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Ultrasound detection of white matter injury in very preterm neonates: practical implications

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ABSTRACT

Aim: Diffuse white matter injury is not well detected by cranial ultrasonography (CUS). The aim of the study was twofold:

- To assess in very preterm neonates the predictive values of individual CUS abnormalities for white matter injury on MRI and neurological outcome
- To develop a strategy optimizing CUS detection of white matter injury.

Method: Very preterm neonates (n=67; 44 males) underwent serial CUS and single MRI. Predictive values of CUS findings for a white matter classification on MRI, individual MRI findings and neurological outcome at 2 years corrected age were calculated. The effects of timing and frequency of CUS were evaluated.

Results: Periventricular echo densities (PVE) predicted abnormal white matter on MRI, but absence of PVE did not predict absence of white matter changes. Peri- and intraventricular hemorrhage (P/IVH) was highly predictive of abnormal white matter on MRI. Frequency and timing of CUS did not influence predictive values.

P/IVH and abnormal ventricular size/shape were reasonably predictive of unfavorable outcome, whereas absence of CUS abnormalities predicted a favorable outcome.

Interpretation:
1. If PVE are present, there is a significant chance of abnormal white matter on MRI.
2. Increasing frequency of CUS does not increase its diagnostic performance for white matter injury.
3. P/IVH is highly predictive of abnormal white matter on MRI and reasonably predictive of unfavorable outcome.
4. Absence of PVE or P/IVH on CUS does not guarantee normal white matter, but predicts a favorable outcome.
**INTRODUCTION**

White matter (WM) injury is one of the most frequently occurring forms of brain injury in infants born very prematurely (gestational age <32 weeks).

During recent decades, the character of WM injury has shifted from “classic periventricular leukomalacia” to more subtle or diffuse WM injury. The latter, occurring in more than 80% of infants born very preterm, cannot be reliably diagnosed by ultrasonography.\(^1\) On T2-weighted MRI, it is assumed to be represented by areas of altered signal intensity throughout the WM, so-called diffuse excessive high signal intensity (DEHSI) (Figure 1) and by focal signal intensity changes, so-called punctate white matter lesions (PWML).\(^4\) PWML are better visualized on T1-weighted MRI (Figure 2).

Although MRI is increasingly used in neonates and has proved safe and reliable to detect various forms of neonatal brain injury, it is not suitable for repetitive examina-

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**Figure 1.** (left) T2-weighted MR image in a very preterm infant, scanned at TEA, showing DEHSI in the frontal and occipital WM (arrows). The figure also shows mildly dilated and abnormally shaped lateral ventricles.

**Figure 2.** (right) T1-weighted MR image in a very preterm infant, imaged around TEA, showing bilateral, multiple, confluent PWML (arrows) in the central WM.
Therefore, cranial ultrasonography (CUS) is still the preferred modality for serial neuro-imaging during the neonatal period. In this perspective it is important to develop a CUS screening system, enabling optimal detection of WM injury and selection of neonates needing MRI. A recent study, considering MRI as the criterion standard, showed a good reliability of CUS in very preterm infants with severely abnormal WM. However, CUS was less reliable in demonstrating mild and moderate WM abnormalities. In that study, CUS and MRI classifications of WM injury were introduced, based on respectively echogenicity- and signal intensity changes in the WM and on loss of WM volume. However, we did not test the performance of individual CUS findings for predicting WM injury and did not analyse the influence of frequency and timing of CUS examinations on the reliability of CUS.

Early detection of brain injury may be important for timely intervention in high-risk neonates. With the present study we aim to develop a strategy to optimize CUS detection of WM injury, focusing on specific CUS findings and on the number and timing of CUS examinations. We hypothesized that specific CUS findings, including inhomogeneous and grade 2 periventricular echo densities (PVE), are predictive of WM injury on MRI. In addition we hypothesized, based on the results of former studies that PVE on CUS predict DEHSI on MRI and that increasing the number of CUS examinations increases the reliability of CUS for detecting WM injury. The specific aims were to assess the predictive values of individual CUS findings for:

