Chapter 10

Hyperechogenicity of the thalamus and basal ganglia in very preterm infants: radiological findings and short-term neurological outcome

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Abstract

Cranial ultrasound (cUS) of preterm infants may show diffuse, bilateral, hyperechogenic “haze” over the thalami and basal ganglia (hyperechogenicity BGT). This phenomenon is not present on cUS scans of healthy (near) term infants. We explored whether this could be a pathological phenomenon. All cUS examinations performed in 2001 on infants < 35 weeks of age were reviewed. This resulted in a hyperechogenicity and a non-hyperechogenicity group. The character of the hyperechogenicity BGT and the presence of concomitant brain lesions were noted. Detailed clinical and follow-up data from a selected group of infants < 32 weeks were reviewed and compared between the two groups. The incidence of hyperechogenicity BGT was 11% (39/359) in infants < 35 weeks and 26% (37/143) in infants < 32 weeks. Birth weight and gestational age were significantly lower and clinical course was more complicated in the hyperechogenicity group. Concomitant brain lesions were always present. In 12 out of 39 infants with hyperechogenicity BGT, magnetic resonance imaging (MRI; always performed for other reasons) was available, showing signal intensity changes in the thalamic region in five infants. The neurological outcome at term was less favourable in the hyperechogenicity group, but similar at 1 year. Thus hyperechogenicity BGT mainly occurred in very small, sick infants and was always associated with cerebral pathology. MRI did not consistently show abnormalities in the thalamic region. It was not associated with a poorer outcome at 1 year.
Introduction

Localized unilateral thalamic lesions are frequently encountered, especially in very sick and preterm infants (1-3). The short-term neurological prognosis of these infants seems to be less favourable than that of preterm infants without these lesions (3).

It is well known that hyperechogenicity of the periventricular white matter (WM), so-called periventricular flaring or periventricular echodensity, represents ischaemic changes of the WM (1,4) and, if long-lasting, can have consequences for the neurological development of preterm infants (5-6).

On cranial ultrasound (cUS) scans of very preterm infants, bilateral, subtle hyperechogenicity of the thalamus and/or basal ganglia (BGT), recognized as a diffuse haze over that area, can be observed, especially during the first weeks of life (personal observation). In the following, this will be referred to as hyperechogenicity BGT. This phenomenon is also frequently seen on ultrasound scans of fetuses between 20 and 30 weeks' gestational age (GA) (7). The origin and clinical significance of this diffuse hyperechogenicity BGT are not known.

Thus we were prompted to investigate whether hyperechogenicity BGT might be a pathological phenomenon and, if so, whether it can have consequences for the neurological development of preterm infants. The aims of this study were:

1. To determine the incidence of hyperechogenicity BGT in preterm infants,
2. To evaluate which perinatal factors are associated with the development of hyperechogenicity BGT,
3. To explore whether there is a correlation between the findings on cUS and MRI, and, if so,
4. To evaluate whether MRI can be helpful in exploring the origin of hyperechogenicity BGT,
5. To determine whether hyperechogenicity BGT is associated with concomitant brain lesions, and
6. To evaluate the short-term neurological outcome of infants with hyperechogenicity BGT compared to infants without this finding.
Patients and Methods

Patients
All cUS scans performed in all preterm infants born after a GA of < 35 weeks, who were admitted to the neonatal intensive or high care unit of the Leiden University Medical Center (a tertiary neonatal referral centre) between January 2001 and January 2002, were reviewed. The infants were divided in two groups; a group with hyperechogenicity of the BGT ("hyperechogenicity group") and a group without hyperechogenicity BGT ("non-hyperechogenicity group").

A number of infants, all with a GA of < 32 weeks (very preterm infants), both from the hyperechogenicity and the non-hyperechogenicity group, were documented in detail because very preterm infants, when living in or near Leiden, were included in an ongoing standardized follow-up program. Inclusion in this follow-up program was independent of cUS findings.

