Cranial ultrasound and MRI at term age in extremely preterm infants

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Running title: MRI and ultrasound at term in extremely preterm infants

Key words: ultrasonography, magnetic resonance tomography, preterm infants, outcome, newborn

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There are no competing interests.
Abstract

Objectives: Conventional magnetic resonance imaging (MRI) at term age has been reported to be superior to cranial ultrasound (cUS) in detecting white matter (WM) abnormalities and predicting outcome in preterm infants.[1] However, in that study cUS was performed during the first 6 weeks only and not in parallel to MRI at term age. Therefore, we aimed to study brain injuries in preterm infants performing concomitant cUS and MRI at full-term age.

Methods: In a population based cohort of 72 extremely low gestational age infants paired cUS and conventional MRI were performed at term age. Abnormalities on MRI were graded according to a previously published scoring system.[1,7,8] On cUS images the lateral ventricles, the corpus callosum, the interhemispheric fissure and the subarachnoidal spaces were measured and the presence of cysts, grey matter abnormalities and gyral folding were scored.

Results: Moderate or severe WM abnormalities were detected on MRI in 17% and abnormalities of the grey matter in 11% of infants. Amongst infants with normal ultrasound (n=28, 39%) none had moderate or severe WM abnormalities or abnormal grey matter on MRI. All infants with severe abnormalities (n=3, 4%) were identified as severe on both MRI and cUS.

Conclusion: All severe white matter abnormalities identified on MRI at term age were also detected by cUS at term, providing the examinations were performed on the same day. Infants with normal cUS at term age were found to have a normal MRI or only mild WM abnormalities on MRI at term age.
Introduction
Cranial ultrasound (cUS) is the most commonly used brain imaging technique in the neonatal intensive care of preterm infants. It reliably detects major intracranial lesions such as intraventricular haemorrhage, parenchymal hemorrhagic infarctions or cystic periventricular leukomalacia, all strongly predictive for the development of cerebral palsy and severe cognitive impairment.[2,3,5] The advantages of cUS are that it is a fast and cheap bedside technique that allows scanning directly after birth and sequentially as often as clinically indicated until term age. However, its sensitivity to detect subtle non-cystic white matter injuries has been matter of debate.[1-6]

In contrast, conventional magnetic resonance imaging (MRI) has been shown to also allow the detection of microstructural (non-cystic) white matter injury in a high number of extremely preterm infants.[1,4,5,6,7,8,12]

cUS and conventional MRI have previously been compared in preterm cohorts. In a recent study Woodward et al demonstrated that abnormal findings on cerebral MRI at term equivalent age predict adverse neurodevelopmental outcome at two years of age significantly better than cUS.[1] This finding raises the question whether MRI at term should be introduced as a screening tool for all extremely preterm infants. However, in Woodward’s study cUS were performed only during the first 6 weeks of life and not in parallel to the MRI at term. Hence potentially important information generated from cUS at term age was not taken into account.[9] Moreover, it has to be considered that MRI is an expensive, time- and manpower consuming technique that usually requires transport and sometimes sedation. Furthermore, MRI is not available in all hospitals and if available, waiting lists are usually long.

The aim of the present study was to compare both imaging techniques, cUS and conventional MRI, performed on the same day at term equivalent age, in a population based cohort of extremely low gestational age infants (below 27 weeks gestation, ELGA) and to determine what proportion of infants with completely normal cranial ultrasound findings have clinically significant MRI abnormalities.
Patients and Methods

Patients and perinatal data

From August 2004 to November 2006 all infants born with a gestational age below 27 weeks in the Stockholm region were included. A cUS and an MRI scan of the brain were performed on the same day at term equivalent age [38-42 weeks postmenstrual age]. The study was approved by the regional ethical committee. Informed consent was obtained from all parents of infants included in the study. Perinatal data and clinical courses were prospectively collected. Infants with chromosomal disorders, congenital abnormalities, congenital infections, and proven metabolic or malignant disorders were excluded from further analysis.

MR Imaging

All MR scans were performed at the Astrid Lindgren Children’s Hospital at Karolinska University Hospital in Stockholm, Sweden, using a 1.5 Tesla magnetic resonance system (Philips Intera, Philips, Best Holland). According to our standard clinical protocol for neonatal MRI, infants were fed and given chloral hydrate (30 mg/kg orally or rectally) 15-30 min prior to the examination. However, if infants were already deeply asleep prior to the examination or if the parents did not give consent to the use of sedative medication, infants were scanned during natural sleep.

