Imaging the preterm infant's brain

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Chapter 7

Frequently encountered cranial ultrasound features in the white matter of preterm infants: correlation with MRI

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Abstract

Background and Aim:

Bilateral symmetrical echogenic and echolucent areas in the white matter are frequently seen on the cranial ultrasound scans of apparently well preterm infants without overt pathology. Our aim was to determine whether these features reflect maturational processes as seen on magnetic resonance imaging (MRI).

Patients and Methods:

Preterm and term-born infants without overt pathology on contemporaneous brain ultrasound and MRI were studied. Ultrasound scans were compared with T_2-weighted MRI to identify MR-correlates for the bilateral and symmetrical echogenic and echolucent phenomena in the white matter seen on ultrasound.

Results:

Forty-four sets of scans (26 preterm, eight term-born infants) were assessed. Echogenic features were better and more frequently seen on early ultrasound as compared to nearer term age. Echogenic blushes in the white matter correlated well with high signal intensity areas and echogenic lines with low signal intensity lines on MRI. Echolucent areas correlated with the site of the internal capsule and the myelinated posterior pons. The subplate was not reliably identified.

Conclusions:

Many echogenic and echolucent features in the white matter of well preterm and some term-born infants correlated well with areas of differing signal intensity on MRI. They most likely reflect normal maturational processes but the echogenic hemispheric features may represent delayed or abnormal maturation.

Introduction

In newborn infants, especially those born prematurely, many maturational processes take place in the brain after birth (1-3). Preterm infants are at high risk of hypoxic, haemorrhagic and inflammatory brain lesions (4-6) and disturbed cerebral development (7-10). They are also at risk of abnormal neurological development (11-13), even when no overt cerebral lesions are detected (14-15).

Cranial ultrasound (cUS) reliably demonstrates many forms of cerebral injury (11,15-18) and shows anatomical features and their changes with gestation. However, magnetic resonance imaging (MRI) shows maturational processes in greater detail (1-3,16-21) and it enables quantification of brain growth and maturation (7-10).

There are several MRI and pathological studies on normal and abnormal cerebral white matter (WM) development in newborn infants (2,5,16,21-27), but few equivalent cUS studies (12,16,28) or studies comparing cUS to MRI (16-17). As cUS is the most readily available and usually the initial technique used for imaging the newborn brain (4,11), it is desirable that its capability for assessing maturational features is understood. To do this, it is important to define appearances representing normal developmental processes as visualized on neonatal scans.

Bilateral symmetrical areas of increased echogenicity are frequently encountered on the cUS scans of apparently well preterm infants. These areas are mainly located periventricularly in the frontal WM and at the margins of the lateral ventricles (LV) and do not evolve into lesions. They tend to be linear or smoothly rounded. Some of these areas have correlated anatomically with areas of glial cell migration in the preterm brain before term equivalent age (TEA) (16). Areas of altered signal intensity (SI) in the periventricular WM may represent features of developing WM on MRI (16,22-25,27). Echolucent areas are seen in more peripheral regions of the hemispheres and more centrally where defined WM tracts run; these areas have not been compared to MRI but might represent the subplate, the internal capsule and the posterior myelinated pons. We hypothesize that bilateral symmetrical echogenic or echolucent areas on cUS, seen in apparently normal (preterm) newborn infants and not evolving into lesions, reflect maturational rather than pathological processes in the newborn infant brain. Our aim was to determine whether such features reflect maturational processes as seen on contemporaneous brain MR imaging.

Materials and Methods

Patients

During the study-period (February 2005-February 2006), all preterm and term-born infants admitted to the neonatal unit of the Hammersmith and Queen Charlotte's Hospital, London, with a cUS and MRI examination performed on the same day were included. All infants were examined prior to scanning and their growth characteristics were recorded. Ethical approval for brain MR imaging studies was given by the Hammersmith Hospitals Research Ethics Committee and parental consent was always obtained. All cUS scans were done as part of routine assessment. Some MRI examinations were part of ongoing research cohort studies of apparently well newborn infants. Other infants were scanned for different clinical indications, including neonatal encephalopathy and suspected but unconfirmed metabolic and neuromuscular disorders. No infant with overt pathology on their cUS was included.