1) The WM classification on MRI
2) Individual MRI findings
3) Neurological outcome at 2 years corrected age

We also assessed whether:
4) Increasing the number of CUS examinations increases the reliability of CUS for detecting WM injury and
5) Timing of CUS examinations influences the reliability of CUS for detecting WM injury

**Method**

**Patients**

Between May 2006 and October 2007 eligible infants, born very preterm and admitted to our tertiary neonatal unit were included in a neuro-imaging study, comprising serial CUS, according to the standard of care for these neonates and a single MRI, preferably performed around term equivalent age (TEA). The study was approved by the Medi-
Ultrasound detection of white matter injury: practical implications

cal Ethics Committee and informed consent was obtained from the parents. Results on prevalence of CUS and MRI abnormalities and on prediction of WM injury by CUS, based on the WM classification, were published elsewhere.1,4,12

Cranial Ultrasonography
CUS examinations were performed within 24 hours after birth, thereafter at least weekly until discharge or transfer to another hospital and again around TEA, on the same day as the MRI, according to a standard protocol.9

All CUS examinations were assessed by LML and GvW-M or LML and SJS, focusing on individual CUS findings. The following echogenicity changes in the WM were recorded: non-physiological PVE, cystic lesions (small and localized or more extensive), and focal WM echodensity presenting periventricular hemorrhagic infarction. The appearance of PVE (homogeneous, inhomogeneous and grade 1 or grade 2) was noted.11 In addition, peri-and intraventricular hemorrhages (P/IVH) grade 1 to 3 according to the classification of Volpe,13 and the size and shape of the lateral ventricles were recorded. The latter was only done for the CUS examination performed around TEA. The size and shape of the ventricles were visually scored as normal/mildly abnormal, moderately abnormal and severely abnormal.

MRI
MRI examinations were performed according to a standard protocol for imaging the newborn infant’s brain, using a 3.0 T MR system (Philips Medical Systems, Best, the Netherlands) as recently described.7 In summary, scans included at least 3D T1-weighted gradient echo MRI (TR/TE: 9.7/4.6 ms, flip angle 8), T2-weighted TSE MRI (TR/TE: 6269/120 ms, turbofactor 18), diffusion-weighted images in three directions (TR/TE: 2406/64 ms) and T2* susceptibility-weighted MRI (TR/TE: 735/16 ms) in the transverse plane. All MRI examinations were assessed by LML and FTdB or by SJS and FTdB, who were blinded to the CUS findings. For this part of the study the T1- and T2-weighted images were assessed. Particular attention was paid to the WM by using a recently described classification to score the grade of WM injury. In summary, the WM was scored as normal or mildly abnormal if no signal intensity changes or only homogeneous DEHSI and/or few (≤6) PWML were seen and if the shape and size of the lateral ventricles were normal or only mildly abnormal. A moderately abnormal WM score was applied if multiple (>6) PWML and/or small localized cystic lesions and/or inhomogeneous DEHSI and/or moderately abnormal lateral ventricles were seen. The WM was scored as severely abnormal in the case of more serious abnormalities.4
Follow up
Around 2 years of age, the infants were seen by an experienced neonatologist for clinical follow up. The children underwent a standardized neurologic examination to assess the presence of cerebral palsy or abnormal muscular tone.

Cognitive and psychomotor development was assessed using the Dutch version of the Bayley Scales of Infant Development (BSID-III). A mental developmental index score and psychomotor developmental index score were calculated for the corrected age. A score of \( \geq 1 \) SD below the normative mean was defined as a developmental delay.

Statistical methods
Firstly, sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of individual CUS findings (presence, aspect, duration and grade of PVE; focal WM echodensity; P/IVH; and shape and size of the lateral ventricles on the CUS performed around TEA) for the MRI WM classification were calculated. Secondly, predictive values of PVE on CUS for DEHSI on MRI and of inhomogeneous PVE on CUS for PWML on MRI were calculated.