In order to reduce acoustic noise we used a combination of three passive hearing protections: commercially available dental putty (Affinis dental putty soft, Coltene AG, Switzerland) and pediatric ear muffs (Bilsom Junior) as well as an in-house developed acoustic hood that reduces noise levels by 16-22 dBA depending on the pulse sequence. [10]

Our conventional MRI protocol consisted of anatomical high-resolution imaging including a T1-weighted turbo spin echo scan, an inversion recovery scan and a 3D gradient echo sequence (TR/TE/flip = 40 ms/4.6 ms/30 deg, voxel size = 0.7 x 0.7 x 1 mm³). Further, T2-weighted turbo spin echo images were acquired in both sagittal and coronal slice orientations.

MR scoring system

MR images were evaluated independently by three observers blinded to the clinical course of the infants. We used a previously described scoring system to grade grey and white matter abnormalities. [1,7,8] We have previously reported an interobserver agreement of > 98% using this scoring system with the same observers.[8] Remaining discrepancies were resolved by discussion and consensus was thus reached in all cases. Five different WM-variables were assigned a score 1, 2 or 3: I- WM signal abnormality [on T1 and/or T2 images], II- reduction in WM volume, III- cystic abnormalities, IV- lateral ventricular size, V- corpus callosum size/myelination stage. WM abnormalities were further classified by the composite score of these five categories (potential range in scores, 5–15) into no WM abnormality (score 5–6), mild WM abnormality (score 7–9), moderate WM abnormality (score 10–12), or severe WM abnormality (score 13–15). Further, three different grey matter abnormalities were assigned a score 1, 2 or 3: I- cortical grey matter signal, II- cortical gyration maturation and
III- size of the subarachnoidal spaces. Scores were added and grey matter appearance was divided into two groups: normal (score 3–5) or abnormal (score 6–9) grey matter.

**Cranial ultrasound**
cUS was performed the same day as the MRI scan. Infants were scanned by one of two examiners (SH and BS) experienced in neonatal cUS using the ACUSON Sequoia ultrasound system (Siemens Medical Solutions, Germany) equipped with a multifrequency sector transducer (5-8 MHz). cUS was performed in coronal and sagittal/parasagittal planes through the anterior fontanelle obtaining sequential images according to Levene.[11] The images were stored digitally. From these, three independent observers measured the size of lateral ventricles, the corpus callosum, the interhemispheric fissure and the subarachnoidal spaces. The presence of cysts, abnormal echogenicity in the cortical grey matter and gyral folding was also evaluated. Details on how measurements and scoring where done are presented in the appendix.

The cUS was considered **Normal** if none of the 8 measured or scored items (frontal horn size, ventricular midbody size, interhemispheric fissure, subarachnoidal spaces, cysts, corpus callosum size, gyral folding, abnormal echogenicity in the cortical grey matter, please find details of the measurements in the appendix) was abnormal/outside the normal range.

**Severe abnormalities** were predefined as cystic periventricular leukomalacia, cystic defects/white matter loss after periventricular haemorrhagic infarctions and global white and/or grey matter loss without focal lesion usually coinciding with severe ventriculomegaly.

All ultrasound findings that were neither normal nor severely abnormal according to the above mentioned definitions were classified as mild-moderate abnormalities.
During the study period 132 infants were live-born with a gestational age (GA) below 27 weeks (w) in the Stockholm region. 20 infants (17 with GA of 22 w, 3 with GA of 23 w) died in the delivery room after receiving comfort care only. Five infants (4 with GA of 24 w, one with GA of 26) died in the delivery room despite active treatment. In addition, 23 infants died after admission to the NICU before term age (2 with GA of 22w, 2 with GA of 23w, 6 with GA of 24w, 7 with GA of 25w, 6 with GA of 26w). Of the surviving infants (n=84) three infants met the exclusion criteria (1 meningomyelocele, 1 oesophageal atresia, 1 hemophagocytic lymphohistiocytosis). In 5 infants parents did not give consent. Seventy-six infants were scanned, representing 94% of all eligible survivors. In 4 infants full data analysis was not possible, due to motion artifacts on MRI (n=2) or incomplete cUS (n=2) leaving 72 infants for analysis. Patient characteristics are presented in table 1.