Exclusion criteria were major congenital anomalies or acquired injurious brain abnormalities, brain abnormalities on cUS scans, chromosomal disorders, metabolic disorders or neonatal meningitis.

Neuro-imaging

Ultrasonography

All cUS scans were performed by the same observer (LML), using a Siemens Antares ultrasound scanner with a multifrequency transducer (Siemens, Bracknell, UK). Scanning was done through the anterior fontanel in at least six coronal and five sagittal planes. The transducer frequency was set at 7.3 MHz. To evaluate the peripheral regions of the hemispheres where the cortical subplate and the subcortical WM can be identified on T_2-weighted MR images of very preterm infants, higher frequencies were applied. cUS scans were evaluated during and immediately after the procedure by the examiner and all scans were digitally stored and later analyzed by LML and FMC by consensus, using the software program Escape Medical Viewer (Escape Medical Imaging, Thessaloniki, Greece).

All scans were assessed for presence, location and appearance of the following echogenic features in the WM. These comprised:

- Frontal echogenic blush
- Echogenic lines around/below the LV
- Echogenicity running supero-laterally from the LV
- Echogenic lines running parallel to the LV
- Temporo-occipital echogenic blush

Scans were also assessed for areas of persistent echolucency in the WM that might represent:

- The cortical subplate
- The internal capsule
- WM tracts in the pons

MRI

MRI was performed according to a standard protocol for newborn infants, using a 3 Tesla Philips MR system (Philips Medical Systems, Best, the Netherlands). If needed, infants were sedated using oral chloral hydrate (30-50 mg/kg), a regimen we have found safe and effective. They were placed supine and snugly swaddled. Ear protection was used (5) and the head immobilized using a polystyrene bead-filled pillow from which the air was evacuated. The infant's temperature, heart rate and oxygen saturation were monitored throughout the procedure by an experienced neonatologist.

The MR sequence parameters were as follows:

T_1-weighted magnetization prepared rapid-acquisition gradient echo volumes: repetition time, 17 ms; echo time, 4.6 ms; flip angle, 30°; field of view, 210 mm; matrix, 256 x 256; number of acquisitions, 1; and voxel size, 0.8 x 0.8 x 1.6 mm;

T_2-weighted fast-spin echo pseudo volumes: repetition time, 12,000 ms; echo time, 160 ms; flip angle, 90°; field of view, 220 mm; matrix, 224 x 224; voxel size 0.86 x 0.86 x 2.0 mm.

T_1-weighted volume images were acquired in the sagittal plane and reformatted into transverse and coronal planes. T_2-weighted images were acquired in the transverse plane.

All MRI examinations were evaluated by two experienced observers (LS and MAR) to exclude focal pathology. The MR images were then assessed using the software program ViewForum (Philips Medical Systems, Best, the Netherlands). With this program different planes, including coronal and sagittal planes, comparable to those obtained with cUS scanning, could be reconstructed, enabling the best possible comparison between cUS and MRI examinations. For this study, T_2-weighted MR images were used as they have been shown to be a more sensitive indicator for assessing brain development (29), particularly before TEA.

The T_2-weighted MR examinations were assessed for presence of features possibly correlating with the echogenic features in the WM detected on cUS, as well as evaluated for presence of the cortical subplate, visibility of the internal capsule and WM tracts in the pons. For comparing the cUS and MRI examinations, the MR image most closely resembling the cUS plane in which the cUS feature was detected was evaluated.

Data analysis

All contemporaneous cUS and MRI examinations were first assessed separately and later assessed simultaneously to obtain the most accurate comparison of both examinations. Statistical analyses were performed using StatsDirect statistical software (StatsDirect Ltd, Cheshire, UK). The predictive values, including sensitivity, specificity, positive predictive value and negative predictive value, of the cUS features for the presence of correlating features on MRI were calculated. The level of significance was taken at 0.05.

Results

Patients

Twenty-six preterm (13 male) and eight term-born infants (all male) without overt pathology on their cUS and MRI examinations were studied. Mean gestational age (GA) and birth weight were, respectively, 29.5 (range 24.4-32.7) weeks and 1230 (586-1848) grams for preterm infants and 39.4 (38.0-40.6) weeks and 3218 (2986-3400) grams for term-born infants. In nine of 26 preterm and one of eight term-born infants two sets

of cUS and MRI examinations were performed on different days; mean time-interval between the sets of scans was 7.4 (3.7-14.9) weeks. In total 44 sets of examinations were analyzed. Mean postmenstrual age (PMA) and weight at scanning were, respectively, 37.5 (27.1-57.0) weeks and 2296 (870-4210) grams for preterm infants and 42.9 (38.9-49.0) weeks and 4007 (3127-5450) grams for term-born infants. Nineteen of the 35 sets of examinations of preterm infants were performed around TEA (36.0-44.0 weeks' PMA).