Neuro-imaging

Ultrasonography
Serial bedside cUS were done in all infants from birth until discharge or transfer to another hospital by an experienced neonatologist according to standard scanning protocols. cUS scans were performed within 24 hours of birth, on the third day after birth, and at least weekly until discharge or transfer to another hospital. Scanning was done in the six coronal and five sagittal planes as described by Levene et al. (8) with an Aloka 5000 scanner with a multifrequency transducer. Scans were evaluated during and immediately after the cUS procedure by one of the neonatologists. All images were saved on magneto-optical disks and later reviewed by GvWM and LML. Special attention was paid to the echogenicity of the BGT. If, on at least one cUS scan, the echogenicity of the BGT was more intense on both coronal and sagittal planes as compared to the surrounding area of the brain, the BGT were considered to be hyperechogenic (Figures 1 and 2). All cUS scans of infants in whom hyperechogenicity BGT was detected at least once were further evaluated.
Special emphasis was put on the following:
1. Diffuse or localized hyperechogenicity
2. Homogeneous or inhomogeneous hyperechogenicity
3. Unilateral or bilateral hyperechogenicity
4. Presence and incidence of concomitant cerebral pathology, e.g. haemorrhagic and/or ischaemic lesions. Peri- and intraventricular haemorrhages (P/IVH) were graded according to the classification of Volpe (9) and periventricular leukomalacia (PVL) was graded according to the classification of de Vries et al. (1)

Moreover, the age of onset (days) and the total duration (days) of the hyperechogenicity BGT were noted. Finally, the presence and incidence of cerebral pathology in the total group of preterm infants was recorded.

Figure 1. Coronal (a) and sagittal (b) cUS scans in a preterm infant, postconceptional age 26.0 weeks, showing diffuse, bilateral hyperechogenicity of the thalamus and basal ganglia (arrows) and periventricular echodensity.
In some infants with hyperechogenicity BGT, MRI had been performed during the neonatal period. The reason for MRI was never hyperechogenicity BGT as sole cUS finding but the presence or suspicion of serious parenchymal lesions (such as PVL grade 3, or P/IVH with intra-parenchymal echodensity), as detected by cUS. MRI was performed on a 1.5 Tesla MRI system (Philips Medical Systems, Best, the Netherlands) according to our standard MRI protocol for newborn infants. This protocol comprised T1-, T2-, and diffusion-weighted images in the axial plane (slice thickness 4-5 mm, field of view 18-20 cm²); T1-weighted images were also obtained in the sagittal plane. MRI scans were evaluated immediately after the scanning procedure by the attending neuroradiologist. The T1-, T2-, and diffusion weighted images were reviewed later by LL and GvWM, who were not informed of (LL) or blinded to (GvWM) the cUS findings. Special attention was paid to the signal intensity of the thalamus, basal ganglia, and periventricular WM. Cerebral abnormalities were recorded. Moreover, the time-lag (days) between the last day hyperechogenicity BGT was seen on cUS and the MRI procedure was noted.

Clinical parameters during the neonatal period and neurological follow-up

Of the infants who participated in the follow-up program, the following parameters were reviewed: GA, birth weight, duration of admission until discharge or transfer to another hospital, total duration of mechanical ventilation, continuous positive airway pressure and oxygen supply, presence of persistent ductus arteriosus, neonatal

Figure 2. Coronal cUS scan in a preterm infant, postconceptional age 33.4 weeks, showing a localized area of increased echogenicity in the right thalamic region (arrow) and intraventricular haemorrhages.
respiratory distress syndrome, episodes of pneumonia, sepsis and (suspicion of) necrotizing enterocolitis, and episodes of apneas, bradycardias or cyanosis.

