Imaging the preterm infant's brain

Leijser, L.M.

Chapter 5

Brain imaging findings in very preterm infants throughout the neonatal period: Part I. Incidences and evolution of lesions, comparison between ultrasound and MRI

Lara M. Leijser
Francisca T. de Bruïne
Sylke J. Steggerda
Jeroen van der Grond
Frans J. Walther
Gerda van Wezel-Meijler

Early Human Development 2009; 85(2): 101-109

Abstract

This study describes the incidence and evolution of brain imaging findings in very preterm infants (gestational age < 32 weeks), assessed with sequential cranial ultrasound (cUS) throughout the neonatal period and magnetic resonance imaging (MRI) around term age. The accuracy of both tools is compared for findings obtained around term.

Periventricular echodensities and intraventricular haemorrhage were the most frequent cUS findings during admission. Frequent findings on both cUS and MRI around term included ventricular dilatation, widened extracerebral spaces, and decreased cortical complexity. MRI additionally showed punctate white matter lesions and diffuse and excessive high signal intensity, but did not depict lenticulostriate vasculopathy and calcifications, and was less reliable for germinolytic and plexus cysts.

cUS detected most abnormalities that have been associated with abnormal neurodevelopmental outcome.

Introduction

Very preterm infants have a high risk of brain injury, including intraventricular haemorrhage (IVH), periventricular haemorrhagic infarction (PVHI), cystic periventricular leukomalacia (PVL), and more diffuse white matter (WM) injury. These abnormalities are associated with suboptimal or abnormal neurodevelopmental outcome. Early neuro-imaging studies in preterm infants were mainly directed at the detection of IVH, PVHI, and cystic PVL, but the incidence of these abnormalities has decreased considerably. Recent studies have focused more on the detection and implications of more diffuse or subtle WM changes (1-4).

Sequential cranial ultrasound (cUS) is the most readily available technique for imaging the neonatal brain. It is reliable for detecting frequently occurring abnormalities in preterm infants and for following brain growth and development (5). However, magnetic resonance imaging (MRI) is generally considered to be more sensitive for detecting diffuse and subtle abnormalities, assessing the exact site and extent of abnormalities, and assessing cerebral maturation, especially as it shows more detail than cUS and depicts myelination (1-5).

Several studies have described the prevalence and clinical relevance of various cerebral abnormalities in very preterm infants, and have increased the knowledge on associations between abnormalities and neurodevelopmental outcome (1-3,6-8). However, cUS and MR imaging techniques and protocols have improved considerably over recent years and the distribution of WM injury in preterm infants has changed (1,3-4). The primary aim of our study was, therefore, to describe the incidences of brain imaging findings in a cohort of very preterm infants admitted to a tertiary neonatal referral centre, assessed with modern neuro-imaging techniques. Secondary aims were to assess the evolution of lesions on cUS between admission and term equivalent age (TEA), to compare the findings on contemporaneous cUS and MRI performed around TEA, and to assess whether abnormalities were missed with either technique.

Patients and Methods

Patients

Very preterm infants born at a gestational age (GA) of < 32 weeks who were admitted to the tertiary neonatal intensive care unit of the Leiden University Medical Center between May 2006 and October 2007, were eligible for a neuro-imaging study, including sequential, standardized cUS examinations throughout the neonatal period and one MRI examination around TEA. Ethical approval for the study was given by the Medical Ethics Committee and informed consent from the parents was obtained for each infant. Exclusion criteria were congenital anomalies of the central nervous system, severe other congenital anomalies, chromosomal disorders, metabolic disorders, and neonatal meningitis.

Cranial ultrasound

As part of the routine standard of care, sequential cUS scans are performed by the attending (fellow) neonatologists in all preterm infants. This is done within 24 hours of birth, at least weekly from the day of birth or admission until discharge or transfer to another hospital, and on the day of the term equivalent MRI examination. Scanning is done through the anterior fontanel as recently described, using an Aloka α10 scanner with a multifrequency transducer (Biomedic Nederland B.V., Almere, the Netherlands) (5). The whole brain is scanned and at least six coronal and five sagittal planes are recorded. In addition, images are recorded in two planes of each (suspected) abnormality. The transducer frequency is set at 7.5 MHz. For detection of cortical and/or subcortical abnormalities, higher frequencies up to 10.0 MHz are used, whereas, if necessary, deeper structures are visualized with lower frequencies down to 5.0 MHz. cUS scans are assessed during and immediately after the procedure by the examiner and all images are stored digitally (5). For the neuro-imaging study, only the cUS scans performed weekly by the same, experienced examiners (LML, GvWM, SJS) were assessed. From now on all cUS scans performed between birth or admission and discharge or transfer will be referred to as adm-cUS and the cUS scan performed on the day of the MRI as MRI-cUS.

Of all included infants, the sequential cUS scans were evaluated by at least two experienced investigators (LML, GvWM, SJS) by consensus, using the software programme Clinical Assistant (version 6; RVC B.V., Baarn, the Netherlands). The investigators were blinded to the MR imaging findings of the infants.

