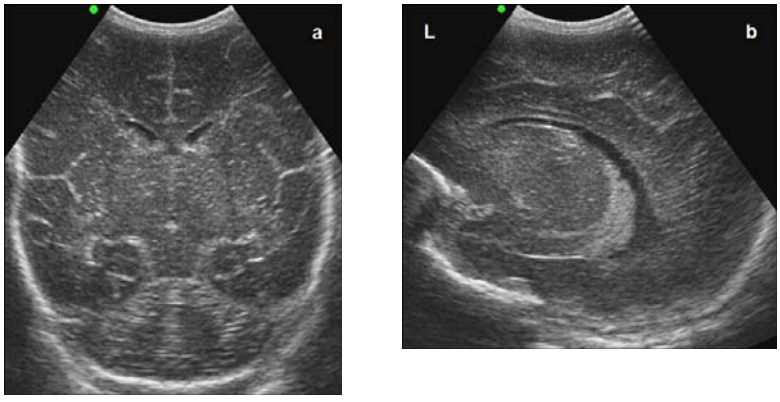


Figure 2. Coronal (a) and sagittal (b) cUS of preterm infant (gestational age 28.0 weeks), scanned at postmenstrual age 28.1 weeks, showing homogeneous grade 1 periventricular echodensities in parieto-occipital white matter (arrows) (Adm-cUS white matter score: normal/mildly abnormal).

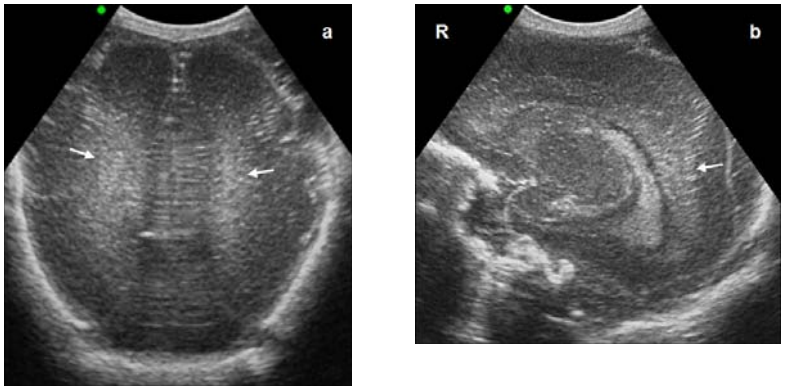
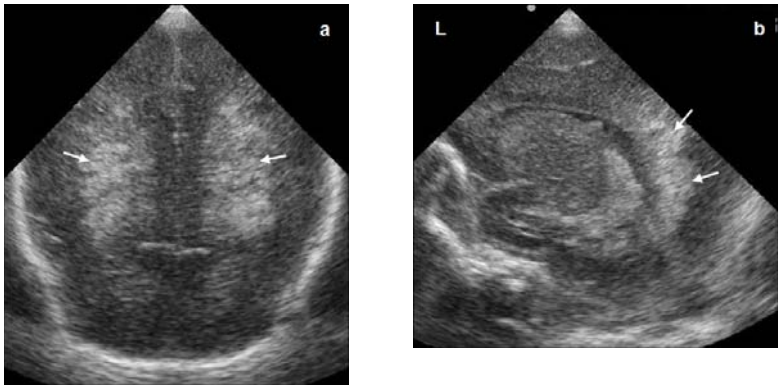


Figure 3. Coronal (a) and sagittal (b) cUS of preterm infant (gestational age 29.3 weeks), scanned at postmenstrual age 29.7 weeks, showing inhomogeneous grade 2 periventricular echodensities in parieto-occipital white matter (arrows) (Adm-cUS white matter score: moderately abnormal).



Unilateral or asymmetrical, more localized areas of high echogenicity within the WM were scored as focal WM echodensities. If co-existing with an intraventricular haemorrhage on the ipsilateral side, these mostly represent periventricular haemorrhagic infarction (PVHI; Figure 4) (23). When in doubt whether an echodensity in the WM represented PVE or a focal echodensity, it was scored as inconclusive. Porencephalic cyst was defined as a large cystic lesion, communicating with the lateral ventricle (Figure 5) (23).

Figure 4. Coronal (a) and sagittal (b) cUS of preterm infant (gestational age 25.6 weeks), scanned at postmenstrual age 25.7 weeks, showing left-sided periventricular haemorrhagic infarction in the parietal white matter (arrows), complicating an intraventricular haemorrhage (not shown) (Adm-cUS white matter score: severely abnormal).