In addition, to explore whether increasing the number of CUS examinations improved the predictive value of CUS for MRI, the predictive values of PVE present on the first CUS examination and also respectively on any CUS performed during the first week, first 2 weeks or first 4 weeks of life were calculated. Furthermore, to assess the influence of timing of CUS examinations on the predictive value of CUS, predictive values of PVE, seen in a certain period (first, second, third, or fourth week after birth) were calculated. For statistical analysis, WM on MRI was divided into two groups: normal and mildly abnormal versus moderately and severely abnormal WM. The aspect of the lateral ventricles on CUS and MRI was also divided in two groups: normal versus abnormal shape and/or size of the lateral ventricles.

Finally, the predictive values of individual CUS findings for unfavorable neurological outcome at 2 years corrected age, defined as either a developmental delay and/or cerebral palsy, were calculated.

Results
Patients
A total of 130 very preterm infants were included in the study of which 108 underwent MRI. In 67 of the 108 infants, MRI was performed before the postmenstrual age of
Table 1. General characteristics and ultrasound findings of total group included (N=108) and group with MRI at PMA < 44 weeks (N=67).

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>Total group</th>
<th>PMA at MRI &lt; 44 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients included</td>
<td>108</td>
<td>67</td>
</tr>
<tr>
<td>Male (%)</td>
<td>67 (62.0)</td>
<td>44 (65.7)</td>
</tr>
<tr>
<td>Mean weight at birth (range)</td>
<td>1205.7 (585-1960)</td>
<td>1228.2 (585-1960)</td>
</tr>
<tr>
<td>Mean GA in weeks (range)</td>
<td>29.0 (25.6-31.9)</td>
<td>28.9 (25.6-31.2)</td>
</tr>
<tr>
<td>Mean PMA at MRI in weeks (range)</td>
<td>44.9 (39.1-62.1)</td>
<td>42.5 (39.1-44.0)</td>
</tr>
</tbody>
</table>

MRI findings
- Normal/mildly abnormal MRI (%) 26 (24.1) 18 (26.9)
- Moderately/severely abnormal MRI (%) 82 (75.9) 49 (73.1)
- DEHSI on MRI (%) 76 (70.4) 59 (88.1)
- >6 PWML on MRI (%) 18 (16.7) 13 (19.4)

CUS findings
- PVE (%) 87 (80.6) 55 (82.1)
- Grade 2 PVE (%) 11 (10.2) 8 (11.9)
- Inhomogeneous PVE (%) 72 (66.7) 46 (68.7)
- Duration PVE > 14 days (%) 43 (39.8) 29 (43.3)
- P/IVH grade 1-2 (%) 23 (21.3) 15 (22.4)
- P/IVH grade 3 (%) 8 (7.4) 4 (6.0)
- Abnormal size and/or shape ventricles (%) 56 (51.9) 28 (41.8)

44 weeks. In the other 41 infants, MRI was postponed owing to their instable condition. As DEHSI is currently only described in children scanned around TEA, statistical analysis was confined to the 67 infants with MRI around TEA.

Table 1 shows the general characteristics and CUS findings of the whole study group and the subgroup of 67 infants scanned around TEA.

Predictive value of CUS for MRI
The predictive values of the CUS findings for the MRI WM classification are listed in Table 2. This table shows that presence of PVE, regardless of characteristics (aspect, grade and duration) is predictive of abnormal WM on MRI. However, absence of PVE does not predict normal WM.

In addition, presence of P/IVH is highly predictive of abnormal WM on MRI, but again with a low NPV. Repeating our analysis for the 48 children without P/IVH, we found comparable predictive values of PVE for abnormal WM. Abnormal size and/or shape of the lateral ventricles, as seen around TEA, was also highly predictive of abnormal WM, whereas normal size and shape of the ventricles did not predict normal WM.
We found no obvious improvement of predictive values, increasing the number of CUS examinations: if PVE were seen in the first week, this predicted abnormal MRI in 73% of infants, with a sensitivity of 78%, specificity of 31% and NPV of 42%. While if PVE were also seen in 4 consecutive weeks after the first week, the PPV remained 73%, and the sensitivity and NPV increased slightly towards respectively 87% and 50%, but with a specificity decreasing to 25%. In addition, there was no influence of age at CUS examination on the predictive values of CUS: predictive values of PVE seen in the first week were in the same range as those seen at later age.