For this specific part of the neuro-imaging study, attention was paid to presence of the following findings, using previously described classifications:

- Periventricular echodensities (PVE) (Figure 1), defined and classified according to van Wezel-Meijler et al. (9) and adapted by Sie et al. (10)
- Cystic lesions in the periventricular WM (cystic PVL) (11)
- IVH, classified according to Volpe (Figure 2) (12); if IVH was bilateral, it was classified according to the most severe side
- Intraparenchymal echodensity (IPE) (Figure 2), defined as an unilateral or asymmetric, rather localized area of high echogenicity within the WM, co-existing with an IVH on the ipsilateral side, also referred to as PVHI (13)
- Porencephalic cysts, defined as a large cystic lesion, communicating with the lateral ventricle (13)
- Post-haemorrhagic ventricular dilatation (PHVD), defined as ventricular dilatation following IVH
- Basal ganglia and/or thalamus (i.e. deep grey matter) abnormalities, defined as local or more diffuse echogenicity changes within the area of the basal ganglia and/or thalami with the exception of diffuse, subtle, symmetric increased echogenicity (14)
- Structural anomalies
- Others, such as lenticulostriate vasculopathy (LSV) (defined as punctate, linear or branching echogenic structure in the distribution of the thalamo-striatal vessels within the basal ganglia and thalamus region), calcifications (defined as highly echogenic lesion within the WM and/or basal ganglia), other cystic lesions including germinolytic cysts (defined as clearly demarcated cystic lesion of the germinal matrix, located directly adjacent to the lateral ventricle, at or just below the supero-lateral angle of the frontal horns or body of the ventricle), and choroid plexus cysts (defined as small echolucent area within the choroid plexus)

Figure 1. Coronal (a) and parasagittal (b) cUS scans of a preterm infant (gestational age 29.4 weeks) at a postmenstrual age of 29.6 weeks showing bilateral inhomogeneous periventricular echodensities in the parietal white matter (arrows).

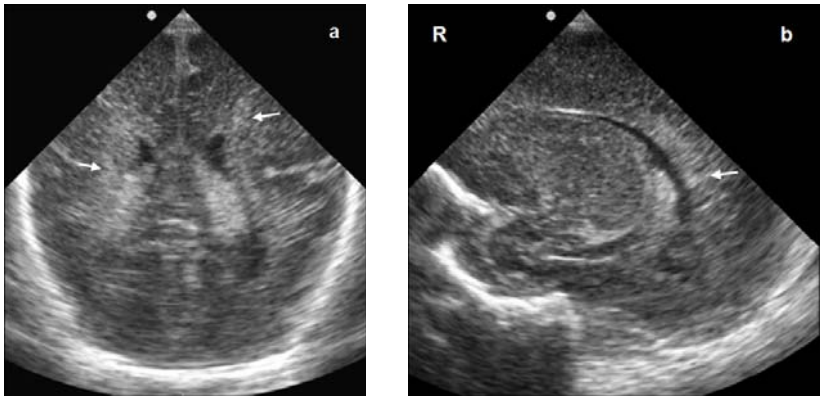
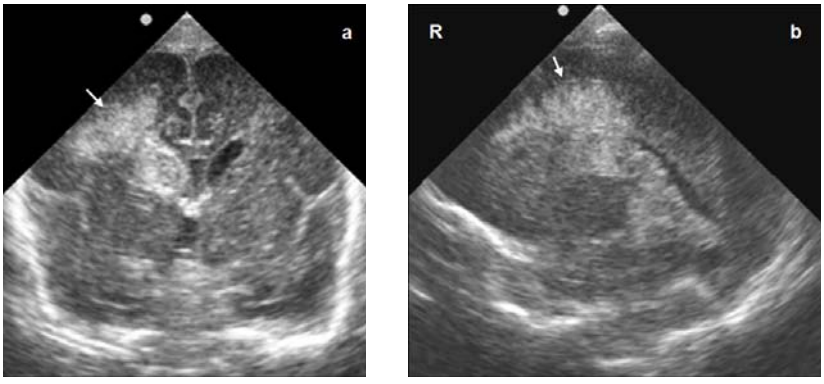


Figure 2. Coronal (a) and parasagittal (b) cUS scans of a preterm infant (gestational age 29.0 weeks) at a postmenstrual age of 29.7 weeks showing right-sided grade 3 intraventricular haemorrhage with co-existing ipsilateral intraparenchymal echodensity (periventricular haemorrhagic infarction) in the fronto-parietal white matter (arrows).

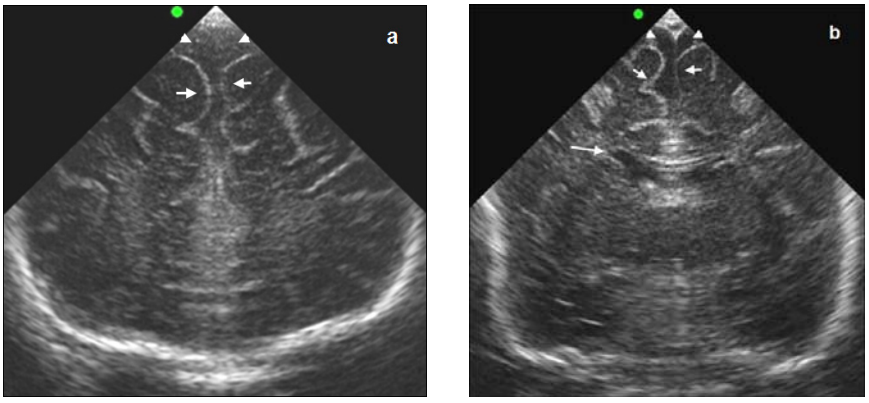


In addition, possible signs of atrophy, including ventricular dilatation (with the exception of PHVD), widened extracerebral spaces, and/or decreased complexity of gyration, were scored on the MRI-cUS (Figure 3) (8). The size and shape of the lateral ventricles and extracerebral spaces were scored visually and graded as normal, mildly abnormal, or severely abnormal. This was done separately by two investigators and in case of discordance consensus was reached. If applicable, for all findings the side, location, grade, and extent were recorded.

Abnormalities in the posterior fossa, including cerebellar injury, will be reported separately.

For all included infants, the overall presence and characteristics of findings as detected on sequential adm-cUS and on MRI-cUS were recorded.