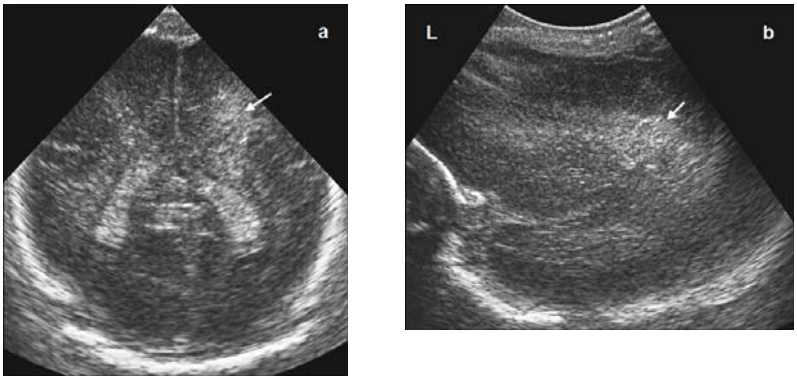
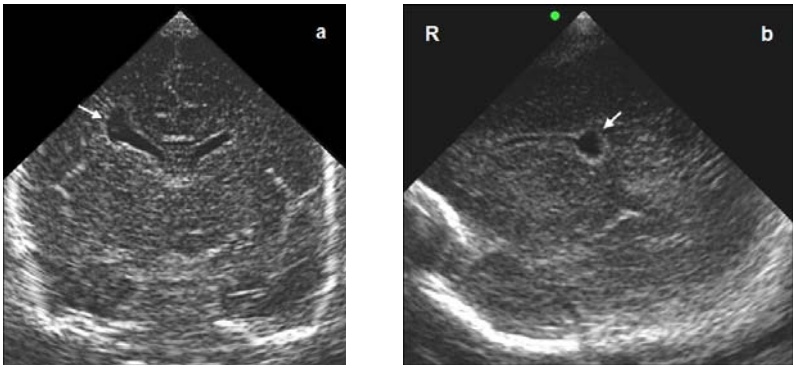


Figure 5. Coronal (a) and parasagittal (b) cUS of preterm infant (gestational age 27.0 weeks), scanned around term equivalent age (postmenstrual age 44.7 weeks), showing a porencephalic cyst in parietal white matter (arrows) (MRI-cUS white matter score: severely abnormal).



Ventricles. The size and shape of the lateral ventricles were visually assessed on the cUS performed within several hours of the MRI (i.e. MRI-cUS) by two separate investigators (LML and GvWM or SJS), and graded as normal/mildly abnormal (i.e. normal or mildly dilated and/or abnormal shape) (Figures 6 and 7), moderately abnormal (i.e. moderately dilated and/or abnormal shape, including irregular, plump or square-shaped ventricles) or severely abnormal (i.e. severely dilated and/or abnormal shape) (Figure 7). In case of discordance consensus was reached.

Figure 6. Coronal (a) and sagittal (b) cUS of preterm infant (gestational age 26.0 weeks), scanned at postmenstrual age 42.7 weeks, showing normal white matter and size and shape of lateral ventricles (MRI-cUS white matter score: normal/mildly abnormal). Also note lenticulostriate vasculopathy.

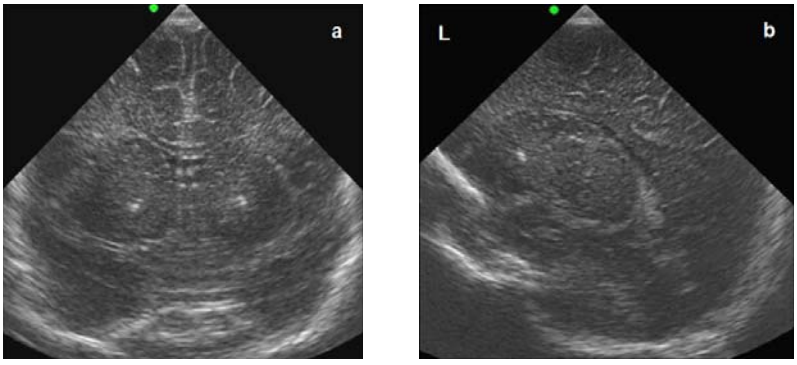
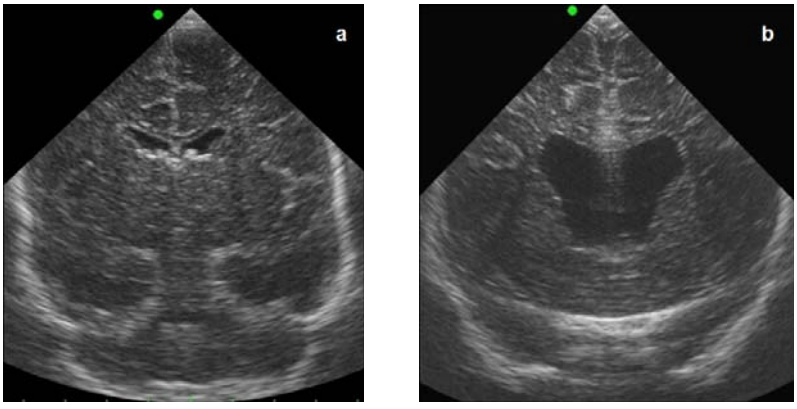