Calculating predictive values of individual CUS findings for individual MRI findings, we found high PPV and sensitivity of PVE for DEHSI, the NPV again being low. Inhomogeneous PVE did not predict PWML, but the NPV was high (Table 2).

### Table 2. Predictive values of individual ultrasound findings for WM classification on MRI, of PVE for DEHSI§ and of inhomogeneous PVE for PWML§§§ for patient group with MRI at PMA < 44 weeks (N=67),

<table>
<thead>
<tr>
<th>CUS finding</th>
<th>WM classification on MRI</th>
<th>DESHI and PWML on MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>PVE</td>
<td>81.6 (40/49)</td>
<td>16.7 (3/18)</td>
</tr>
<tr>
<td>Inhomogeneous PVE</td>
<td>67.3 (33/49)</td>
<td>27.8 (5/18)</td>
</tr>
<tr>
<td>Grade 2 PVE</td>
<td>14.3 (7/49)</td>
<td>94.4 (17/18)</td>
</tr>
<tr>
<td>Duration &gt; 14 days</td>
<td>46.9 (23/49)</td>
<td>66.7 (12/18)</td>
</tr>
<tr>
<td>P/IVH grade 3</td>
<td>8.2 (4/49)</td>
<td>100.0 (18/18)</td>
</tr>
<tr>
<td>P/IVH grade 1-3</td>
<td>34.7 (17/49)</td>
<td>88.9 (16/18)</td>
</tr>
<tr>
<td>Size and shape ventricles</td>
<td>55.1 (27/49)</td>
<td>94.4 (17/18)</td>
</tr>
<tr>
<td>PVE§</td>
<td>81.4 (48/59)</td>
<td>12.5 (1/8)</td>
</tr>
<tr>
<td>Inhomogeneous PVE§§§</td>
<td>69.2 (9/13)</td>
<td>31.5 (17/54)</td>
</tr>
</tbody>
</table>

Follow up

Of the 67 infants who underwent MRI before the postmenstrual age of 44 weeks, follow up was available for 50 (75%). A total of 7 children (14%) had an unfavorable outcome at 2 years corrected age. Two children had a mental developmental index score ≥ 1 SD below the standard mean, six had a psychomotor developmental index score ≥ 1 SD below the standard mean and four had cerebral palsy. All the children with cerebral palsy had a psychomotor delay and one also a mental delay.
Predictive value of CUS for outcome

P/IVH and abnormal size and/or shape of the ventricles were predictive of outcome at 2 years corrected age (PPV respectively 34 and 31%, negative predictive values 94%). The PPV of the other CUS findings were 14 to 17%, with NPV 88 to 93%, indicating a high chance of a normal outcome when the CUS finding was absent.

Discussion

WM injury is probably responsible for the most disabilities in very preterm neonates. As CUS is the most frequently used imaging modality for detecting brain injury in high-risk neonates, its detection of WM injury may be useful in targeting interventional therapy. This study assessed the predictive values of individual CUS findings for WM injury on MRI and the influence of timing and frequency of CUS, aiming to optimize CUS protocols for detecting WM injury. In addition, we assessed the predictive values of individual CUS findings for neurologic outcome at 2 years corrected age. We found that presence of PVE on CUS was predictive of abnormal WM on MRI. However, absence of PVE was not predictive of normal WM. In other words, absence of changes in the WM on CUS is no guarantee of a normal MRI. In addition, increasing the number of CUS examinations and varying the timing of CUS did not influence the reliability of CUS for detecting WM injury.

To our surprise P/IVH were more predictive of abnormal WM on MRI than PVE. This may be for several reasons: First, P/IVH is reliably detected by CUS, therefore false positive and false negative diagnoses of P/IVH are rare. Second, P/IVH originates from and might damage the germinal matrix. This might have consequences for further development of glial cell precursors and astrocytes, originating from the germinal matrix, possibly contributing to WM injury. In addition, elevated free iron in the cerebrospinal fluid resulting from intraventricular hemorrhage might catalyse radical formation and WM injury may ensue. Furthermore, even mild ventricular dilatation may influence WM development and P/IVH may cause microglial activation.