At term age and at 1 year corrected age these infants underwent standardized neurological examinations according to Prechtl et al. (10) and Touwen et al. (11), respectively. Staff neonatologist specially trained and experienced in developmental and neurological assessments performed the examinations. The neurological findings at term (Prechtl examination) were classified as normal, mildly abnormal, or definitely abnormal. Definitely abnormal means the presence of a full-blown neonatal neurological syndrome, such as apathy or hyperexcitability, hypotonia or hypertonia, hypokinesia or hyperkinesias, or asymmetry. Mildly abnormal denotes the presence of only part of such a syndrome. Examples of minor neurological signs are abnormal posture, abnormal head control, frequently occurring tremors or startles, and absent or abnormal responses or reflexes. At the corrected age of 1 year (Touwen examination) the children were considered definitely abnormal when more than one of the five clusters cranial nerves, muscle tone, reflexes, fine and gross motor performance were abnormal, mildly abnormal when only one cluster was abnormal, or normal. The specialists performing the follow-up examinations were aware of the clinical course and cUS findings of the infants, but unaware whether there had been hyperechogenicity BGT during the neonatal period.

Data analysis
Statistical analyses of the obtained data was performed using SPSS software (version 10.0; SPSS inc., Chicago, Illinois, USA). Comparison of continuous data between the hyperechogenicity BGT and non-hyperechogenicity BGT group was performed using the 2-sample Student’s t-test. Nominal values were compared using the $\chi^2$ test. The level of significance was 5%.
Results

Patients
During the study-period a total number of 359 preterm infants (GA < 35 weeks; 205 male, 154 female) were admitted to our hospital. Mean GA of these infants was 32.5 ± 3.2 (mean ± SD) weeks and mean birth weight was 1895 ± 730 grams. Out of the 359 preterm infants, 39 infants (33 male, six female) were selected whose cUS scans at least once showed hyperechogenicity of the thalamic region, implicating a hyperechogenicity BGT incidence of 10.9% in this high-risk population. Mean GA and birth weight in the hyperechogenicity group were significantly lower (p<0.001) than in the total group of preterm infants, respectively 28.1 ± 2.2 weeks and 1109 ± 352 grams. Three of the 39 infants with hyperechogenicity BGT died during the neonatal period. Permission for autopsy was not obtained.

Of the 39 preterm infants showing hyperechogenicity BGT, 37 infants were born after a GA of < 32 weeks, while during the study-period a total of 143 very preterm infants were admitted. This implicates a hyperechogenicity BGT incidence of 25.9% (37/143) in very preterm infants. Hyperechogenicity BGT did not occur in infants with a GA of over 34.7 weeks. Because complete standardized follow-up was only available from infants born at a GA of < 32 weeks, and hyperechogenicity BGT occurred almost exclusively in these very preterm infants, the comparison of clinical data and neurological outcome between the hyperechogenicity and the non-hyperechogenicity group was limited only to the very preterm infants. Fourteen out of the 37 (38%) very preterm infants of the hyperechogenicity group and 49 out of the 106 (46%) very preterm infants of the non-hyperechogenicity group were included in the standardized follow-up program and were therefore documented in detail.

Neuro-imaging

Ultrasonography

cUS scans of 38 of the 39 preterm infants with hyperechogenicity BGT (97%) showed diffuse hyperechogenicity BGT (mean GA 28.1 weeks) (Figure 1, parts a and b). cUS scans of three infants (8%) showed a localized area of hyperechogenicity (mean GA 27.9 weeks) (Figure 2). In two of these three infants this localized area was seen
within the diffuse hyperechogenicity BGT (diffuse and localized). In all 38 infants with diffuse hyperechogenicity BGT, this was bilateral. In six the hyperechogenicity had an inhomogeneous appearance (Figure 3). In one of the three infants with a localized area of hyperechogenicity, this was present on both sides of the brain. Mean age and mean postconceptional age at onset of the hyperechogenicity were respectively 2 (range 0-23) days and 28.1 (range 25.1-34.7) weeks in the infants with diffuse hyperechogenicity BGT and 10 (range 0-29) days and 29.3 (range 26.4-32.0) weeks in the three infants with a localized area of hyperechogenicity. In 33 infants (87%) with diffuse hyperechogenicity BGT and in two infants (67%) with a localized hyperechogenicity, this was present on the first cUS scan, which was performed within 24 hours of birth. In 26 infants with diffuse hyperechogenicity BGT, this was still seen on cUS scans on the day of discharge or transfer to another hospital. Therefore, it was not possible to calculate the total duration of hyperechogenicity BGT or to evaluate whether hyperechogenicity BGT is a transient phenomenon. All infants with hyperechogenicity BGT showed concomitant cerebral pathology on cUS, including periventricular echodensity in 38 infants (37 infants PVL grade 1, 1 infant PVL grade 2), P/IVH grade 1 (n=9), P/IVH grade 2 (n=10), P/IVH grade 3 (n=4), IVH with post-haemorrhagic ventricular dilatation (n=4), and IVH with intraparenchymatous echodensity (n=3). The incidence of cerebral abnormalities in the total group of 359 preterm infants was 19% (n=70) for PVL grade 1, 1.4% (n=5) for PVL grade 2, 0.3% for PVL grade 3, 13% (n=43) for P/IVH grade 2, 3% (n=9) for IVH with post-haemorrhagic ventricular dilatation, and 2% (n=7) for IVH with intraparenchymatous echodensity.

