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Clinical value of gradient echo MRI for brain imaging in preterm infants

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ABSTRACT

Purpose: Gradient echo techniques are the most sensitive MRI sequences for detecting hemorrhages in the brain. Still, reports on its use in neonates are scarce. The aim of this study is to correlate presence of hemosiderin deposits in the brain of very preterm infants (gestational age <32 weeks) detected by T2*-w gradient echo MRI to white matter (WM) injury and neurodevelopmental outcome at two years.

Methods: In 101 preterm infants presence and location of hemosiderin were assessed on T2*-w gradient echo MRI performed around term equivalent age. White matter injury was defined as the presence of more than 6 punctate white matter lesions (PWML), cysts and/or ventricular dilatation. Six infants with post hemorrhagic ventricular dilatation detected by ultrasound in the neonatal period were excluded. Infants were seen for follow up at two years. Univariate and regression analysis assessed the relation between presence and location of hemosiderin, WM injury and neurodevelopmental outcome.

Results: In 38/95 (40%) infants hemosiderin was detected. Twenty percent (19/95) of the infants were lost to follow up. There was a correlation between hemosiderin in the ventricular wall with more than 6 PWML (p<0.001) and cysts (p<0.001) at term equivalent age, and with a lower psychomotor development index (PDI) (p=0.02) at 2 years. After correcting for known confounders (gestational age, gender, intrauterine growth retardation and WM injury) the correlation with PDI was no longer significant.

Conclusion: The clinical importance of detecting small hemosiderin deposits is limited as there is no independent association with neurodevelopmental outcome.
INTRODUCTION

Magnetic resonance imaging (MRI) is a safe and valuable tool to assess development and pathology of the preterm infant’s brain.\textsuperscript{1-4} In infants born very prematurely, germinal matrix and intraventricular hemorrhage (GMH/IVH) and white matter injury are frequently encountered,\textsuperscript{5-7} while cerebellar hemorrhage is increasingly recognized.\textsuperscript{8-11} All are associated with later cognitive and motor impairment.\textsuperscript{5,12-15}

Elevation of free radicals and iron in cerebrospinal fluid is associated with both hemorrhages and white matter injury in very preterm and low birth weight infants.\textsuperscript{16,17} Therefore an independent influence of hemorrhages on neurodevelopmental outcome can not be excluded.

Although the T2*-w gradient echo technique has a much higher sensitivity for detection of (small) hemorrhages, in particular hemosiderin deposits, than T1-w and T2-w MR techniques\textsuperscript{10,18,19} its added clinical value for brain imaging in preterm infants has not been determined yet.

In the present study, we used a T2*-w gradient echo sequence for detection and location of small hemosiderin deposits in an unselected cohort of very preterm infants who underwent MRI within 3 months after term equivalent age. We investigated the clinical significance of these hemosiderin deposits by evaluating the association with white matter injury and neurodevelopmental outcome around the corrected age of two years.

PATIENTS AND METHODS

Very preterm infants

As part of a prospective neuro-imaging study performed in an unselected group of very preterm infants (gestational age <32 weeks), admitted to the tertiary neonatal unit of our hospital, 113 infants underwent MRI, preferably around term at a postmenstrual age of 40 – 44 weeks. For infants who were unstable around that age, MRI was postponed, resulting in an age range of 40 – 60 postmenstrual weeks at imaging. Ethical approval for the study was given by the institutional review board and informed parental consent was obtained for each infant.

In three infants congenital malformations of the central nervous system were found on MRI and they were excluded from the study. In nine infants a T2*-w gradient echo sequence was not performed. Six infants diagnosed with a grade III-IV intraventricular hemorrhage and post hemorrhagic ventricular dilatation (PHVD) on brain ultrasound
in the neonatal period were excluded from further analysis to ascertain that ventricular
dilatation on the term MRI’s resulted ex-vacuo from white matter injury.

Therefore, for this part of the study, data of 95 infants were included. Clinical param-
eters were collected from the patients’ files.