<table>
<thead>
<tr>
<th>Birth weight (median, range)</th>
<th>849g (494-1161g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (median, range)</td>
<td>25+4 weeks (23+3w-26+6w)</td>
</tr>
<tr>
<td>Singleton</td>
<td>56/72 (77%)</td>
</tr>
<tr>
<td>Prenatal steroids</td>
<td>68/72 (94%)</td>
</tr>
<tr>
<td>Cesarean</td>
<td>30/72 (42%)</td>
</tr>
<tr>
<td>Boys</td>
<td>36/72 (50%)</td>
</tr>
<tr>
<td>Days on ventilator (median, range)</td>
<td>8 days (0-50 days)</td>
</tr>
<tr>
<td>Postnatal steroids (betamethasone)</td>
<td>15/72 (21%)</td>
</tr>
<tr>
<td>BPD (O2 at 36w GA)</td>
<td>28/72 (38%)</td>
</tr>
<tr>
<td>IVH III/PHI</td>
<td>10/72 (14%)</td>
</tr>
<tr>
<td>NEC</td>
<td>4/72 (5.6%)</td>
</tr>
</tbody>
</table>

Table 1: Patient characteristics

MRI Scoring Results.

No or only mild abnormalities were found in 83% of infants, while 17% had moderate or severe white matter abnormalities. In more detail, no WM abnormalities were found in 31/72 (43%) infants, mild WM abnormalities in 29/72 (40%), moderate in 9/72 (13%) and severe in 3 infants (4%) Representative images are presented in figure 1. Abnormal grey matter was found in 8 (11%) infants (see figure 2). These incidences confirm earlier reported low incidences of moderate and severe white matter disease in the Stockholm cohort [8]. Four infants had a small punctate cerebellar haemorrhage. Three of the four infants with cerebellar haemorrhage had also supratentorial abnormalities. In one infant the cerebellar haemorrhage was the only pathological finding.

Ultrasound Results

In 28/72 (39%) of infants the cUS at term age was found to be normal. Mild-moderate abnormalities (not normal, not severe) were found in 41/72 infants (57%) and severe abnormalities in 3 infants (4%). Representative images are presented in figure 1.
**MRI and Ultrasound comparison**

All infants with severe abnormalities (n=3) were scored as severely abnormal on cranial US and MRI. Out of 28 infants with normal ultrasound at term age, 18 (64%) had a completely normal MRI and 10 (36%) had only mild WM abnormalities on MRI. Thus, none of the infants with normal cUS had moderate or severe WM abnormalities or abnormal grey matter (figure 3). Representative images are presented in figure 1. Ten infants who were scored as normal on MRI were scored as mild-moderate (=not normal/not severe) in cUS.

In four infants small punctate cerebellar haemorrhage was diagnosed with MRI. None of the cerebellar haemorrhages were diagnosed with cUS via the anterior fontanelle.
Discussion

In this study we present population based data on paired cUS and conventional MRI performed on the same day at term age in a cohort of extremely low gestational age infants. Our two main findings are: Firstly, infants with normal ultrasound at term age had a normal MRI (64%) or only mild (36%) WM abnormalities on MRI. Thus, none of the infants with a normal ultrasound at term age had moderate-severe WM abnormalities or abnormal grey matter on MRI. Secondly, all infants with severe abnormalities were scored as severe with conventional MRI and ultrasound.

cUS and conventional MRI have been systematically compared before. Both, Woodward et al [1] and Mirmiran et al [5], found conventional MRI to be superior to ultrasound in predicting adverse neurodevelopmental outcome at 2 years and cerebral palsy, respectively. This has initiated an ongoing discussion if conventional MRI should be introduced as a screening tool for preterm infants at term age.

However, in both these studies the sensitivity of ultrasound for predicting cerebral palsy (sensitivity/ specificity: Woodward 18%/ 95%; Mirmiran 29%/86%) was inferior compared to results published by other groups, e.g. de Vries et al (79%/95%).[2] This is likely due to a major difference in study design. While de Vries et al scanned infants weekly from birth until term age, Woodward et al performed only 3 ultrasound scans within the first six week of life and Mirmiran et al 2 scans in the first two weeks of life. Thus, information generated from cUS after six (two) weeks of life were not taken into account neither in Woodward’s nor in Mirmiran’s study. Late cUS can provide information about impaired brain growth, diffuse grey and white matter loss (also referred to as signs of brain atrophy) and it has been shown that signs of poor brain growth/brain atrophy are related to adverse neurodevelopmental outcome at 3 years.[9] Therefore, we argue that the superiority of MRI at term to sequential cUS from birth to term age still needs to be proven.