Figure 7. Coronal cUS (a) of preterm infant (gestational age 25.0 weeks), scanned at postmenstrual age 42.0 weeks, showing mild dilatation of lateral ventricles (MRI-cUS white matter score: normal/mildly abnormal), and coronal cUS (b) of another infant (gestational age 30.3 weeks), scanned at postmenstrual age 41.9 weeks, showing severe lateral ventricular dilatation (MRI-cUS white matter score: severely abnormal).



WM classification

WM classification for adm-cUS:

- Normal/mildly abnormal: no PVE or homogeneous grade 1 PVE (21)
- Moderately abnormal: inhomogeneous grade 1 PVE (regardless of duration), grade 2 PVE (regardless of appearance and duration), and/or small, localized cystic lesions (periventricular leukomalacia (PVL) grade 2) (21,24)

- Severely abnormal: multicystic lesions (PVL grades 3 and 4), focal WM echodensity, and/or porencephalic cyst (24)

The WM score of the adm-cUS was based on the most severe changes over time.

WM classification for MRI-cUS:

- Normal/mildly abnormal: homogeneous WM and normal/mildly abnormal lateral ventricles
- Moderately abnormal: inhomogeneous WM and/or moderately abnormal lateral ventricles
- Severely abnormal: multicystic PVL, focal WM echodensity, porencephalic cyst, and/or severely abnormal lateral ventricles

The WM score of the MRI-cUS was based on the most severe changes.

WM classification for adm-cUS combined with MRI-cUS:

The WM score for the sequential cUS during admission combined with the cUS around TEA (adm-cUS combined with MRI-cUS) was based on the most severe changes over time.

MRI

Image acquisition

MRI examinations were performed in all very preterm infants according to our standard protocol for imaging the newborn infant's brain, using a 3 Tesla Philips MR system (Philips Medical Systems, Best, the Netherlands) as recently described (25). The MRIs were preferably performed around or just after TEA (40-44 weeks' postmenstrual age (PMA)). For infants who were still unstable and/or ventilator dependent around that age, MRI was postponed. The T_1- and T_2-weighted sequences were analyzed by at least two experienced investigators (FTdB, LML, SJS, GvWM).

Visual assessment

WM. The signal intensity (SI) of the brain WM was graded according to Sie et al. (2), indicating increasingly severe WM changes (Figures 8, 9, 10 and 11).

Figure 8. Transverse T_1- (a) and T_2-weighted (b) MRI at mid-ventricular level of preterm infant (gestational age 27.1 weeks), scanned at postmenstrual age 42.1 weeks, showing normal signal in periventricular white matter. Also showing normal size and shape of lateral ventricles (MRI white matter score: normal/mildly abnormal).