Ultrasound imaging and comparative cUS-MRI data

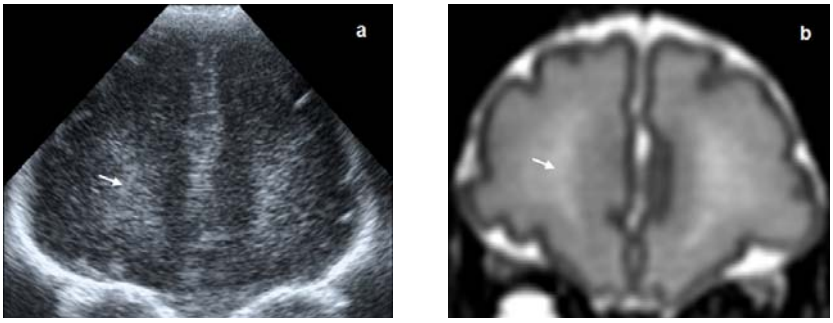
Areas of increased echogenicity

Frontal echogenic blush

An echogenic blush in the frontal WM was seen in 32 of 35 (91%) preterm infant cUS scans and five of nine (56%) term-born infant scans (Figure 1). This feature was always bilateral and homogeneous in appearance. No significant differences in mean GA, birth weight and PMA and weight at day of scanning for preterm infants with and without this feature were found; nor were these parameters different between term-born infants with and without this feature except that weight at scanning was significantly lower for infants in whom the blush was seen (p=0.006).

In all preterm and four term-born infants with frontal blushes on cUS, bilateral areas of marked high SI were detected in the same location on the T_2-weighted MR images (Figure 1). In two preterm infants and the four term-born infants without these blushes, areas of high SI were also seen in the frontal WM on MRI. The predictive values of the frontal echogenic blushes for correlating features on MRI are shown in Table 1.

Figure 1. Bilateral frontal echogenic blushes on an anterior coronal cUS (a, arrow) of a preterm infant (gestational age 26.0 weeks) with a postmenstrual age at day of scanning of 33.6 weeks correlating with high signal intensity areas on contemporaneous reconstructed coronal T_2-weighted MR image (b, arrow).

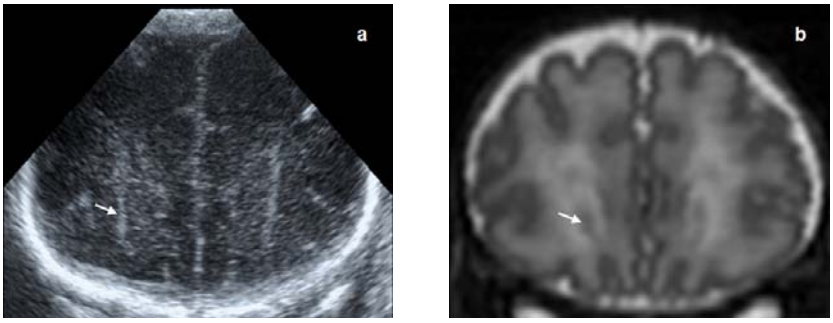


Echogenic lines around/below the LV

Echogenic lines around/below the anterior horns of the LV were seen in 29 of 35 (83%, 26 bilateral, three unilateral) preterm infant scans and four of nine (44%, all bilateral) term-born infant scans (Figure 2). GA, birth weight and PMA and weight at day of scanning were not significantly different between the preterm and term-born infants with and without these lines.

In all preterm infants and in all but one term-born infant with and without these echogenic lines, low SI lines were seen in the same location on MRI (Figure 2). The predictive values of the echogenic lines for correlating features on MRI are shown in Table 1.

Figure 2. Bilateral echogenic lines around/below the lateral ventricles on an anterior coronal cUS (a, arrow) of a preterm infant (gestational age 27.7 weeks) with a postmenstrual age at day of scanning of 38.3 weeks correlating with low signal intensity lines on contemporaneous reconstructed coronal T_2-weighted MR image (b, arrow).