Figure 3. Coronal cUS scan in a preterm infant, postconceptional age 26.1 weeks, showing diffuse hyperechogenicity BGT with an inhomogeneous appearance (arrow).
**MRI**

MRI was available from 12 of the 39 infants (31%) with hyperechogenicity BGT. Mean age on the day of scanning was 51.1 (range 19-82) days and mean postconceptional age was 35.6 (range 30.4-41.0) weeks. MRI scans of five of the 12 infants (42%) showed changes in the area of the BGT, including haemorrhage (n=1) (Figure 4) and inhomogeneous signal intensity (n=4). In all infants MRI showed cerebral pathology, including P/IVH (n=6), PVL (small punctate or cystic WM lesions, n=5), signal intensity changes of the periventricular WM (n=8), confirming the cUS findings in all. In 10 of the 12 infants (83%) a time-lag was noted between the last day hyperechogenicity BGT was detected and MRI day. Mean time-lag was 24.5 (range 0-65) days.

**Clinical parameters during the neonatal period**

Data on clinical parameters of the very preterm infants of the hyperechogenicity and the non-hyperechogenicity group, who participated in the follow-up program, are presented in Table 1. In summary, infants in the hyperechogenicity group were significantly younger, had a lower birth weight, and had a more complicated clinical course than infants in the non-hyperechogenicity group. There was an overrepresentation of boys in the hyperechogenicity group.
Neurological follow-up

Conclusions of the neurological examinations at term and 1 year corrected age are presented in Table 2. One infant of the hyperechogenicity group and two infants of the non-hyperechogenicity group were lost to follow-up at term age and two more infants of the non-hyperechogenicity group were lost to follow-up at 1 year corrected age. In summary, the incidence of mildly abnormal and definitely abnormal neurological outcome at term age was higher in the hyperechogenicity group as compared to the non-hyperechogenicity group. However, at 1 year corrected age this difference was no longer observed.

Table 1. Clinical parameters (number (%) / mean ± SD) during the neonatal period of very preterm infants participating in the follow-up program (*, statistically significant; CPAP, continuous positive airway pressure; H, hyperechogenicity; n, number of infants; SD, standard deviation)

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>H-BGT (n=14)</th>
<th>Non-H-BGT (n=49)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male / female)</td>
<td>12 / 2</td>
<td>23 / 26</td>
<td>0.01*</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>27.6 ± 1.6</td>
<td>29.6 ± 1.5</td>
<td>0.001*</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>1047 ± 322</td>
<td>1211 ± 294</td>
<td>0.10</td>
</tr>
<tr>
<td>Duration of admission (days)</td>
<td>47 ± 25</td>
<td>26 ± 24</td>
<td>0.07</td>
</tr>
<tr>
<td>Duration of ventilation (days)</td>
<td>25 ± 18</td>
<td>9.5 ± 11</td>
<td>0.007*</td>
</tr>
<tr>
<td>Duration of CPAP (days)</td>
<td>13.1 ± 9.9</td>
<td>6.3 ± 8.7</td>
<td>0.05*</td>
</tr>
<tr>
<td>Duration of oxygen administration (days)</td>
<td>26.4 ± 23.5</td>
<td>7.2 ± 11.4</td>
<td>0.003*</td>
</tr>
<tr>
<td>Apneas and/or bradycardias and/or cyanosis ≥ 5 days</td>
<td>13 / 14 (92.9)</td>
<td>32 / 49 (65.3)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Persistent ductus arteriosus</td>
<td>8 / 14 (57.1)</td>
<td>18 / 48 (37.5)</td>
<td>0.19</td>
</tr>
<tr>
<td>(Suspicion of) necrotizing enterocolitis</td>
<td>4 / 14 (28.6)</td>
<td>7 / 46 (15.2)</td>
<td>0.26</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>12 / 14 (85.7)</td>
<td>33 / 48 (68.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 / 14 (14.3)</td>
<td>3 / 48 (6.3)</td>
<td>0.33</td>
</tr>
<tr>
<td>Sepsis</td>
<td>8 / 14 (56.1)</td>
<td>21 / 47 (44.7)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