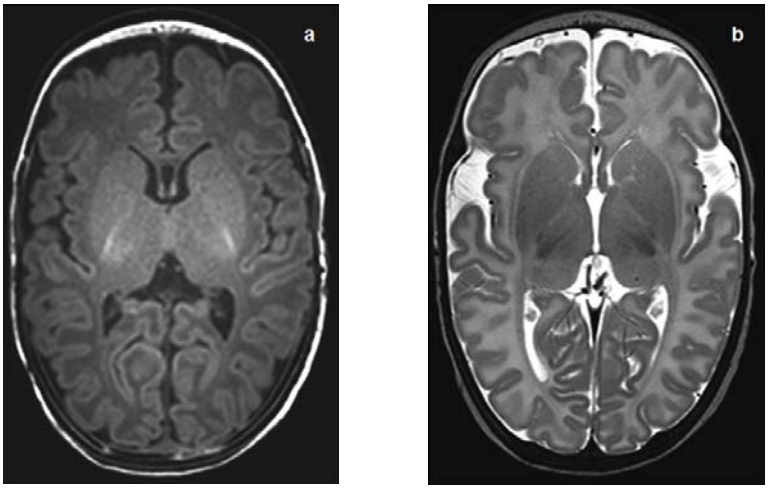


Figure 9. Transverse T_1- (a) and T_2-weighted (b) MRI at mid-ventricular level of preterm infant (gestational age 27.9 weeks), scanned after term equivalent age (postmenstrual age 48.7 weeks), showing a single punctate white matter lesion adjacent to the optic radiation (short arrows). Also showing mildly dilated, square-shaped occipital horns of lateral ventricles (long arrows) (MRI white matter score: normal/mildly abnormal).

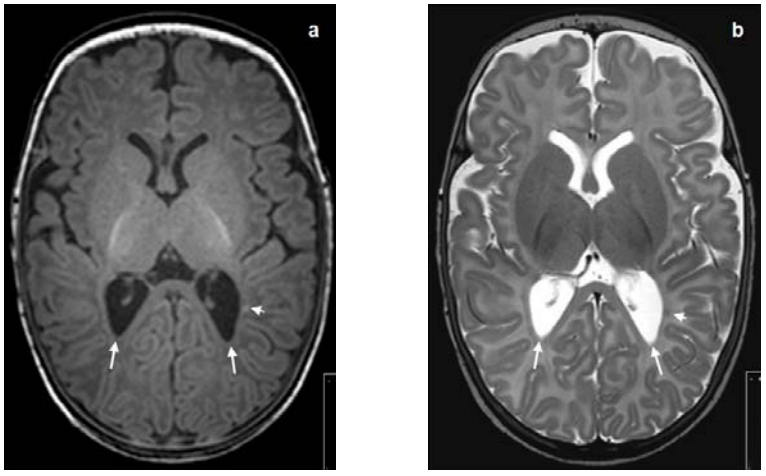


Figure 10. Transverse T_1- (a) and T_2-weighted (b) MRI of preterm infant (gestational age 26.9 weeks), scanned at postmenstrual age 42.7 weeks, showing bilateral, multiple punctate white matter lesions (short arrows). Also showing dilated, irregularly shaped lateral ventricles and widening of extracerebral spaces. T_2 additionally shows diffuse and excessive high signal intensity in occipital white matter (long arrows) (MRI white matter score: moderately abnormal).