**Image and data acquisition**

All MRI examinations were performed on a 3T MRI system (Philips Medical Systems,
Best, the Netherlands) according to a standard protocol for imaging the newborn infant’s
brain. The infants were sedated using chloral hydrate (55mg/kg), lay supine and were
swaddled during the scanning procedure. Ear protection consisted of neonatal earmuffs
(Natus Mini Muffs; Natus Medical Inc., San Carlos, CA, USA) covered by a headphone.

All MRI examinations included a 3D T1-Turbo Field Echo sequence (TR 9.7 ms, TE 4.6 ms,
FOV 180 mm, matrix size 192x152, flip angle 8º, TFE factor 128, slice thickness 1 mm), a
T2-Turbo Spin Echo sequence (TR 6269 ms, TE 120 ms, FOV 180 mm, matrix size 336x234,
TSE factor 18, slice thickness 2 mm), and a T2* Fast Field Echo sequence (TR 735 ms, TE
16 ms, FOV 230 mm, matrix size 256x163, flip angle 18º, slice thickness 4 mm).

**Hemosiderin deposits**

To assess the presence of hemosiderin, two investigators (FTdB and SJS) examined the
T2*-w gradient echo images together by consensus.

Hemosiderin deposits, originating from hemorrhages occurring in the perinatal pe-
riod were defined as hypointense signal intensity lesions or blooming effects (Figure 1).
The location of hemosiderin was noted in anatomic regions as shown in Table 2.

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Figure 1. Hemosiderin deposits detected in the germinal matrix / lateral ventricular walls (arrows)
on T2*-w gradient echo images (A), but not noted on T1-w and T2-w MR images (B, C).
White matter injury and ventricular size
Two investigators (FTdB and LML) analyzed all T1-w and T2-w sequences together by consensus for presence of white matter injury and ventricular dilatation. White matter injury was defined as more than 6 (non-hemorrhagic) punctate white matter lesions (PWML) and/or cystic white matter lesions and/or ventricular dilatation with the exclusion of PHVD. PWML were defined as punctate hyperintense lesions on T1-w sequences, slightly hypointense on T2-w sequences, not visible on T2*-w gradient echo sequences, in order to differentiate these from small hemorrhages. On coronal reconstructions from the three-dimensional T1-w images the ventricular index was measured as the total width of the lateral ventricles, divided by 2, in analogy to ventricular index measurements on ultrasound.20 A ventricular index between 12 – 16 mm was considered moderate dilatation and a ventricular index of more than 16 mm severe dilatation.21 Diffuse Excessive High Signal Intensity (DEHSI) was not considered part of the spectrum of white matter injury.22

Follow up
Around two years of age, the infants were seen by an experienced neonatologist, who was unaware of the neuro-imaging findings. Each child underwent a standardized neurologic examination to assess the presence of cerebral palsy or abnormal muscular tone. A Gross Motor Function Classification System (GMFCS) level was assigned.23 A GMFCS level of 2 or more was considered cerebral palsy.

The cognitive and psychomotor development was assessed by a psychology assistant, who was unaware of the neuro-imaging findings, using the Dutch version of the Bayley Scales of Infant Development (BSID-III). A mental developmental index score (MDI) and a psychomotor developmental index score (PDI) were calculated for the corrected age of the child. Five infants diagnosed with cerebral palsy, in whom testing the gross and fine motor function with the BSID-III was not feasible, were assigned a PDI score of 50.

To evaluate child behavior, the Dutch version of the Child Behavior Checklist 1½ to 5 (CBCL)24 was sent to the child’s home address prior to the follow up visit, to be completed by either parent or caretaker. The questionnaire consists of 99 items rated on a 3-point scale. By summing the scores an internalizing, externalizing, total and other problem score can be computed. These raw scores were transformed into normalized T-scores and used as secondary outcome parameters in the analyses, where a higher score represented more severe behavioral problems.