Echogenic areas running supero-laterally from the LV

Echogenic areas running supero-laterally from the LV were seen in 29 of 35 (83%, bilateral in all but one) preterm scans and in seven of nine (78%, always bilateral) term-born infant scans (Figures 3 and 4). GA, birth weight and PMA and weight at day of scanning were not significantly different between preterm and term-born infants with and without these areas.

In 27 preterm and three term-born infants with supero-lateral echogenic areas, high SI areas were seen in the same location on the MR images (Figures 3 and 4 and also well illustrated on the parasagittal view in Figure 5). In three of six preterm infants without the echogenic areas, high SI areas were detected supero-laterally from the LV on MRI. No term-born infants without echogenic areas had high SI areas on MRI. The predictive values of these echogenic areas for correlating features on MRI are shown in Table 1.

Figure 3. Bilateral echogenic lines parallel to the lateral ventricles on a coronal cUS (a, short arrow) of a preterm infant (gestational age 27.7 weeks) with a postmenstrual age at day of scanning of 33.0 weeks correlating with low signal intensity lines on contemporaneous reconstructed coronal T_2-weighted MR image (b, short arrow). The cUS scan also illustrates bilateral echogenic areas supero-laterally from the lateral ventricles (a, long arrow) correlating with high signal intensity areas on the T_2-weighted MR image (b, long arrow).

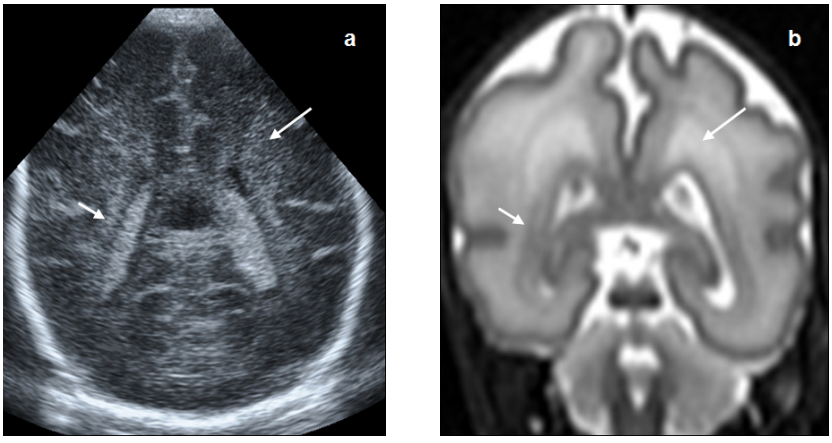


Table 1. Prevalence of echogenic cUS features and predictive values of cUS features for correlating features on contemporaneous T_2-weighted MRI
(LV, lateral ventricles; n, number of infants; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value)

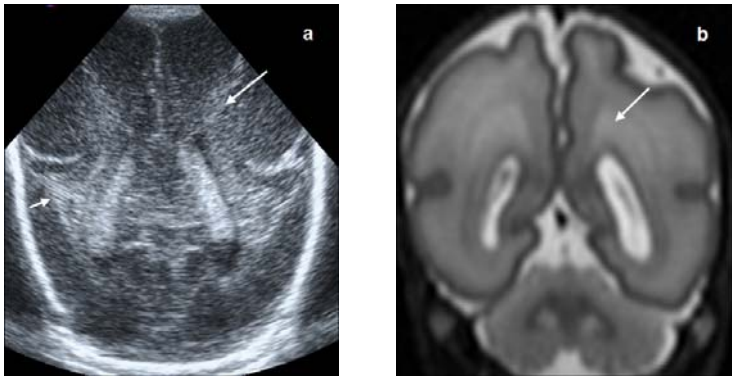
cUS features	Group of infants	Prevalence on cUS (%) (n seen)	Predictive values of correlation cUS – MRI (%)			
			Sensitivity	Specificity	PPV	NPV
Frontal echogenic blush	Preterm (n=35)	91 (32)	100	33	94	100
	Term (n=9)	56 (5)	80	NA	50	NA
Echogenic lines around/ below LV	Preterm (n=35)	83 (29)	100	NA	83	NA
	Term (n=9)	44 (4)	100	20	50	100
Echogenicity supero-laterally of LV	Preterm (n=35)	83 (29)	93	50	90	60
	Term (n=9)	78 (7)	43	100	100	33
Echogenic lines parallel to LV	Preterm (n=35)	51 (18)	89	53	67	82
	Term (n=9)	11 (1)	100	50	20	100
Temporo-occipital echogenic blush	Preterm (n=35)	26 (9)	NA	100	NA	74
	Term (n=9)	0 (0)	NA	100	NA	100