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Table 2. Conclusions of the neurological examinations (number (%)) of infants in the follow-up program (BGT, basal ganglia and thalami; H, hyperechogenicity; n, number of infants)

<table>
<thead>
<tr>
<th>Neurological examination</th>
<th>H-BGT (n=13)</th>
<th>Non-H-BGT (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prechtl (term age)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4 / 13 (30.8)</td>
<td>27 / 47 (57.4)</td>
</tr>
<tr>
<td>Mildly abnormal</td>
<td>8 / 13 (61.5)</td>
<td>18 / 47 (38.3)</td>
</tr>
<tr>
<td>Definitely abnormal</td>
<td>1 / 13 (7.7)</td>
<td>2 / 47 (4.3)</td>
</tr>
<tr>
<td>Touwen (1 year corrected age)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>9 / 13 (69.2)</td>
<td>31 / 45 (68.9)</td>
</tr>
<tr>
<td>Mildly abnormal</td>
<td>3 / 13 (23.1)</td>
<td>7 / 45 (15.6)</td>
</tr>
<tr>
<td>Definitely abnormal</td>
<td>1 / 13 (7.7)</td>
<td>7 / 45 (15.6)</td>
</tr>
</tbody>
</table>

Discussion

Bilateral lesions of the BGT mainly occur in (near) term infants and are usually the result of hypoxic-ischaemic damage of the brain (12-16). In general, these lesions are associated with serious clinical symptoms of hypoxic-ischaemic encephalopathy (17-18). Outcome is usually poor (14,18-19). The lesions, which are the result of haemorrhage, infarction or calcification (13,16), are detected on cUS as areas of increased echogenicity of the BGT (16). MRI shows signal intensity changes in the thalamic region (12,15,18-19). Localized unilateral thalamic lesions, which are ascribed to haemorrhage (20-21) or infarction in the region of the middle cerebral artery with involvement of lenticulostriate branches (2), have been described in both term and preterm infants (2-3,20-21). Term infants with unilateral thalamic lesions have a more favourable prognosis than term infants with bilateral lesions (21). Little is known about the prognosis of preterm infants with unilateral thalamic lesions. In preterm infants unilateral thalamic lesions are associated with a more complicated respiratory course, a significantly longer duration of ventilation, and a less favourable neurological development during infancy (3). Bilaterally increased echogenicity of the BGT with a more diffuse appearance, hyperechogenicity BGT, has, so far, not been described in very preterm infants. In our study, the incidence of hyperechogenicity BGT was 11% in preterm infants with a GA of < 35 weeks and even 26% in infants with a GA of < 32 weeks. Hyperechogenicity BGT did not occur in infants with a GA of over 34.7 weeks. Mean GA and birth weight were significantly lower in infants with hyperechogenicity BGT than in infants without...
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Hyperechogenicity BGT. Hence, hyperechogenicity BGT may be a normal physiological phenomenon in the immature brain. It may be the result of a relative difference in echogenicity due to differences in water content and/or myelination between the immature deep grey and white matter. Immature WM is not yet myelinating and has a very high water content (22), while myelination in the deep grey matter starts very early, at the beginning of the third trimester of gestation (22-24). Hyperechogenicity BGT may also be accounted for by differences in cell content and/or density of fibres between these structures.