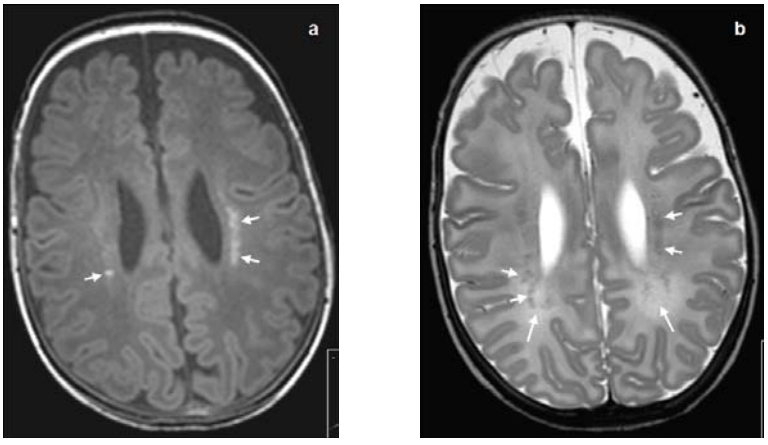
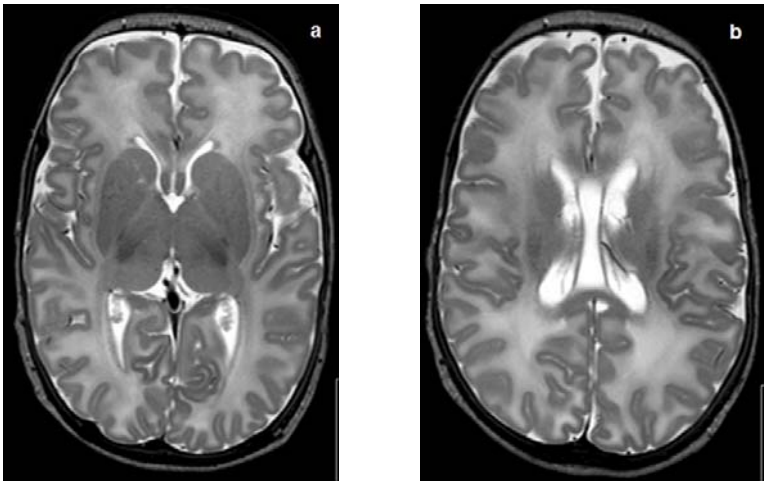
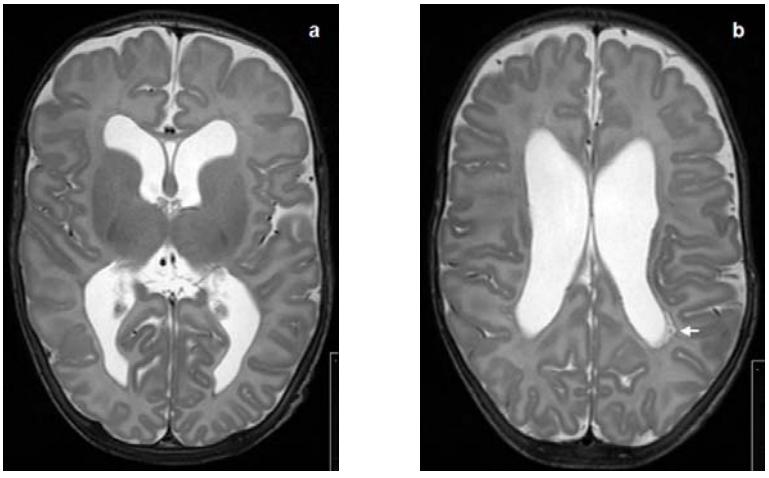


Figure 11. Transverse T_2-weighted MRI at mid- (a) and high-ventricular (b) level of preterm infant (gestational age 30.6 weeks), scanned at postmenstrual age 41.9 weeks, showing inhomogeneous, diffuse SI changes in periventricular and subcortical white matter (MRI white matter score: severely abnormal). Also showing normal lateral ventricles and cavum septum pellucidum and vergae.



Ventricles. The size and shape of the lateral ventricles were assessed visually by two separate investigators (LML and FTdB), and graded as normal/mildly abnormal (Figures 8, 9 and 11), moderately abnormal or severely abnormal (Figure 12) as described for MRI-cUS. In case of discordance consensus was reached.

Figure 12. Transverse T_2-weighted MRI at mid- (a) and high-ventricular (b) level of preterm infant (gestational age 31.6 weeks), scanned at postmenstrual age 43.4 weeks), showing severely dilated and abnormally shaped lateral ventricles (MRI white matter score: severely abnormal). Also showing cystic degeneration along the occipital horn of left lateral ventricle (arrow).



WM classification

WM classification for MRI:

- Normal/mildly abnormal: WM grade 1, 2 or 3, and normal/mildly abnormal lateral ventricles (2)
- Moderately abnormal: WM grade 4 and/or moderately abnormal lateral ventricles (2)
- Severely abnormal: WM grade 5 or 6 and/or severely abnormal lateral ventricles (2)

The WM score was based on the most severe changes.

Data analysis

Statistical analyses were performed using SPSS software (version 14.0; SPSS inc., Chicago, Illinois, USA). Predictive values of the WM classifications of adm-cUS, MRI-cUS and adm-cUS combined with MRI-cUS for the WM classification of MRI were calculated.