Statistical analyses
Data were analyzed using SPSS 17.0.1. Frequency counts and percentages were used
Table 1. Distribution of categorical clinical parameters (N (%)), continuous clinical parameters (mean (SD)) and white matter injury (N (%)) N=95.

<table>
<thead>
<tr>
<th>Categorical clinical parameters</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>58 (61.1)</td>
</tr>
<tr>
<td>Female</td>
<td>37 (38.9)</td>
</tr>
<tr>
<td>GA &lt; 28 wk</td>
<td>33 (34.7)</td>
</tr>
<tr>
<td>Birth weight &lt; 1000 gram</td>
<td>32 (33.7)</td>
</tr>
<tr>
<td>IUGR</td>
<td>12 (12.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Continuous clinical parameters</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA (weeks)</td>
<td>29.0 (2.0)</td>
</tr>
<tr>
<td>Birth weight (gram)</td>
<td>1199 (372.8)</td>
</tr>
<tr>
<td>GA at MRI (weeks)</td>
<td>45.1 (4.0)</td>
</tr>
<tr>
<td>Weight at MRI (gram)</td>
<td>4078.0 (805.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>White matter injury</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 6 PWML</td>
<td>16 (16.8)</td>
</tr>
<tr>
<td>Moderate ventricular dilatation</td>
<td>49 (51.6)</td>
</tr>
<tr>
<td>Severe ventricular dilatation</td>
<td>17 (17.9)</td>
</tr>
<tr>
<td>Cysts</td>
<td>6 (6.3)</td>
</tr>
</tbody>
</table>

GA=gestational age, IUGR=intrauterine growth retardation, PWML=punctate white matter lesions

Table 2. Frequency of hemosiderin deposits on MRI per location (N (%))

<table>
<thead>
<tr>
<th>Location</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial</td>
<td>25 (26.3)</td>
</tr>
<tr>
<td>Germinal matrix/caudo thalamic groove</td>
<td>13 (13.7)</td>
</tr>
<tr>
<td>Ventricular wall</td>
<td>21 (22.1)</td>
</tr>
<tr>
<td>Intraventricular</td>
<td>16 (16.8)</td>
</tr>
<tr>
<td>Periventricular</td>
<td>9 (9.5)</td>
</tr>
<tr>
<td>Deep white matter</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>23 (24.2)</td>
</tr>
<tr>
<td>4th ventricular wall</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>5 (5.3)</td>
</tr>
<tr>
<td>Cerebellar hemispheres</td>
<td>19 (20.0)</td>
</tr>
<tr>
<td>Total</td>
<td>38 (40.0)</td>
</tr>
</tbody>
</table>
to summarize categorical parameters. For continuous parameters, mean and standard deviations are reported.

The clinical parameters of the infants with and without two year follow up were compared with chi-square, Fisher-exact and Mann-Whitney U tests where appropriate.

The association between presence of hemosiderin per location and WM injury (more than 6 PWML, cystic lesions and ventricular dilatation) and outcome parameters was evaluated using chi-square, Fisher-exact and Mann-Whitney U tests. For the relation with outcome backward linear and logistic regression were subsequently used to adjust for known potentially confounding neonatal characteristics (gestational age, gender, intra uterine growth retardation) and white matter injury on MRI. Statistical significance was defined by two-tailed p value <0.05.

**RESULTS**

**Clinical parameters**

The clinical parameters of infants (N=95) are shown in Table 1. The numbers of infants with white matter injury (more than 6 PWML, cystic white matter lesions, ventricular dilatation) are mentioned separately.

**Hemosiderin deposits**

Table 2 shows the number of infants with hemosiderin deposits and the location as seen on T2*-w gradient echo. Hemosiderin deposits were detected in 38/95 (40%) infants. These were supratentorially located in 25/95 (26.3%) and infratentorially located in 23/95 (24.2%) infants (Figure 2). In 10/23 infants with infratentorial hemosiderin deposits, supratentorial hemosiderin deposits co-existed.