Figure 3. Coronal cUS scans through the frontal white matter (a) and the bodies of the lateral ventricles (b) of a preterm infant (gestational age 31.7 weeks) at a postmenstrual age of 43.4 weeks showing widening of the extracerebral spaces (arrow heads) and mildly dilated lateral ventricles, more prominent on the right than on the left side (long arrow). Also showing decreased complexity of gyration (short arrows).



MRI

MRI examinations were performed in all very preterm infants according to our standard protocol for imaging the newborn infant's brain, using a 3 Tesla Philips MR system (Philips Medical Systems, Best, the Netherlands). The MRI examinations were preferably performed around TEA (40-44 weeks' postmenstrual age (PMA)). For infants who were still unstable and/or infant flow, CPAP, or ventilator dependent around that age, MRI was performed later as soon as they were in a stable condition. For details on the MRI procedure, including the scan protocol, we refer to another article in this issue (15).

All MRI examinations were assessed by at least two experienced investigators (LML, FTdB, GvWM, SJS) by consensus. FTdB, being a paediatric neuroradiologist, was present during all assessments. Investigators were unaware of (FTdB) or blinded to (LML, GvWM, SJS) the clinical course and cUS findings of the infants.

While evaluating the MRI examinations, attention was paid to presence of the following findings, using previously described classifications:

- Punctate white matter lesions (PWML) (Figures 4 and 5), defined as small areas of high signal on T_1-weighted and low signal on T_2-weighted images within the WM (16)
- Diffuse and excessive high signal intensity (DEHSI) (Figure 5), defined as areas of excessive high signal intensity diffusely distributed within the periventricular or subcortical WM on T_2-weighted MR images (1); DEHSI was only assessed on MRI scans performed between 40 and 44 weeks' PMA
- Other signal intensity changes in the periventricular WM, classified according to Sie et al. (10)
- Cystic lesions in the periventricular WM
- IVH
- PVHI
- Porencephalic cysts
- PHVD
- Basal ganglia and/or thalamus (i.e. deep grey matter) abnormalities
- Structural anomalies
- Possible signs of atrophy, including ventricular dilatation (with the exception of PHVD), widened extracerebral spaces, and/or reduced complexity of gyration (Figure 5)
- Others, including other cystic lesions, and calcifications

Figure 4. Transverse T_1- (a) and T_2- (b) weighted MR images at the level of the basal ganglia of a preterm infant (gestational age 29.4 weeks) at a postmenstrual age of 42.4 weeks showing bilateral, few (< 6) punctate white matter lesions in the periventricular white matter on the T_1- and T_2-weighted images (short arrows), and mild widening of the extracerebral spaces (long arrows). Also note the germinolytic cysts (arrow heads).

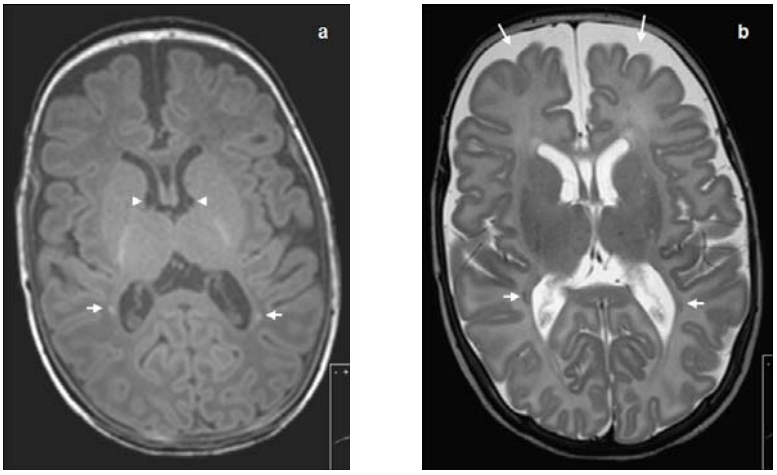
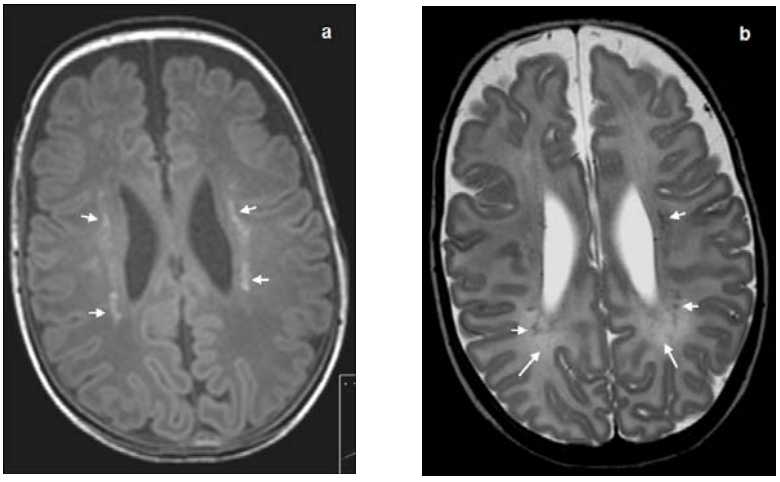


Figure 5. Transverse T_1- (a) and T_2- (b) weighted MR images at high ventricular level of a preterm infant (gestational age 26.9 weeks) at a postmenstrual age of 42.7 weeks showing bilateral, multiple punctate white matter lesions in the periventricular white matter (short arrows), being more obvious on the T_1- than on the T_2-weighted MR image. Also showing widening of the extracerebral spaces and dilated, irregularly shaped lateral ventricles. The T_2-weighted image additionally shows diffuse and excessive high signal intensity (DEHSI) in the periventricular white matter around the occipital horns of the lateral ventricles (long arrows).