In our study, the clinical course was more complicated in the very preterm infants with hyperechogenicity BGT than in the very preterm infants without hyperechogenicity BGT. Hyperechogenicity BGT mainly occurs in very small, sick preterm infants. Boys were overrepresented in the hyperechogenicity BGT group. The more complicated clinical course may be related to the significantly lower mean GA and birth weight in the hyperechogenicity BGT group, making the infants more vulnerable to prematurity-related problems. It may also indicate that hyperechogenicity BGT represents (pathological) change to the BGT, analogous to periventricular echodensity of the WM. As shown on cUS and MRI, hyperechogenicity BGT is strongly associated with concomitant brain lesions, mostly PVL and P/IVH, which may influence the overall cUS appearance of other brain structures, including BGT. However, in most infants we observed hyperechogenicity BGT before cerebral lesions such as P/IVH and/or PVL occurred. So, very preterm infants, known to be very vulnerable to haemorrhagic and ischaemic brain damage (9,25), may also be vulnerable to (ischaemic) change of the deep grey matter. On the other hand, P/IVH and PVL result in echogenicity changes within the ventricles and/or periventricular WM, and this may influence echogenicity of the deep grey matter.

Hyperechogenicity was diffuse in almost all preterm infants (38/39). Three infants showed localized lesions, of whom two also had diffuse hyperechogenicity BGT. Only few MR examinations from infants with hyperechogenicity BGT were available, because this is a retrospective study and MRI was done only in infants with (suspected) serious parenchymal damage on cUS. These MRI scans did not consistently show abnormalities (i.e. subtle signal intensity changes) in the thalamic region. This might be due to the long time-lag between the last day hyperechogenicity BGT was detected and the day MRI was performed. Consequently, based on this retrospective study
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it is difficult to investigate whether there is a correlation between the findings on cUS and MRI and to evaluate whether MRI can be helpful in exploring the origin of hyperechogenicity BGT.

The incidence of mildly abnormal and definitely abnormal outcome in the Prechtl examination at term age in infants participating in the follow-up program was higher in the hyperechogenicity group than in the non-hyperechogenicity group. The differences in neurological outcome between the hyperechogenicity and the non-hyperechogenicity group were no longer observed in the Touwen examination at 1 year corrected age. As hyperechogenicity BGT occurred in more immature infants and cerebral damage (i.e. PVL and P/IVH) co-existed, we need to be careful about drawing conclusions from the neurological findings. PVL and P/IVH may have consequences for the neurological development of preterm infants (5,26-27) and very preterm infants may exhibit transient neurological dysfunction, even without demonstrable cerebral pathology (5,28-29). So, the less favourable neurological outcome at term age of infants with hyperechogenicity BGT may not be a direct consequence of hyperechogenicity BGT, but of one or more of the associated cerebral lesions and/or of the lower GA.

Because it is not possible to explore the origin of hyperechogenicity BGT with cUS alone, and the few available MRI scans did not consistently show abnormalities in the thalamic region, the origin of hyperechogenicity BGT could not be determined. Studies including MRI scans in the acute phase of hyperechogenicity BGT are required to assess the correlation between cUS and MRI findings. These studies may help to determine whether hyperechogenicity BGT is a pathological phenomenon. Histological examination of the BGT of preterm infants with hyperechogenicity BGT who died during the neonatal period, will probably give essential information about the origin of hyperechogenicity BGT. Moreover, studies evaluating both short- and long-term neurological implications of hyperechogenicity BGT should be performed.

In conclusion, hyperechogenicity BGT mainly occurred in sick, very preterm infants with a more complicated clinical course during the neonatal period and a less favourable outcome at term age. However, it was not associated with a poorer neurological outcome at 1 year corrected age. Hyperechogenicity BGT was always associated with cerebral pathology. Further studies are needed to determine whether hyperechogenicity BGT is a reflection of immaturity of the brain or a pathological phenomenon.
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