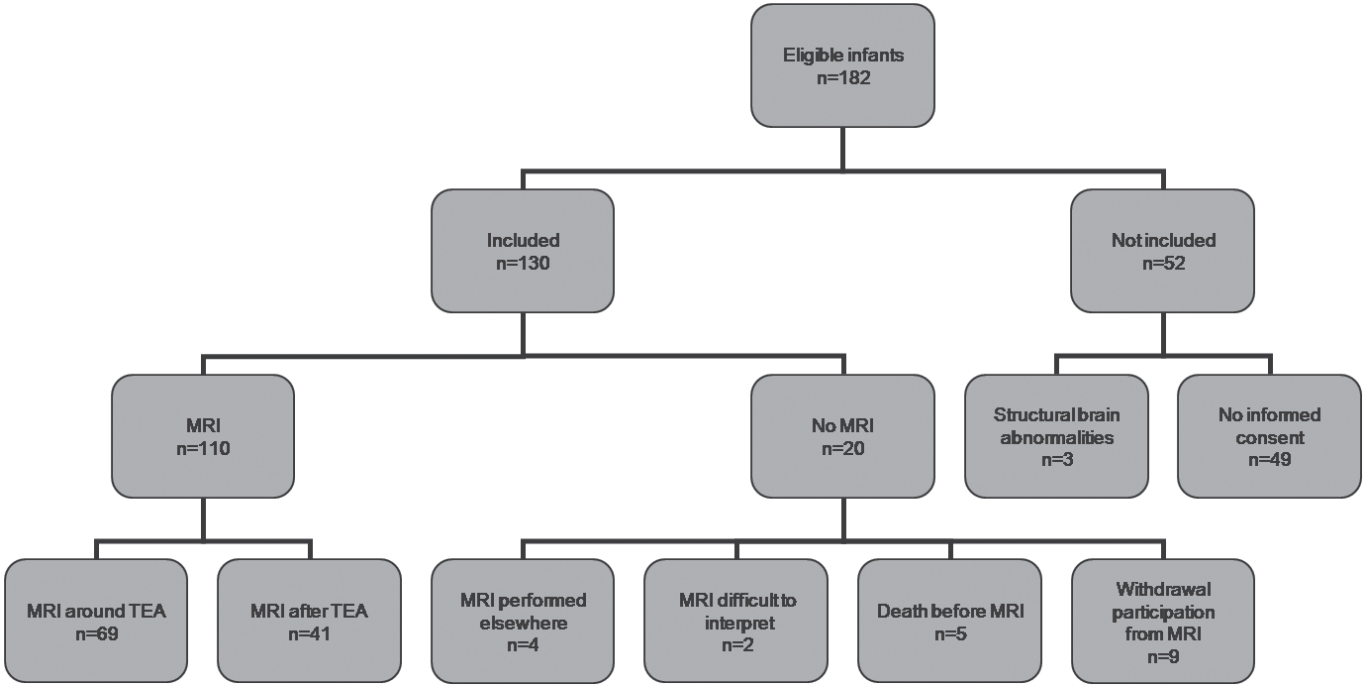
Results

Patients

During the study-period, 182 very preterm infants were eligible for the study, of which 130 infants (80 male) were included. Fifty-two infants were excluded from the study; three because of structural brain abnormalities and 49 because informed parental consent was not obtained (Figure 13). Reasons for not obtaining consent included transfer to another hospital or death within a very short period of birth, rejection of participation, and practical problems such as language barrier and travel distance to hospital. Median GA and birth weight of included infants were 29.0 (range 25.6-31.9) weeks and 1141 (520-1960) grams. There were no significant differences in GA and birth weight between infants with and without informed consent.

In all 130 infants, sequential adm-cUS scans (median 8, range 4-22) were performed. In 20 infants no or inadequate MRI-cUS and MRI were obtained (Figure 13). So, in 110 infants (68 male) contemporaneous cUS and MRI were obtained at a median PMA of 43.4 (40.1-55.9) weeks. In 69 infants this was around TEA, and in 41 infants between 44.0 and 55.9 weeks' PMA.

Figure 13. Flow diagram showing the number of infants eligible for the study, the number of infants included and not included in the study, and the final number of infants with sequential cUS and MRI around term equivalent age
(n, number of infants)



Cranial ultrasound

Adm-cUS

In 27 infants (24.5%) the WM classification was scored as normal/mildly abnormal, in 75 (68.2%) as moderately abnormal, and in eight (7.3%) as severely abnormal.

MRI-cUS

In 50 infants (45.5%) the WM classification was scored as normal/mildly abnormal, in 46 (41.8%) as moderately abnormal, and in 14 (12.7%) as severely abnormal.

Adm-cUS combined with MRI-cUS

In 16 infants (14.5%) the WM classification for sequential cUS throughout the neonatal period was scored as normal/mildly abnormal, in 80 (72.7%) as moderately abnormal, and in 14 (12.7%) as severely abnormal.

MRI

In 27 infants (24.5%) the WM classification was scored as normal/mildly abnormal, in 63 (57.3%) as moderately abnormal, and in 20 (18.2%) as severely abnormal.