The size and shape of the lateral ventricles and extracerebral spaces were scored visually and graded as normal, mildly abnormal, or severely abnormal. This was done separately by two investigators and in case of discordance consensus was reached. If applicable, for all findings the side, location, grade and extent were recorded.

Data analysis

Statistical analyses were performed using SPSS software (version 14.0; SPSS inc., Chicago, Illinois, USA). The incidence and, if applicable, characteristics of brain findings detected on sequential adm-cUS and on contemporaneous cUS and MRI around TEA were calculated. For calculating the incidence on adm-cUS, a finding was considered present when detected on at least one cUS occasion, and for findings classified into different grades the highest grade seen during admission was used. In addition, the incidence and characteristics of findings on MRI-cUS and MRI were compared, using a Fisher's Exact test or Pearson χ^2 test where appropriate.

In order to explore whether there were significant differences in incidence of brain imaging findings between very preterm infants included and not included in the study, the cUS findings of the non-included infants, admitted during the same period, as documented by the attending neonatologists, were recorded. The level of significance was 5%.

Results

Patients

During the study-period, 182 very preterm infants were admitted to our neonatal unit and eligible for this study. Informed parental consent was obtained for 133 infants (80 male, 53 female). Reasons for not obtaining parental consent included transfer to another hospital within a very short period of birth, death within several hours of birth, rejection of participation by the parents, and practical problems such as language barrier and travel distance between hospital and parental home.

The mean number of cUS scans performed per infant was 8.3 (range 2-23), and mean total duration of admission was 25.7 (range 2-114) days. Five infants died during

admission, before the term cUS and MRI examinations were obtained, at a mean postnatal age of 6.2 (range 2-11) days. In four infants MRI was performed in another hospital, using different protocols, as the infants were too unstable to be transported to our hospital, in two infants the MR images were difficult to interpret due to movement artefacts, and in nine infants the parents decided to withdraw participation from the MRI examination. So, in 113 infants (68 male, 45 female) contemporaneous cUS and MRI around or shortly after TEA were obtained, at a mean PMA of 44.7 (range 40.0-55.9) weeks. In 70 infants MRI was performed between 40 and 44 weeks' PMA, in the other 43 infants between 44.1 and 55.9 weeks' PMA. General characteristics of included infants are shown in Table 1. There were no significant differences in GA and birth weight between the infants with and without informed consent.

Table 1. General characteristics of the 133 very preterm infants included in the study (GA, gestational age; IUGR, intrauterine growth restriction; n, number of infants)

Characteristics	Value
GA (weeks), mean (range)	28.9 (25.6-31.9)
Birth weight (g), mean (range)	1176 (520-1960)
Male gender, n (%)	80 (60.2)
IUGR, n (%)	17 (12.8)
Number of cUS, n (range)	8.3 (2-23)
Died during admission, n (%)	5 (3.8)
Duration of admission (days), mean (range)	25.7 (2-114)

Cranial ultrasound

Adm-cUS *(n=133/113)*

In 32 infants (24.1%) one finding and in 96 infants (72.2%) two or more findings were present. The incidences and characteristics of findings as seen on sequential adm-cUS for all included infants (n=133) and for the infants in whom cUS and MRI were obtained around TEA (n=113) are shown in Table 2. No significant differences were found for incidences and characteristics of findings detected on adm-cUS between infants included in the study and those not included, and between the total group of included infants (n=133) and the group of infants with cUS and MRI around TEA (n=113).

Table 2. Incidences and characteristics of findings on adm-cUS (all included infants and infants with both adm-cUS and MRI-cUS) and MRI-cUS, and comparison of findings detected on adm-cUS and MRI-cUS in 113 very preterm infants
(BGT, basal ganglia / thalamus; IVH, intraventricular haemorrhage; LSV, lenticulostriate vasculopathy; n, number of infants; PHVD, post-haemorrhagic ventricular dilatation; PVE, periventricular echodensities; PVHI, periventricular haemorrhagic infarction; WM, white matter)

Neuro-imaging finding	Characteristics		Number (%)			Number (%)		
			Adm-cUS (n=133)	Adm-cUS (n=113)	MRI-cUS (n=113)	Both adm-cUS and MRI-cUS	Only on adm-cUS	Only on MRI-cUS
PVE	Total		107 (80.5)	90 (79.6)	13 (11.5)	13	77	0
	Grade	1	89 (83.2)	77 (85.6)	12 (92.3)	9	68	3
		2	18 (16.8)	13 (14.4)	1 (7.7)	0	13	1
	Appearance	Homogeneous	22 (20.6)	16 (17.8)	0 (0)	0	16	0
		Inhomogeneous	85 (79.4)	74 (82.2)	13 (100)	8	66	5
Cystic lesions in WM			10 (7.5)	7 (6.2)	2 (1.8)	2	5	0
IVH	Total		37 (27.8)	32 (28.3)	2 (1.8)	1	31	1
	Grade	1	17 (45.9)	15 (46.9)	2 (100)	0	15	2
		2	9 (24.3)	8 (25.0)	0 (0)	0	8	0
		3	2 (5.4)	2 (6.3)	0 (0)	0	2	0
		1 plus PVHI	0 (0)	0 (0)	0 (0)	0	0	0
		2 plus PVHI	2 (5.4)	2 (6.3)	0 (0)	0	2	0
		3 plus PVHI	7 (18.9)	5 (15.6)	0 (0)	0	5	0
	Side	Unilateral	20 (54.1)	17 (53.1)	2 (100)	0	17	2
		Bilateral	17 (45.9)	15 (46.9)	0 (0)	0	15	0
PHVD	Total		21 (15.8)	17 (15.0)	12 (10.6)	10	7	2
	With IVH grade	1	4 (19.0)	4 (23.5)	0 (0)	0	4	0
		2	7 (33.3)	6 (35.3)	0 (0)	0	6	0
		3	10 (47.6)	7 (41.2)	0 (0)	0	2	0
PVHI			9 (6.8)	7 (6.2)	0 (0)	0	7	0
Porencephalic cyst			0 (0)	0 (0)	6 (5.3)	0	0	6
Structural anomalies	Total		2 (1.5)	2 (1.8)	1 (0.9)	1	1	0
	Corpus callosum agenesis		1 (50.0)	1 (50.0)	1 (100)	1	0	0
	Septum vergae agenesis		1 (50.0)	1 (50.0)	0 (0)	0	0	0
Others	Plexus cyst(s)		20 (15.0)	20 (17.7)	6 (5.3)	5	15	1
	Germinolytic cyst(s)		7 (5.3)	6 (5.3)	5 (4.4)	5	1	0
	BGT lesions		5 (3.8)	5 (4.4)	1 (0.9)	0	5	1
	LSV		25 (18.8)	23 (20.4)	18 (15.9)	15	8	3
	Calcification in WM		6 (4.5)	6 (5.3)	2 (1.8)	2	4	0