Echogenic lines running parallel to the LV

Echogenic lines running parallel to the posterior horns of the LV were seen in 18 of 35 (51%, 14 bilateral, four unilateral) preterm infant scans and in one of nine (11%, all bilateral) term-born infant scans (Figure 3). For the preterm infants mean PMA and weight at scanning were significantly lower for the infants with the lines than for those without (p=0.004 for both).

In 16 preterms and the one term-born infant with echogenic lines parallel to the LV, low SI lines were seen in the same location on MRI (Figure 3). In eight of 17 preterm infants and four of eight term-born infants without these echogenic lines, low SI lines were seen on MRI. The predictive values of these echogenic lines for correlating features on MRI are shown in Table 1.

Figure 4. Bilateral temporo-occipital echogenic blushes on a coronal cUS (a, short arrow) of a preterm infant (gestational age 26.6 weeks) with a postmenstrual age at day of scanning of 27.1 weeks and contemporaneous reconstructed coronal T_2-weighted MR image without correlating feature (b). The cUS scan also illustrates bilateral echogenic areas supero-laterally from the lateral ventricles (a, long arrow) correlating with high signal intensity areas on the T_2-weighted MR image (b, long arrow).



Temporo-occipital echogenic blush

A temporo-occipital echogenic blush was detected in nine (26%, bilateral in all) of the preterm cUS scans and in none of term-born infant scans (Figure 4). Mean PMA and weight at scanning were significantly lower for the preterm infants with the blushes than for those without (p=0.0004 and p=0.002, respectively).

No correlating feature for the temporo-occipital echogenic blushes was seen on the T_2-weighted MRI for either preterm or term-born infants (Figure 4). The predictive values of the echogenic blushes for correlating features on MRI are shown in Table 1.

Areas of echolucency

Cortical subplate

In the more peripheral regions of the hemispheres echogenicity was generally low and lower than in the more central areas of the hemispheric WM but was, even when higher frequencies up to 10 MHz were applied, not specifically lower in the regions identified as representing subplate on the MRI scans (Figures 5 and 6). On the T_2-weighted MR images, regions corresponding to the cortical subplate were seen in 29 preterm infants and one term-born infant.

Figure 5. The cortical subplate visible as a high signal intensity layer on a sagittal T_2-weighted MR image (b, asterisks) of a preterm infant (gestational age 26.6 weeks) with a postmenstrual age at day of scanning of 27.1 weeks. On the contemporaneous parasagittal cUS scan of the same infant the cortical subplate cannot be identified (a). The cUS scan illustrates an echogenic area supero-laterally from the lateral ventricles (a, arrow) correlating with a high signal intensity area on the T_2-weighted MR image (b, arrow), as shown in Figures 3 and 4.

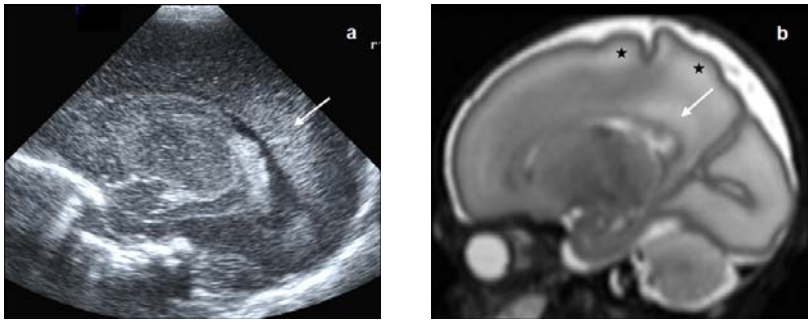
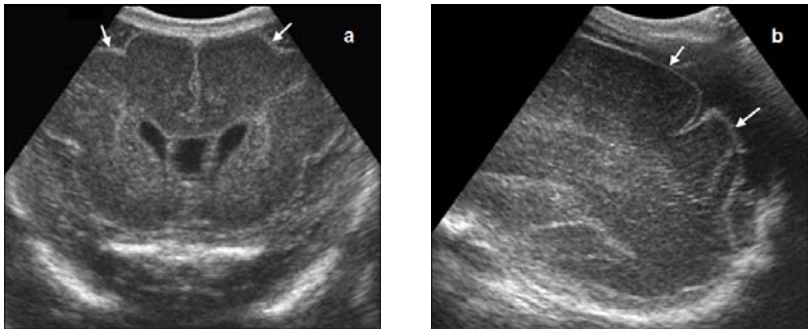