Relation between cUS and MRI

Details on the relation between the WM classifications of cUS and MRI are given in Tables 1, 2 and 3. Predictive values of the WM classifications of adm-cUS, MRI-cUS and adm-cUS combined with MRI-cUS for the WM classification of MRI are presented in Table 4.

Table 1. Relation between white matter classifications of adm-cUS and MRI (n, number of infants; WM, white matter)

WM classifications		MRI, *n*		
		Normal/mild (n=27)	Moderate (n=63)	Severe (n=20)
Adm-cUS, *n*	Normal/mild (n=27)	9	14	4
	Moderate (n=75)	18	48	9
	Severe (n=8)	0	1	7

Table 2. Relation between white matter classifications of MRI-cUS and contemporaneous MRI
(n, number of infants; WM, white matter)

WM classifications		MRI, *n*		
		Normal/mild (n=27)	Moderate (n=63)	Severe (n=20)
MRI-cUS, *n*	Normal/mild (n=50)	25	25	0
	Moderate (n=46)	2	35	9
	Severe (n=14)	0	3	11

Table 3. Relation between white matter classifications of adm-cUS combined with MRI-cUS and term equivalent MRI
(n, number of infants; WM, white matter)

WM classifications		MRI, *n*		
		Normal/mild (n=27)	Moderate (n=63)	Severe (n=20)
Adm-cUS and MRI-cUS, *n*	Normal/mild (n=16)	8	8	0
	Moderate (n=80)	19	52	9
	Severe (n=14)	0	3	11

Table 4. Predictive values of the white matter classifications of adm-cUS, MRI-cUS and adm-cUS combined with MRI-cUS for the white matter classification of MRI
(NPV, negative predictive value; PPV, positive predictive value; WM, white matter)

cUS WM classification		Predictive values for MRI WM classification			
		Sensitivity	Specificity	PPV	NPV
Adm-cUS	Normal/mild	0.33	0.78	0.33	0.78
	Moderate	0.76	0.43	0.64	0.57
	Severe	0.35	0.99	0.88	0.87
MRI-cUS	Normal/mild	0.93	0.70	0.50	0.97
	Moderate	0.56	0.77	0.76	0.56
	Severe	0.55	0.97	0.79	0.91
Adm-cUS and MRI-cUS	Normal/mild	0.30	0.90	0.50	0.80
	Moderate	0.83	0.40	0.65	0.63
	Severe	0.55	0.97	0.79	0.93

Discussion

To our knowledge, this is the first prospective study comparing WM injury on cUS and MRI in very preterm infants based on newly designed classification systems, not only including changes within the WM but also scoring other changes in the brain thought to be related to WM injury. We considered MRI as reference standard for WM injury.

The appearance of the lateral ventricles was incorporated in the classification, as WM injury in preterm infants is associated with reduced WM and grey matter volumes and increased cerebrospinal fluid volumes (16-18). In addition, cystic PVL and PVHI may lead to prominent changes in ventricular size and shape (24,26-27). Finally, around TEA echogenicity changes within the WM are only rarely encountered on cUS, while widening of the ventricular system is a frequent finding (20,26-27).

The positive predictive value of the cUS WM classification for the MRI WM classification was high for severely abnormal WM; (nearly) all infants classified as severely abnormal for cUS were also classified as severely abnormal for MRI. However, cUS was less predictive for the moderately abnormal and normal/mildly abnormal groups. So, even when our classification system, based on frequent, sequential cUS and evaluating not only WM changes but also other changes indicative of WM injury, is used, cUS may underestimate WM injury.

There are several possible explanations for these results. MRI was performed with a 3 Tesla MR system, providing a high resolution that cannot be obtained with ultrasonography. Using this high field strength and a special neonatal imaging protocol, small lesions, including very small punctate WM lesions (PWML), are depicted (20,25). In addition, in accordance with Sie et al. (2), we used six as cut-off number for 'few' (mildly abnormal WM) or 'multiple' (moderately abnormal WM) PWML on MRI, which is rather arbitrary. In 12 of the 14 infants whose MRI classification was based on 'multiple' PWML, just over six lesions were detected, mostly isolated in organization and located in the periventricular WM at the level of the centrum semiovale and/or adjacent to the optic radiation. Only in two infants, the number of PWML was considerably higher and lesions were more widely distributed in the WM and organized linearly and/or in clusters. We therefore feel that, by using this cut-off, we may have overrated the severity of WM changes on MRI in several infants. Another explanation may be the discrepancy

between contemporaneous cUS and MRI for detecting ventricular dilation. In our recent study in very preterm infants, describing incidences of brain imaging findings and comparing cUS and MRI for these findings, ventricular dilatation was more often scored on MRI than on cUS (20). So, visual scoring of ventricular size may not be reliable (enough) and if quantitative measurements of ventricular size had been included in the classification systems, this might have improved the agreement between cUS and MRI and the reliability of cUS for detecting WM injury.

cUS not only underestimated, but also overestimated WM injury in some cases. This was especially true for adm-cUS and can be explained by the fact that the WM score of adm-cUS was based on the most severe changes over time and by the transient nature of some WM changes (20).