We additionally found that presence of PVE on CUS predicted DEHSI on MRI. In recent literature there is doubt whether DEHSI indeed presents WM injury. We therefore feel it is not justified to conclude that PVE are the CUS representative of diffuse WM injury. We found no association between inhomogeneous PVE and PWML. This seems to be in conflict with results of an older study, in which a fair association between inhomogeneous PVE on CUS and PWML on MRI was found. However, the latter study was retrospective, fewer infants were included and the MRI was performed at variable ages, often during the preterm period.
P/IVH and abnormal lateral ventricles were reasonably predictive of unfavorable outcome at 2 years corrected age, whereas all the other individual CUS findings did not predict unfavorable outcome. This is partly in agreement with another study, finding a higher incidence of neurological abnormality during the first year of life in very preterm infants with prolonged PVE, P/IVH grade 2 or 3, and ventricular dilation than in infants without these CUS abnormalities. Amess et al. assessed the predictive value of CUS for neurological outcome at 12 months corrected age and found high risk CUS findings to be predictive of abnormal neurological outcome (sensitivity 83%), but their high risk CUS findings included more serious abnormalities than the individual CUS findings we assessed. Rademaker et al. found significant differences in motor and mental outcome at school age between very preterm infants with normal/mild CUS findings and severely abnormal CUS findings. They included more infants and their follow up period was much longer. De Vries et al. in a large prospective study among preterm infants found major CUS abnormalities to be highly predictive of cerebral palsy. Again, their major CUS abnormalities were more severe and differed from the individual CUS findings we assessed. Comparison of our study with the aforementioned studies is difficult, because of the changes in the character and definition of WM injury over recent years. We found high negative predictive values of CUS for outcome around 2 years corrected age, indicating a high chance of a normal outcome when CUS abnormalities were absent. This is in accordance with the study by de Vries et al. showing high negative predictive values of absence of major CUS abnormalities for cerebral palsy around 2 years of age.

We acknowledge the limitations of this study: First, MRI could not be performed around TEA in all patients. We could therefore only analyse the data in a subgroup of our infants, implying a limited number of patients per WM group and with individual CUS and MRI findings. Therefore the number of infants with some individual CUS findings, especially P/IVH grade 3 and PVE grade 2, was too low to draw final conclusions about the prediction of these CUS findings for unfavorable outcome. Secondly, it is uncertain whether DEHSI represents WM injury. Finally, our follow up period is short. More subtle cognitive deficits, with possible consequences on school performance, may still develop. With respect to these limitations, we make the following conclusions:

- If PVE is present on CUS, regardless of timing, duration, and appearance, there is a significant chance of abnormal WM on MRI.
- If PVE is seen any time during the neonatal period, additional CUS examinations do not increase the diagnostic performance of CUS for detecting WM abnormality. Therefore, increasing the number of CUS examinations in these cases is of limited clinical importance.
Ultrasound detection of white matter injury: practical implications

• P/IVH is highly predictive of abnormal WM on MRI.
• Absence of PVE and P/IVH on CUS does not guarantee normal WM on MRI.
• P/IVH and ventricular dilatation, but not PVE, seems to be reasonably predictive of abnormal neurological outcome at 2 years corrected age.
• Absence of any CUS abnormality in the WM or lateral ventricles is highly predictive of a normal outcome at 2 years corrected age.

The practical consequences of these conclusions are as follows (Figure 3):
1. In very preterm neonates, CUS examinations in the first week of life are necessary to detect P/IVH.
2. If P/IVH is seen during the first week, frequent follow up CUS is indicated for detecting complications that may need intervention (24).
3. If no P/IVH is seen in the first week, low frequency CUS examinations throughout the neonatal period are indicated to follow the brain growth and maturation and to detect changes related to clinical instability.
4. If medical complications or instability occur, CUS examinations should be intensified.
5. For reliable detection of WM injury in very preterm infants an MRI examination, performed around TEA is needed. This is, however, of little clinical relevance in infants without any CUS abnormality.
REFERENCES