MRI-cUS *(n=113)*

In 30 infants (26.1%) one finding and in 75 infants (65.2%) two or more findings were present. The incidences and characteristics of findings as seen on MRI-cUS are shown in Table 2.

Relation between adm-cUS and MRI-cUS *(n=113)*

Comparison of the incidences of findings detected on adm-cUS and on MRI-cUS is shown in Table 2. The table also shows whether findings were detected on both adm-cUS and MRI-cUS, only on adm-cUS, or only on MRI-cUS.

MRI (n=113)

In 16 infants (14.2%) one finding and in 91 infants (80.5%) two or more findings were present. The incidences and characteristics of findings as seen on MRI are shown in Table 3.

In 55 of the 70 infants (78.6%) in whom MRI was obtained between 40 and 44 weeks' PMA, DEHSI was seen; in 10 infants combined with a solitary finding, and in 45 infants combined with two or more findings.

Relation between MRI-cUS and MRI (n=113)

Comparison of the incidences of findings detected on MRI-cUS and on MRI is shown in Table 3. The table also shows whether findings were detected on both MRI-cUS and MRI, only on MRI-cUS, or only on MRI.

Table 3. Incidences and characteristics of findings on MRI around term equivalent age, and comparison of findings detected on MRI-cUS and contemporaneous MRI in 113 very preterm infants
(BGT, basal ganglia / thalamus; DEHSI, diffuse and excessive high signal intensity within periventricular or subcortical white matter; IVH, intraventricular haemorrhage; LSV, lenticulostriate vasculopathy; n, number of infants; NA, not applicable; PHVD, post-haemorrhagic ventricular dilatation; PVE, periventricular echodensities; PVHI, periventricular haemorrhagic infarction; PVWM, periventricular white matter; PWML, punctate white matter lesions; SI, signal intensity; signs of atrophy was defined as ventricular dilatation [with the exception of PHVD], widened extracerebral spaces, and/or reduced complexity of gyration; WM, white matter)

Neuro-imaging finding	Characteristics	Number (%)		Number (%)		
		MRI-cUS (n=113)	MRI (n=113)	Both cUS and MRI	Only / more on cUS	Only / more on MRI
PVE / SI changes in PVWM (other than DEHSI)		13 (11.5)	15 (13.3)	1	12	14
PWML	Total	0 (0)	27 (23.9)	0	0	27
	Number					
	- ≤ 6	0 (0)	8 (29.7)	0	0	8
	- > 6	0 (0)	19 (70.4)	0	0	19
	Site					
	- PVWM	0 (0)	19 (70.4)	0	0	19
	- PVWM + optic radiation	0 (0)	8 (29.7)	0	0	8
DEHSI (of 70 infants with MRI around TEA)		NA	55 (78.6)	NA	NA	55
Cystic lesions in WM		2 (1.8%)	2 (1.8%)	2	0	0
(Remnants of) IVH		2 (1.8)	33 (29.2)	1	1	32
PHVD		12 (10.6)	12 (10.6)	12	0	0
PVHI		0 (0)	0 (0)	0	0	0
Porencephalic cyst		6 (5.3)	6 (5.3)	6	0	0
Ventricular dilatation (excluding PHVD)	Total	48 (42.5)	69 (61.1)	45	3	24
	Mild	41 (85.4)	57 (82.6)	30	11	27
	Severe	7 (14.6)	12 (17.4)	4	3	8
Widening extracerebral spaces	Total	86 (76.1)	91 (80.5)	78	8	13
	Mild	56 (65.1)	64 (70.3)	44	12	20
	Severe	30 (34.9)	27 (29.7)	23	7	4
Structural anomalies	Total	1 (0.9)	5 (4.4)	1	0	4
	Corpus callosum agenesis	1 (100)	3 (60.0)	1	0	2
	(Cortical) heterotopias	0 (0)	2 (40.0)	0	0	2

	(Cortical) heterotopias	0 (0)	2 (40.0)	0	0	2
Decreased complexity of gyration		40 (35.4)	9 (8.0)	3	37	6
Signs of atrophy		98 (86.7)	103 (91.2)	94	4	9
Others	Plexus cyst(s)	6 (5.3)	0 (0)	0	6	0
	Germinolytic cyst(s)	5 (4.4)	2 (1.8)	2	3	0
	Subarachnoid cyst	0 (0)	2 (1.8)	0	0	2
	Subdural haemorrhage	0 (0)	2 (1.8)	0	0	2
	BGT lesions	1 (0.9)	3 (2.7)	1	0	1
	LSV	18 (15.9)	0 (0)	0	18	0
	Calcification in WM	2 (1.8)	0 (0)	0	2	0

Discussion

To our knowledge, this is the first study describing the incidence and evolution of brain imaging findings as seen on sequential cUS throughout the neonatal period and on MRI around or shortly after TEA in a large cohort of very preterm infants admitted to a tertiary neonatal referral centre.