We here show that severe abnormalities are equally well diagnosed with both methods which is coherent with earlier studies. [2,3,5] More important, our data show that approximately 40% of extremely low gestation age infants had a completely normal cUS at term age and that none of these infants had moderate or severe WM abnormalities or abnormal grey matter on conventional MRI. Consequently, all infants with normal cUS have either a normal MRI (64%) or only mild (36%) WM abnormalities on MRI.

This raises the question if mild WM abnormalities on MRI found in one third of infants are of clinical relevance; does the knowledge about these mild WM abnormalities change our clinical decision making and/ or parental counseling? Woodward et al demonstrated that infants with mild WM abnormalities had a 7.2 points lower mean MDI and a 3.9 points lower mean PDI score compared to infants with normal white matter.[1] However, the specificity for predicting severe cognitive and motor delay, cerebral palsy and neurosensory delay decreased from 82-84% (for moderate to severe WM abnormalities) to 30-31% when all
white matter abnormalities - including mild WM abnormalities - were taken into account. Considering that these data were acquired in centers of excellence in neonatal MRI, it must be assumed that sensitivity and specificity might be reasonably lower in centers with less experience in neonatal MRI.

From our results, we hypothesize that in infants with normal cUS at term age, conventional MRI adds marginally clinically relevant information. Consequently, it is unlikely in this group of infants that MRI at term age will change clinical decisions making or parental counseling. This implies that ultrasound can be used as a screening method to identify infants with low risk of severe disability and thereby reduce number of MRIs. This is important as MRI is at this moment an expensive technique with limited access and sometimes logistic challenges (transport, sedation).

Nevertheless, it has to be emphasized that our results refer to conventional MRI in preterm infants at term in a clinical setting only. The high impact of neonatal MRI in a research setting is certain and undisputed. Conventional MRI and more advanced MRI methods (incl. image post-processing techniques) like diffusion tensor imaging, volumetry, tractography, MR spectroscopy and functional MRI have and will greatly enhance our knowledge about physiology and pathophysiology of the developing newborn brain [12-16]. Implementing these more advanced techniques into the clinical setting might improve the information gained by an MRI at term age in the future.

One limitation of the study is that cUS was performed through the anterior fontanel only. Ultrasound examinations that add to the view through the anterior fontanel the view through the posteriolateral and posterior fontanel have been found to be superior in the detection of posterior fossa abnormalities. [17,18] In our study four infants had a small punctate cerebellar haemorrhage not seen on cUS but diagnosed on MRI images.

The strength of the present study is that we compare cUS and conventional MRI performed on the same day at term age. Furthermore, the cohort is population based, thus, the data represents the true spectrum of brain abnormalities in high risk group of ELGA infants. Moreover, we focus on clinical point of view in order to determine the clinical advantages of MRI compared to the cheaper and faster ultrasound examination in daily routine.

In conclusion, we compared cUS and conventional MRI performed on the same day at term age in ELGA infants and suggest that in a clinical setting cUS can be used as a screening method to identify infants in who conventional MRI adds marginally clinically relevant information to the cUS result.
What is already known on this subject?
Brain abnormalities are common in preterm infants with low gestational age. Cranial ultrasounds detects reliable the major brain abnormalities which are predictive for neurological outcome. MRI at term has been shown to be superior to early (≤ 6weeks) ultrasound in predicting outcome at 2 years of age.