**Association between hemosiderin deposits per location and white matter injury**

Table 3 shows the associations per location between the presence of hemosiderin deposits on T2*-w gradient echo sequences and white matter injury on MRI. The presence of hemosiderin in the wall of the lateral ventricles was strongly associated with more than 6 PWML (p<0.001). Furthermore there were associations between hemosiderin deposits in and around the ventricle and more than 6 PWML (p= 0.03 and p=0.04) and between intraventricular hemosiderin deposits and severe ventricular dilatation (p=0.02). There were significant associations between hemosiderin deposits at most locations and cystic white matter lesions. There were no associations between infratentorial cerebellar hemosiderin deposits and supratentorial white matter injury.
Figure 2. (A) T2*-w gradient echo image showing hemosiderin in the cerebellum (arrow), not visible on the T2-w image (B).

Table 3. Association between hemosiderin and white matter injury (> 6 PWML/ex-vacuo ventricular dilatation/cysts) on MRI.

<table>
<thead>
<tr>
<th></th>
<th>&gt; 6 PWML</th>
<th>Ex-vacuo ventricular dilatation</th>
<th>Cysts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>N</td>
</tr>
<tr>
<td>Supratentorial</td>
<td>15</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Germinal matrix</td>
<td>9</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Ventricular wall</td>
<td>11</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Intraventricular</td>
<td>10</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Periventricular</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Deep white matter</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>18</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>4th ventricular wall</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cerebellar hemispheres</td>
<td>16</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
Table 4. Regression analysis: significant relations (p< 0.05) between presence of hemosiderin deposits on MRI and neurodevelopmental outcome at two years of age.

<table>
<thead>
<tr>
<th>Psychomotor developmental index (BSID-III)</th>
<th>Unadjusted beta coefficient (SE)</th>
<th>p-value</th>
<th>Adjusted beta coefficient (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial</td>
<td>-8.0 (3.9)</td>
<td>0.04</td>
<td>1.4 (4.2)</td>
<td>0.75</td>
</tr>
<tr>
<td>Ventricular wall</td>
<td>-9.8 (3.9)</td>
<td>0.02</td>
<td>0.8 (4.6)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

\(^\text{Y} \text{ adjusted for gestational age, gender, intra uterine growth retardation and white matter injury on MRI (> 6 PWML/ ventricular dilatation /cysts)}

SE = standard error

Follow up

Follow up was available for 76 (80%) infants. Infants were lost to follow up due to miscellaneous reasons such as rejection of participation or practical problems, including travel distance to the hospital. Mean corrected age at follow up was 29.7 months (range 20.1 – 42.1 months, SD 4.5) No difference in baseline clinical parameters or presence of hemosiderin deposits was found between infants with and without follow up.

Table 4 shows the unadjusted and adjusted associations between hemosiderin deposits per location and the PDI at two years. In infants with hemosiderin deposits supratentorially and/or in the ventricular wall, we found a lower PDI (respectively p=0.04 and p=0.02). However, after correcting for clinical parameters (gestational age, gender and intrauterine growth retardation) and white matter injury, the association was no longer significant. Backward linear regression analyses showed that the presence of more than 6 PWML (p=0.002) and cystic white matter lesions (p=0.02) were independent predictors of a lower PDI. No differences in cognitive or motor delay, cerebral palsy or CBCL scores were found between infants with (N=32) and without (N=44) hemosiderin deposits.

Discussion

In this study we assessed presence of hemosiderin deposits, as detected by T2*-w gradient echo MRI, in an unselected cohort of very preterm infants and correlated presence and location of hemosiderin deposits with white matter injury and neurodevelopmental outcome at two years of corrected age. Our most important finding is that especially hemosiderin deposits located in the ventricular wall are correlated with white matter injury and a less favorable neurodevelopmental outcome. However, after adjusting for
clinical parameters and white matter injury the association between these hemosiderin deposits and a less favorable neurodevelopmental outcome was no longer significant. The presence of more than 6 PWML and cystic white matter lesions were independent predictors for psychomotor delay.