The most frequent findings during admission were PVE and IVH. Our high incidence of PVE (80%) is in agreement with recent studies (1,8,17), reporting an incidence of 48-100% in preterm infants, depending on study-populations and cUS protocols. The majority of PVE was inhomogeneous, but of mild echogenicity. This is in agreement with the study by Sie et al. (10) which also assessed the appearance of PVE (homogeneous or inhomogeneous). In accordance with others (8,17-18), total duration of PVE was longer than 1 week in most cases. PVE were generally seen within the first week of birth, the majority gradually resolving before TEA.

IVH was encountered on adm-cUS in nearly 30% (37/133) of infants. IVH was generally first detected within a few days of birth, mainly of low grade (grade 1 and/or 2), and associated with PHVD in just over half of cases. Not only grade 3 IVH, but also IVH of lower grade was complicated by PHVD, although in a lower frequency. Around TEA, most IVHs were no longer visible on cUS. PHVD also largely decreased or resolved before TEA. This is explained by the fact that in most cases (15/17) dilatation decreased or resolved spontaneously without needing treatment, while the remaining two cases were successfully treated with repetitive lumbar punctures and/or punctures from a ventricular reservoir. None of the infants needed permanent shunting. The incidence, characteristics and evolution of IVH in our study-population are comparable with those reported by others (1-2,6,8,19-22).

In agreement with previous studies (13,23), PVHI was seen in 6% of preterm infants (22% of infants with IVH), and was generally a complication of grade 3 IVH (5/7 cases), but also seen in two of seven cases with grade 2 IVH. On MRI-cUS, PVHI was no longer characterized by asymmetric, inhomogeneous echodensities in the WM; the majority (6/7 cases) had evolved into porencephalic cysts, while in the remaining case asymmetric ventricular dilatation with abnormal shape of the lateral ventricle was seen. This is in agreement with several studies, showing that PVHI eventually leads to cystic change of the periventricular WM (porencephalic cyst) in most cases (13,23).

Ventricular dilatation, widening of extracerebral spaces, and loss of cortical complexity were frequent findings around TEA. In addition, MRI showed PWML and DEHSI. Loss of cortical complexity, dilatation of lateral ventricles and widening of extracerebral spaces are frequent findings on both cUS and MRI (1-3,10). These latter findings may represent WM and/or cortical volume loss and are thought to result from diffuse WM injury (3,6,8). Several ultrasound and MRI studies in preterm infants have shown that cystic lesions in the WM are now only rarely encountered and that the distribution of WM injury has shifted towards more diffuse and subtle WM changes (1,3,6,17). This is consistent with our results including a high incidence of PVE, but low incidence of cystic WM lesions on adm-cUS, and a high incidence of ventricular dilatation, PWML, DEHSI, and loss of cortical complexity around term.

The incidence of LSV was 19% on adm-cUS, being considerably higher than the incidence of 5% as reported in previous studies in preterm infants, but lower than 32% as reported by Paczko et al. (24-26). These differences may be related to cUS protocols, study-populations, and definition of LSV. We also included LSV having a punctate appearance and LSV co-existing with other brain imaging findings. Consistent with a previous study (24), LSV was mostly detected during admission after the first postnatal week and was still visible on MRI-cUS.

Choroid plexus cysts were detected in 15% of infants. The incidence of choroid plexus abnormalities on cUS reported in previous studies varies widely; some reported comparable, while others considerably lower incidences (1,6,19,27). Germinolytic cysts were detected in 5% of our infants. Also for these cysts reported incidences vary (28-29). The differences between studies may result from inconsistency in defining cysts in the choroid plexus, germinal matrix, caudo-thalamic notch, and walls of the lateral ventricles, and the occasionally encountered difficulty in differentiating these cysts on cUS (30). Since the isolated presence of these cysts is thought to be of no clinical significance (28-30), conflicting results between our and other studies seem to be of limited importance. In nearly all cases choroid plexus cysts and germinolytic cysts were already seen on the first adm-cUS, and mostly still present on MRI-cUS, which is in agreement with studies showing that these cysts develop during the fetal period and tend to persist during the neonatal period (27,29).

The incidences of the other findings detected on adm-cUS, including structural anomalies, deep grey matter abnormalities and calcifications in the WM, was low, being consistent with previous studies (1,6,19).

In most cases, MRI-cUS and MRI showed findings with comparable or equal accuracy. However, some findings were only or better detected by cUS while others by MRI.

Only cUS detected LSV, while germinolytic cysts and plexus cysts were better depicted by cUS than MRI. Calcifications, seen in two infants on MRI-cUS, were not recognized on MRI, even while susceptibility scans, being more sensitive for calcifications than conventional sequences, were included in the scan protocol. This is in agreement with previous studies, showing that LSV and calcifications are not depicted by MRI, and that the choroid plexus, and consequently plexus cysts, and germinolytic cysts are difficult to visualize with MRI (1,31). The reason for this is unclear, but it may partially be related to differences in image orientation between cUS and MRI.