Figure 6. Coronal (a) and parasagittal (b) cUS of a preterm infant (gestational age 26.9 weeks) with a postmenstrual age at day of scanning of 26.9 weeks, performed with a transducer frequency set at 10 MHz and focusing on the cortical area. The cortical layer (arrows) can be nicely distinguished, being of higher echogenicity as compared to the white matter, but the cortical subplate and the subcortical white matter cannot be distinguished separately.

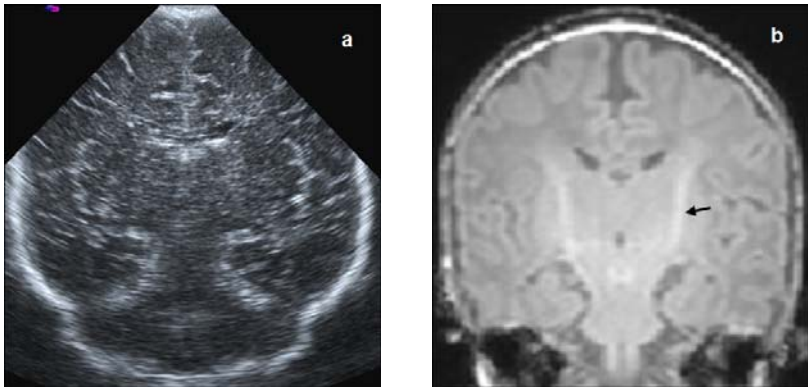


Internal capsule

In five preterm and four term-born cUS scans bilateral echolucent bands were seen running vertically through the basal ganglia between the lentiform and thalamic nuclei at a range of PMAs both before and after TEA. The site of these echolucent bands correlated with the site of the posterior limb of the internal capsule (PLIC) on contemporaneous MRI. On all MR images from both the preterm and term-born infants

the site of the PLIC was distinguished (Figure 7), whether or not the PLIC was myelinated on MRI. On the MR images myelin was detected in the PLIC in 20 preterm infants, who were all > 36 weeks' PMA at time of scanning, and all term-born infants (Figure 7). No significant differences in GA, birth weight and PMA and weight at scanning were found between infants with and without this echolucent band.

Figure 7. Myelination of the posterior limb of the internal capsule visible as high signal intensity at the site of the posterior limb of the internal capsule on a reconstructed coronal T_1-weighted MR image (b, arrow) of a preterm infant (gestational age 31.6 weeks) with a postmenstrual age at day of scanning of 44.0 weeks. On a contemporaneous coronal cUS scan of the same infant myelination of the posterior limb of the internal capsule cannot be identified (a).



Pons

The posterior pons, which myelinates early and before the age at which all scans in this study were obtained, was always very echolucent compared to the anterior pons which was of intermediate echogenicity (Figure 8). The posterior pons was of short T_2 on all the MR images obtained in this study, consistent with myelination. Myelinated tracts were not identified in the anterior pons on the T_2-weighted images as expected at this gestation.

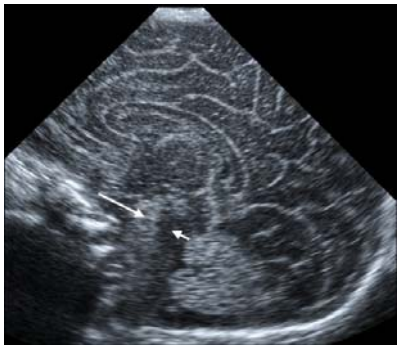


Figure 8. cUS scan in the mid-sagittal plane of a preterm infant (gestational age 31.7 weeks) with a postmenstrual age at day of scanning of 34.3 weeks showing that the posterior part of the pons (short arrow) is relatively echolucent compared the anterior part of the pons (long arrow).