The clinical use of gradient echo techniques, including susceptibility-weighted imaging (SWI), to detect microbleeds or hemosiderin deposits in the elderly is widely accepted.\(^1\)\(^9\),\(^2\)\(^5\),\(^2\)\(^6\) Yet reports on the use of gradient echo techniques in infants are scarce.\(^2\)\(^7\),\(^2\)\(^8\) In a recent study the use of SWI to distinguish hemorrhagic from non hemorrhagic punctate white matter lesions in neonates was reported.\(^2\)\(^9\) However, in this paper the clinical relevance of detecting hemorrhagic lesions in relation to neurodevelopmental follow up was not discussed.

From large cohort studies\(^3\)\(^0\) it is known that amongst other pathologies, intraventricular hemorrhage is predictive of a less favorable neurodevelopmental outcome in very preterm neonates. This is especially true for grade III – IV intraventricular hemorrhages detected by ultrasound in the neonatal period.\(^3\)\(^1\),\(^3\)\(^2\) Ultrasound studies have also reported poorer neurodevelopmental outcomes at 20 months in extremely low birth weight infants with grade I - II intraventricular hemorrhages. However, ultrasound could have missed additional injury associated with intraventricular hemorrhages explaining the poorer outcomes.\(^3\)\(^3\) As we excluded infants with PHVD diagnosed by ultrasound, the ventricular dilatation in our cohort most likely resulted from white matter injury. We found that especially hemosiderin deposits in and around the ventricular walls, without parenchymal involvement are associated with PWML and cystic white matter lesions, and that these hemosiderin deposits are correlated with a less favorable neurodevelopmental outcome. In a recent study it was found that GMH/IVH was associated with hemorrhagic punctate white matter lesions, possibly as a result of impaired venous drainage and increased pressure in the medullary veins resulting in periventricular white matter damage.\(^2\)\(^9\) Our data showed that after correction for clinical parameters and white matter injury, the association between hemosiderin deposits in the ventricular wall and a less favorable neurodevelopmental outcome was no longer significant, while the presence of more than 6 PWML and cystic white matter lesions were independent predictors for a lower PDI. Therefore our data show that the presence of white matter injury is a better predictor for a less favorable neurodevelopmental outcome than small ventricular wall hemorrhages.

A limitation of our study is that we used a T2*-w gradient echo technique, while SWI is increasingly being used in clinical practice.\(^2\)\(^7\),\(^2\)\(^9\) However, the clinical significance of de-
tecting more and/or even smaller hemosiderin deposits with SWI as compared to T2*-w gradient echo MRI\textsuperscript{26} seems to be limited.

In this cohort of preterm infants we defined ventricular dilatation as ex-vacuo ventricular dilatation from white matter injury resulting in volume loss.\textsuperscript{34,35} By excluding infants with PHVD diagnosed by ultrasound during the neonatal period, we intended to differentiate between ex-vacuo ventricular dilatation and PHVD. However, both forms of ventricular dilatation may co-exist and are interrelated. Moreover, we may have missed hemosiderin deposits, as the age range (40 – 60 weeks postmenstrual age) at which the infants were imaged may be of influence on the detectability of hemosiderin originating from hemorrhages occurring in the perinatal period.

Another limitation of our study is that a substantial number of infants (20\%) were lost to follow up. However, at baseline, there were no differences in clinical parameters or presence of hemosiderin deposits between infants with or without clinical follow up. As especially cognitive delay or handicap is difficult to test at this young age, long term follow up at school age may still demonstrate differences in cognitive and behavioral performance.

In conclusion, we demonstrated that T2*-w gradient echo sequences detect and localize small hemosiderin deposits in very preterm infants, especially in and around the ventricular system. The clinical importance of detecting these small hemosiderin deposits is however limited as there is no independent association with neurodevelopmental outcome.
REFERENCES