To our surprise, while MRI shows cortical development in more detail, decreased complexity of gyration was more often seen on cUS than on MRI. We assume that this was rather a result of overestimation on cUS than of underestimation on MRI; on cUS examinations obtained around or after TEA, the field of view is largely taken up by the lateral ventricles and periventricular WM (see Figures 3, 4 and 5).

On the other hand, as expected, some changes were only or better seen on MRI. PWML and DEHSI were frequently seen on MRI, while on MRI-cUS echogenicity changes in the WM were only rarely encountered. Other studies also reported high incidences of PWML and DEHSI, considered to represent diffuse or subtle WM injury, while so far no cUS-correlates were established for these MRI phenomena (1,10,17,19).

Largely in agreement with previous studies and general ideas (1,7,13,31-32), (remnants of) IVH, structural anomalies, subarachnoid cyst, subdural haemorrhage, and deep grey matter abnormalities were only or better detected on MRI. MRI shows more detail than cUS and is better for visualizing the whole brain and deeper and more peripheral cerebral structures (5). In addition, MRI has been described to detect haemorrhages over a longer period, even when no longer visible on cUS, and with more conspicuity (1).

In consistence with previous studies (7,10,31-32), ventricular dilatation, widening of extracerebral spaces, and porencephalic cysts were depicted on cUS and MRI. Of note,

ventricular dilatation was detected in 21 additional cases on MRI. This indicates that around TEA particularly mild ventricular dilatation is more easily depicted by MRI.

We feel that this is a rather unique study on brain imaging findings in very preterm infants. Firstly, cUS examinations were performed frequently (at least weekly until discharge/ transfer) according to a strict, standardized cUS protocol (5). All cUS examinations were performed by the same, experienced examiners. In addition, MRI was performed using a 3 Tesla MR system, again following a strict, standardized protocol, adapted to the neonatal brain (15). Section thickness was 2 mm maximum for the conventional T_1- and T_2-weighted images, without intersection gaps. For these reasons it seems unlikely that we have missed or overlooked abnormalities.

We are also aware of limitations of this study. Firstly, we examined a selected group of very preterm infants, admitted to a tertiary neonatal unit. Although in the Netherlands very preterm infants (GA < 32 weeks) are initially admitted to a tertiary neonatal centre, this may not be the same elsewhere. In addition, in the Netherlands, intensive care is initiated in very preterm infants from a GA of 25 weeks onwards. Infants born at shorter GAs generally only receive palliative care. Therefore, our incidences may not be representative of all populations of very preterm infants. We did not perform sequential MRI examinations, but a single MRI around TEA. As it has been described that mild signal changes in the WM, e.g. PWML, and small cystic lesions may disappear or become less obvious and numerous over a relatively short time-period (3,7), we may have underestimated the incidence and/or severity of some, particularly mild, changes. However, as sequential cUS is reliable for detecting most cerebral abnormalities, incidences of most findings on MRI-cUS and MRI were comparable, and developing new or more severe abnormalities later during the neonatal period is uncommon, we feel that repetitive MRI examinations would not have changed our results considerably (1,5,19). Finally, no long-term neurodevelopmental outcome data are, as yet, available. Consequently, the clinical relevance of brain imaging findings cannot be evaluated. Follow-up studies of included infants are currently ongoing.

In summary, PVE was the most frequent ultrasound finding during admission, while around TEA ventricular dilatation, widening of extracerebral spaces, and decreased complexity of gyration were frequently found. In addition, MRI showed PWML and DEHSI. Most of these findings are associated with diffuse, non-cystic WM injury. IVH

was the second most frequent finding during admission. IVH developed shortly after birth and generally resolved before TEA. It was complicated by PHVD and/or PVHI in the majority of cases. MRI did not depict LSV and calcifications, and was less reliable for detecting germinolytic cysts and choroid plexus cysts than cUS. Although some findings were better depicted by MRI, cUS detected most abnormalities known to be associated with suboptimal or adverse neurological outcome. Further study is needed to assess the significance of certain cerebral abnormalities for short- and long-term neurodevelopmental outcome of very preterm infants, and to assess the clinical significance of the lower sensitivity of cUS for some frequent findings.

References

1. Maalouf EF, Duggan PJ, Counsell SJ, Rutherford MA, Cowan F, Azzopardi D, et al. Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm infants. Pediatrics 2001; 107: 719-727
2. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med 2006; 355: 685-694
3. Dyet LE, Kennea N, Counsell SJ, Maalouf EF, Ajayi-Obe M, Duggan PJ, et al. Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. Pediatrics 2006; 118: 536-548
4. Leijser LM, Liauw L, Veen S, de Boer IP, Walther FJ, van Wezel-Meijler G. Comparing brain white matter on sequential cranial ultrasound and MRI in very preterm infants. Neuroradiology 2008; 50: 799-811
5. van Wezel-Meijler. Neonatal cranial ultrasonography, 1st edition. Springer Verlag, Heidelberg, 2007
6. Perlman JM, Rollins N. Surveillance protocol for the detection of intracranial abnormalities in premature neonates. Arch Pediatr Adolesc Med 2000; 154: 822-826
7. Roelants-van Rijn AM, Groenendaal F, Beek FJA, Eken P, van Haastert IC, de Vries LS. Parenchymal brain injury in the preterm infant: comparison of cranial ultrasound, MRI and neurodevelopmental outcome. Neuropediatrics 2001; 32: 80-89
8. Horsch S, Muentjes C, Franz A, Roll C. Ultrasound diagnosis of brain atrophy is related to neurodevelopmental outcome in preterm infants. Acta Paediatr 2005; 94: 1815-1821
9. van Wezel-Meijler G, van der Knaap MS, Sie LTL, Oosting J, van Amerongen AH, Cranendonk A, et al. Magnetic resonance imaging of the brain in premature infants during the neonatal period. Normal phenomena and reflection of mild ultrasound abnormalities. Neuropediatrics 1998; 29: 89-96
10. Sie LTL, van der Knaap MS, van Wezel-Meijler G, Taets van Amerongen AHM, Lafeber HN, Valk J. Early MR features of hypoxic-ischemic brain injury in neonates with periventricular densities on sonograms AJNR Am J Neuroradiol 2000; 21: 852-861
11. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res 1992; 49: 1-6
12. Volpe JJ. Neurology of the newborn, 5th edition. W.B. Saunders, Philadelphia, 2008