Discussion

Our study has shown that except for the temporo-occipital echogenic blush, bilateral symmetrical areas of increased echogenicity, located in the frontal and periventricular WM, correlate well with areas of altered SI in WM, described as maturational features, on MRI (2,16,21-25,27). Occasionally the site of the PLIC could be distinguished as an echolucent line running vertically between the basal ganglia and the thalami, and the myelinated WM tracts in the posterior pons were always very echolucent compared to the anterior pons. The region of the cortical subplate, which is usually considered as subcortical WM on cUS, could not be reliably identified though this region tended to be of low echogenicity on scans of all gestation.

No significant differences in GA and birth weight were found between preterm and term-born infants with and without the echogenic cUS features. Although the bilateral features were present in preterm and term-born infants, they were better seen in the preterm infants. Their symmetry, prevalence, persistence and gradual diminution with increasing GA in a population of apparently well preterm infants without overt cerebral abnormalities would suggest a non-pathological origin. This is in agreement with van Wezel-Meijler's study describing localized echogenic areas in the frontal periventricular WM, probably comparable to our frontal echogenic blushes and echogenic lines around/below and parallel to the LV in preterm infants scanned before TEA. These echodensities faded or disappeared around TEA, correlated well with areas of altered SI on MRI and were considered a normal phenomenon. They were hypothesized to be remnants of the germinal matrix (16).

Boxma et al. have recently described an echogenic area running parallel to the postero-lateral ventricular margin in 84% of preterm infants < 32 weeks' gestation. They also argued that its location, prevalence, symmetry and unchanged character between 26 and 31 weeks' GA suggests that it represents an anatomical structure, probably part of the optic radiation, and is a normal feature of developing WM (28).

The frontal echogenic blushes and the echogenic areas supero-laterally from the LV correlated well with high SI areas on T_2-weighted MR images, recently called crossroad areas, considered to reflect areas of dense WM fibres (27). The echogenic lines around/below and parallel to the LV correlated well with low SI lines on T_2-weighted images, considered to reflect areas of accumulating microglial cells (27). These altered SI areas are thought to represent features of developing WM (22-25,27).

The reason for the variability in signal on T_2-weighted MR images, i.e. some echogenic features correlated with high SI areas, others with low SI areas, is interesting. On T_2-weighted images, high SI generally represents a higher water content and unmyelinated fibre-rich areas and low SI a lower water content and cell-dense areas, though this may not always be the case with the cortical subplate. Echogenic areas on cUS can represent various normal and abnormal processes and different structures and tissue compositions, making the distinction between cell-dense and fibre-rich areas difficult. To explore the signal inconsistency further precise histological correlates are needed.

The reason that we did not find a MRI-correlate for the temporo-occipital echogenic blush is not clear. Boxma et al. did not see the echogenic area they described via the posterior fontanel (28). They argued that this was related to the direction of insonation of fibres. As different angles are used for obtaining cUS and MR images and, consequently, cerebral structures and tissues are approached differently, this might be an explanation. However, contrary to Boxma et al. we also detected the temporo-occipital blushes via the posterior fontanel (data not given). In addition, for all other cUS features a MRI-correlate was found. Another contributory explanation might be that cUS and MRI are different imaging techniques; ultrasound imaging is based on differences in speed of sound waves between and within tissues, whereas MR imaging exploits differences in tissue proton density and relaxation times. The tissue composition at the site of the temporo-occipital blush may, compared to surrounding tissue, induce a change in speed of sound waves but might not be different with respect to proton density.