Combining the WM classification of adm-cUS with that of MRI-cUS slightly improved the predictive value of sequential cUS for MRI in case of normal/mildly abnormal WM, but did not improve its predictive value for moderately abnormal WM and even decreased it for severely abnormal WM. So, if MRI is performed around TEA in addition to sequential cUS throughout the neonatal period, contemporaneous cUS does not contribute to detecting WM injury.

The results of this study may arouse the erroneous suggestion that frequent, sequential cUS performed until discharge does not contribute to detection of WM injury in very preterm infants. However, our classification systems are used to grade the severity of WM injury and do not provide information on separate imaging findings or the evolution of lesions. By substantially limiting the number of cUS examinations during admission, details on (transient) WM changes will be lost, the evolution of lesions cannot be followed, and distinction between several forms of WM injury (i.e. focal or more diffuse) may not be possible as only the end stages of WM injury are visualized. By restricting cUS to the early neonatal period and TEA, as suggested by some authors (28), no information will be available on the evolution of lesions, lesions may remain undetected, and their severity underestimated (6,24,26,29).

Our results are in agreement with those of others comparing WM findings on cUS and MRI, showing that MRI is more sensitive for detecting (particularly subtle) WM changes than cUS (2-10,24,29). In agreement with our previous, retrospective study (14), in most cases with WM injury detected by cUS, MRI demonstrated the exact site and extent of

lesions more precisely. However, in that study, sequential cUS during admission was reliable for detecting WM changes, including mildly and moderately abnormal changes, on MRI (14). Our current results partially contradict these findings. An explanation may be that in the retrospective study, MRI was obtained within 3 months of birth, well before TEA. This may not be the optimal time in very preterm infants, as MRI before TEA only has additional value for assessing the extent of cystic lesions, PWML and PVHI, but not for other WM changes (4,8,11,29).

We appreciate some limitations of our study. Firstly, the most stable infants with (nearly) normal cUS findings were discharged sooner than those being less stable and/or having more severe findings. We may therefore have missed progression towards more severe changes in some infants with minor changes, or changes developing after discharge. This may have biased our results and negatively influenced the reliability of cUS as cUS was the least reliable in infants with normal/mildly abnormal WM. Secondly, we only performed a single MRI examination around TEA. Therefore, while cUS also reflected early and/or transient WM changes and the evolution of changes, MRI reflected only the later stages of WM injury. Following our standard cUS protocol, we did not investigate the minimum number of cUS scans needed for reliable classification of WM injury. Finally, we are not yet informed on the clinical significance of our WM classifications, and the implications of the milder and subtle WM changes, including PVE without cystic evolution on cUS and PWML and more diffuse SI changes on MRI, for neurological outcome. Follow-up data are currently obtained.

In conclusion, our classification systems enable systematical grading of WM injury and comparison of cUS and MRI. We have further demonstrated that cUS is reliable for the severe spectrum of WM injury, but may underestimate WM injury in cases classified as normal/mildly or moderately abnormal. Routine MRI around TEA is needed in very preterm infants as it may detect (more serious) WM injury in infants with normal to, at the most, moderately abnormal WM on cUS, while in infants with severely abnormal WM on cUS, MRI assesses the site and extent of lesions more precisely. When MRI is performed around TEA, contemporaneous cUS is of no additional value for detecting WM injury. As MRI is a burdening procedure and repetitive MRI examinations are undesirable, sequential cUS throughout the neonatal period is necessary to assess the timing, origin and evolution of lesions and depict transient changes in these vulnerable

patients. Future studies on WM injury in preterm infants should focus on the optimal number of and interval between sequential cUS, on improving the WM classifications, including quantitative measurements of the ventricular system, and on the clinical significance of the WM classifications and the separate changes, both on cUS and MRI, indicative of WM injury.

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