13. de Vries LS, Roelants-van Rijn AM, Rademaker KJ, van Haastert IC, Beek FJ, Groenendaal F. Unilateral parenchymal haemorrhagic infarction in the preterm infant. Eur J Paediatr Neurol 2001; 5: 139-149
14. Leijser LM, Klein RH, Veen S, Liauw L, van Wezel-Meijler G. Hyperechogenicity of the thalamus and basal ganglia in very preterm infants: radiological findings and short-term neurological outcome. Neuropediatrics 2004; 35: 283-289
15. van Wezel-Meijler G, Leijser LM, de Bruïne FT, Steggerda SJ, van der Grond J, Walther FJ. Magnetic resonance imaging of the brain in newborn infants: practical aspects. Early Hum Dev 2009; 85: 85-92
16. Ramenghi LA, Fumagalli M, Righini A, Bassi L, Groppo M, Parazzini C, et al. Magnetic resonance imaging assessment of brain maturation in preterm neonates with punctate white matter lesions. Neuroradiology 2007; 49: 161-167
17. Miller SP, Cozzio CC, Goldstein RB, Ferriero DM, Partridge JC, Vigneron DB, et al. Comparing the diagnosis of white matter injury in premature newborns with serial MR imaging and transfontanel ultrasonography findings. AJNR Am J Neuroradiol 2003; 24: 1661-1669
18. de Vries LS, van Haastert IL, Rademaker KJ, Koopman C, Groenendaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. J Pediatr 2004; 144: 815-820
19. Rademaker KJ, Uiterwaal CSPM, Beek FJA, van Haastert IC, Lieftink AF, Groenendaal F, et al. Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm. Arch Dis Child Fetal Neonatal Ed 2005; 90: F489-493
20. Kadri H, Mawla AA, Kazah J. The incidence, timing, and predisposing factors of germinal matrix and intraventricular hemorrhage (GMH/IVH) in preterm neonates. Childs Nerv Syst 2006; 22: 1086-1090
21. Murphy BP, Inder TE, Rooks V, Taylor GA, Anderson NJ, Mogridge N, et al. Posthaemorrhagic ventricular dilatation in the premature infant: natural history and predictors of outcome. Arch Dis Child Fetal Neonatal Ed 2002; 87: F37-41
22. Kuban K, Sanocka U, Leviton A, Allred EN, Pegano M, Dammann O, et al. White matter disorders of prematurity: association with intraventricular hemorrhage and ventriculomegaly. The Developmental Epidemiology Network. J Pediatr 1999; 134: 539-546

23. Bassan H, Benson CB, Limperopoulos C, Feldman HA, Ringer SA, Veracruza E, et al. Ultrasonographic features and severity scoring of periventricular hemorrhagic infarction in relation to risk factors and outcome. Pediatrics 2006; 117: 2111-2118
24. Chamnanvanakij S, Rogers CG, Luppino C, Broyles SR, Hickman J, Perlman JM. Linear hyperechogenicity within the basal ganglia and thalamus of preterm infants. Pediatr Neurol 2000; 23: 129-133
25. Hemachandra AH, Oravec D, Collin M, Tafari N, Mhanna MJ. Early and late postnatal identification of isolated lenticulostriate vasculopathy in preterm infants: associated findings. Perinatol 2003; 23: 20-23
26. Paczko N, Rotta NT, Silva A, Leiria F. Hyperechogenicity of thalamic vessels in preterm newborn infants. J Pediatr (Rio J) 2002; 78: 371-374
27. van Gelder-Hasker MR, van Wezel-Meijler G, van Geijn HP, de Vries JIP. Ultrasonography of the peri- and intraventricular areas of the fetal brain between 26 and 36 weeks' gestational age; a comparison with neonatal ultrasound. Ultrasound Obstet Gynecol 2001; 17: 34-41
28. Larcos G, Gruenewald SM, Lui K. Neonatal subependymal cysts detected by sonography: prevalence, sonographic findings, and clinical significance. AJR Am J Roentgenol 1994; 162: 953-956
29. Ramenghi LA, Domizio S, Quartulli L, Sabatino G. Prenatal pseudocysts of the germinal matrix in preterm infants. J Clin Ultrasound 1997; 25: 169-173
30. Epelman M, Daneman A, Blaser SI, Ortiz-Neira C, Konen O, Jarrín J, et al. Differential diagnosis of intracranial cystic lesions at head US: correlation with CT and MR imaging. Radiographics 2006; 26: 173-196
31. Leijser LM, de Vries LS, Rutherford MA, Manzur AY, Groenendaal F, de Koning TJ, et al. Cranial ultrasound in metabolic disorders presenting in the neonatal period: characteristic features and comparison with MR imaging. AJNR Am J Neuroradiol 2007; 28: 1223-1231
32. de Vries LS, Verboon-Maciolek MA, Cowan FM, Groenendaal F. The role of cranial ultrasound and magnetic resonance imaging in the diagnosis of infections of the central nervous system. Early Hum Dev 2006; 82: 819-825