Although it is most likely that the bilateral echogenic WM features on cUS represent maturational processes, they may not be entirely normal. A fetal cUS study has shown that echogenic areas in the frontal periventricular WM occurred at a later GA in high-risk than low-risk fetuses (30). Different layers in the WM (i.e. inner periventricular, intermediate and outer subcortical layer), anterior caps and posterior arrowheads, seen as areas of altered SI, are present on almost all early preterm brain MR images and usually become less obvious with increasing GA. Early loss of these features or delay in fading with increasing GA has been associated with cerebral abnormalities (16,22-25). The WM in preterm infants at TEA appears less mature than in term-born infants (9,26). Layers of altered SI on MRI can be distinguished in fetal WM becoming less obvious around 28 weeks' GA, corresponding with the completion of neuronal migration from the ventricular zone to the cortical plate (27,31). Judas et al. have recently described that after 28 weeks' gestation, the periventricular crossroad areas in post-mortem brains of preterm infants retain their MR features only on T_1-weighted images (27). In our study, using T_2-weighted MR images, the cUS and correlating MRI features were seen in all infants scanned at a PMA of > 28 weeks. These findings support the hypothesis that some of the MRI features described as maturational processes of the preterm brain may, in part, be a sign of delayed or abnormal rather than normal maturation. Thus the correlating cUS features we describe may also represent delayed maturation or even mild WM injury and be an imaging correlate for the neurodevelopmental problems in preterm infants without evidence of focal brain injury.

The cortical subplate is a cell- and water-rich layer, visible on T_2-weighted images as a high SI layer (27,32-33). Even when using higher frequencies, we were not able to identify positively the cortical subplate, apparent on our T_2-weighted images, on cUS though the corresponding area was usually of low echogenicity (Figures 5 and 6). An explanation for this may be that although it has a higher cellular content than the adjacent (subcortical) WM and might therefore be expected to be more echogenic, the high water content opposes this, rendering the cortical subplate equally echogenic as the (subcortical) WM.

In a few infants the site of the PLIC was distinguished as an echolucent band running between the normally appearing basal ganglia and thalami. Myelin in the PLIC can probably not be distinguished on cUS, especially as there was no consistency between the PLIC being visible on cUS and myelin being present on MRI and we saw this low

signal line on cUS scans done both before and after TEA. It is interesting to note, however, that on all scans the posterior pons was always very echolucent compared to the anterior part. The posterior pons myelinates early and signs of myelination are seen on T_1-weighted MR images from 23 weeks´ GA, whereas the anterior pons shows myelination only after term age (3). The difference in echogenicity might be explained by a difference in myelination or rather a difference in water content related to myelination and be especially obvious when insonated parallel to fibre orientation. The visibility of the site of the PLIC on some scans may also reflect early tract development of fibres in a similar plane but not been so easily seen as in the pons as the PLIC is small and fibres do not run exactly parallel to the plane of insonation (34). To our knowledge, this has not been described before and needs further investigation. However, the difference in echogenicity in the pons may also be explained by the difference in orientation of fibres between the anterior and posterior pons. Of interest, in an abnormal context, the visibility of the site of the internal capsule has been reported in severe perinatal asphyxia (35) but this may be dependent on the adjacent abnormal echogenicity in the central grey matter structures which is not the explanation in this study.

We accept limitations to our study; it was sometimes difficult to view cUS and MR images in exactly the same planes. No direct histological correlates were obtained and, therefore, the correlation between cUS and histology is presumptive. However, we believe that by matching the cUS scans with contemporaneous MRI and histological data in the literature, the associations described in this study are valid. Serial cUS and MRI data were not obtained and, therefore, it was not possible to explore whether the cUS features fade consistently with increasing GA and, if so, when. We did not include infants with overt cerebral pathology. It would be important to explore whether there are differences in presence and appearance of the cUS features between infants with and without cerebral pathology. This would help to determine whether the features in the WM reflect normal maturational processes or rather abnormal maturation or injury. Finally, assessment of echogenicity by visual analysis is subjective. So far, no easily applicable and reliable technique for quantifying echogenicity is available.

In conclusion, this study has shown that bilateral symmetrical echogenic areas in the frontal and periventricular WM are frequently seen on early preterm cUS scans and, except for the temporo-occipital echogenic blush, correlate well with areas of altered SI in WM on MRI. We could not reliably identity the cortical subplate or the PLIC.

However, the site of the PLIC was sometimes visible and the posterior myelinated pons was always echolucent. The imaging features, both on MRI and cUS, described in this study most likely reflect normal but may in some cases reflect delayed or even abnormal maturational processes in the hemispheres. Approaches to understand their significance include follow-up studies of infants in whom the time-course of these features has been carefully documented from cUS and MRI, histological studies where cUS and MR imaging have been obtained shortly prior to death and studies comparing these features seen in infants born preterm with sequential optimized fetal neuro-imaging studies.

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