What this study adds?
Our study presents population-based data on brain abnormalities in extremely preterm infants detected by cranial ultrasound and conventional MRI, both performed at term age. Approximately 40% of ELGA infants have a normal ultrasound at term age. In the subgroup of infants with normal ultrasound at term age conventional MRI adds marginally clinically relevant information.
Funding

The present study was supported by the following grants: ESPR Young Investigator Exchange Program, Jerring Foundation, Sällskapet Barnavård, Märta och Gunnar V Philipsson Foundation, Swedish Medical Research Council, Foundation Samariten, Free Masonry Foundation Barnhuset in Stockholm, Åke Wiberg Foundation, Jeansson Foundation, Karolinska University Hospital. These fundings financed the research activity of Sandra Horsch and Béatrice Skiöld.
References


Figure Legends

**Figure 1:** Representative images of infants with severe brain abnormalities. 1 a-c: Coronal MRI (a) and cUS (b/c) images of an infant with shunt dependent posthaemorrhagic hydrocephalus and periventricular cysts. 2 a/b: sagittal MRI (a) and cUS (b) images of an infant with big porencephalic cyst after extensive periventricular haemorrhagic infarction and white and grey matter loss. 3 a/b: coronal MRI (a) and cUS (b) images of an infant with cystic defect after periventricular haemorrhagic infarction.

**Figure 2:** MRI scoring result.

**Figure 3:** MRI results of infants with normal cUS at term (n=28).
Appendix

Ultrasound Analysis

All ultrasound examinations were performed by one of two observers. Images were stored digitally and later analyzed by three independent observers blinded to clinical data. All three observers performed all measurements mentioned below. The mean of the measurements of the three observers was used for further analysis for all parameters. The cUS was considered normal if none of the 8 measured or scored items (A frontal horn size, B ventricular midbody size, C interhemispheric fissure, D subarachnoidal spaces, E cysts, F corpus callosum size, G gyral folding, H abnormal echogenicity in the cortical grey matter) was abnormal/outside the normal range.

A. The frontal horn size as an indirect sign of frontal white matter loss was measured in the following way: The short (1) and the long (2) axis of the frontal horn in the coronal view on the level of the 3rd ventricle (see figure A1a) and the frontal horn height (3, figure A1b) in the parasagittal view were measured bilaterally. A cutoff level of 3mm was chosen for (1) and (3), and 13mm for (2).[1] The frontal horn size was considered normal, when none or only one of the 6 measurements were above the cut of level.

B. The size of ventricular midbody (4) as an indirect sign of parieto-occipital white matter loss was measured in the parasagittal view [4, figure A1b). The size of the ventricular midbody was considered normal when bilaterally < 10mm.[2]

C. The width of interhemispheric fissure (IF see figure A2a) was measured in the coronal view at the level of the 3rd ventricle as a mean distance between hemispheres. The width of the interhemispheric fissure was considered normal when < 3mm.

D. The width of the subarchnoidal spaces (SS see figure 2a) was measured as the sino-cortical width in the coronal view in 3 different positions (C1, C4, C8, see figure A 2b). The width of the subarchnoidal space was considered normal when < 4mm in all three measurements.[3]

E. Only the absence of cysts in the grey and white matter was considered normal.

F. The body of the corpus callosum was measured in the sagittal midline view. The size of the corpus callosum was considered normal when > 1.5mm.[4]

G. The complexity of gyral folding was considered normal when appropriate for gestational age in coherence with the definition of the MRI scoring system published by Inder et al/ Woodward et al.[5,6]

H. Only the absence of abnormal echogenicity in the cortical grey matter (e.g. due to haemorrhage or ischaemia) was considered normal.
References

**Figure Legends Appendix:**

Appendix Figure 1: Ultrasound measurements of the lateral ventricle size.  
1 a: coronal view at the level of the 3<sup>rd</sup> ventricle; (1) indicating the short axis and (2) the long axis of the frontal horn. 1b: parasagittal view (3) indicating the measurement of the frontal horn height and (4) of the ventricular midbody.

**Appendix Figure 2:** Ultrasound measurement of the subarachnoidal spaces and interhemispheric fissure. 2a: coronal view at the level of the 3<sup>rd</sup> ventricle; SS indicating the measurement of the sino-corticale width and IF of the interhemispheric fissure. 2b: Illustration of transducer positioning for coronal views. Sino-corticale width was measured in 3 different positions, C1, C3 and C5.
Normal cUS at term
28/72 (39%)

Definition:
- No cysts
- No dilatation of ventricular midbody or frontal horns
- No thinning of corpus callosum
- No enlargement of interhemispheric fissure or subarachnoidal spaces
- Normal gyral folding
- Normal cortical grey matter

MRI at term

- 18/28 (64%): No WM abnormalities
- 10/28 (36%): Mild WM abnormalities
- 28/28 (100%): Normal grey matter
- Abnormal grey matter
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Arch Dis Child Fetal Neonatal Ed published online October 19, 2009

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