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Research article

Incidence of brain lesions in moderate-late preterm infants assessed by cranial ultrasound and MRI: The BIMP-study

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ABSTRACT

Purpose: To evaluate the incidence and characteristics of brain lesions in moderate-late preterm (MLPT) infants, born at 32–36 weeks' gestation using cranial ultrasound (cUS) and magnetic resonance imaging (MRI).
Methods: Prospective cohort study carried out at Isala Women and Children's Hospital between August 2017 and November 2019. cUS was performed at postnatal day 3–4 (early-cUS), before discharge and repeated at term equivalent age (TEA) in MLPT infants born between 32^{+0} and 35^{+6} weeks' gestation. At TEA, MRI was also performed. Several brain lesions were assessed e.g. hemorrhages, white matter and deep gray matter injury. Brain maturation was visually evaluated. Lesions were classified as mild or moderate-severe. Incidences and confidence intervals were calculated.
Results: 166 MLPT infants were included of whom 127 underwent MRI. One or more mild lesions were present in 119/166 (71.7 %) and moderate-severe lesions in 6/166 (3.6 %) infants on cUS and/or MRI. The most frequent lesions were signs suggestive of white matter injury: inhomogeneous echogenicity in 50/164 infants (30.5 %) at early-cUS, in 12/148 infants (8.1 %) at TEA-cUS and diffuse white matter signal changes (MRI) in 27/127 (23.5 %) infants. Cerebellar hemorrhage (MRI) was observed in 16/127 infants (12.6 %). Delayed maturation (MRI) was seen in 17/117 (13.4 %) infants. Small hemorrhages and punctate white matter lesions were more frequently detected on MRI than on cUS.
Conclusions: In MLPT infants mild brain lesions were frequently encountered, especially signs suggestive of white matter injury and small hemorrhages. Moderate-severe lesions were less frequently seen.

1. Introduction

Infants born prematurely (gestational age (GA) < 37 weeks) are at risk of abnormal neurodevelopmental outcome [1]. The association between brain lesions and neurodevelopmental disabilities has extensively been investigated in very preterm infants (GA < 32 weeks) [2–4].

While there is increasing awareness of neurodevelopmental problems in moderate-late preterm (MLPT) infants, born at GA 32–36 weeks, there is only scarce attention for brain lesions in these infants. They have a two-fold higher incidence of developmental delay, and more problems with fine motor skills, communication and personal-social functioning at preschool age as compared to full-term infants. At school age, they have a higher incidence of grade retention and need for special education [5–7]. Some of these problems may possibly be

Abbreviations: CBH, cerebellar hemorrhage; cUS, cranial ultrasound; CI, confidence interval; GA, gestational age; IVH, intraventricular hemorrhage; MLPT, moderate–late, preterm; MRI, magnetic resonance imaging; PMA, postmenstrual age; PWML, punctate white matter lesions; SWI, susceptibility weighted imaging; TEA, term equivalent age.

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related to brain lesions acquired during the perinatal or neonatal period. To optimize functional outcome of MLPT infants by prevention, intervention or supportive care, more knowledge about the incidence and characteristics of acquired brain lesions and of brain development is needed.

So far, only a few studies have described brain lesions in MLPT infants [8–11]. These studies focused mainly on intraventricular hemorrhage (IVH) and cystic white matter lesions. Furthermore, these studies were generally performed in selected cohorts, consisting of infants admitted to the neonatal intensive care unit or not all included infants had a cranial ultrasound (cUS) assessment.

While magnetic resonance imaging (MRI) is most sensitive and reliable for the detection of brain injury in (preterm) infants [12], especially for small and/or subtle lesions, cUS is the primary neuro-imaging modality in this population. cUS is patient friendly, portable, relatively cheap and allows for early and serial imaging [13]. It is, however, unknown whether cUS enables the detection of potentially clinically relevant (subtle) brain lesions in MLPT infants. None of the previous studies on brain lesions in MLPT infants combined cUS and MRI [11].

The primary aims of our study were 1) to evaluate the incidence of brain lesions including delayed brain maturation (myelination and gyration) and 2) to compare brain-imaging findings on cUS and MRI in MLPT infants. We hypothesized (subtle) brain lesions, including delayed brain maturation to be frequently present in MLPT infants.

2. Methods

2.1. Study design and setting

This study is part of the BIMP-study ('Brain Imaging in Moderate-late Preterm infants', The Netherlands trial register; NL6310): a prospective cohort study conducted in MLPT infants at Isala Women and Children's Hospital (Zwolle, the Netherlands). Ethical approval was given by the Central Committee in Research Involving Human Subjects, The Hague, The Netherlands (NL52323.075.15). Data were collected between August 2017 - November 2019.

2.2. Participants

Infants born at GA 32^{+0} - 35^{+6} weeks and admitted to the neonatal ward or intensive care unit were eligible. Exclusion criteria were congenital malformations of the central nervous system, chromosomal disorders, inborn errors of metabolism, congenital infections, and significant language barrier. Signed informed consent was obtained from both parents.

2.3. Data collection and outcome

Clinical characteristics (GA, birthweight, multiple gestation, admission to neonatal ward or intensive care unit) were collected from medical charts.

2.3.1. cUS-protocol

cUS was performed at three time-points: early-cUS (postnatal day 3–4), discharge-cUS (shortly before discharge) and term equivalent age (TEA)-cUS (preferably at postmenstrual age (PMA) 38–44 weeks). If discharge was within three days after early-cUS, discharge-cUS was omitted. Serial-cUS was defined as ≥2 cUS-examinations, one of which TEA. If the same lesion was seen on all serial cUS-examinations, this was treated as one lesion. cUS was performed by a research physician (VB) or pediatrician (MKR). They were intensively trained in neonatal cUS prior to the start of the study by GvWM, neonatologist with >25 years of experience in neonatal neuroimaging (VB and MKR both performed and assessed > 100 cUS under supervision, and both attended a course on cUS). Scans were performed with a Hitachi Aloka Prosound Alpha 7 Premier system using a multifrequency convex transducer, set at 8 MHz. The brain was visualized through the anterior and mastoid fontanelles. Images were recorded of six coronal and five sagittal planes using the anterior window and at least one coronal and one axial plane using the mastoid window [13]. Additionally, (suspected) lesions were recorded in two image directions. Scans were assessed during and immediately after the procedure by the examiner (VB or MKR), checking for lesions with likely clinical consequences that might need medical intervention. Images were digitally stored for assessment with special attention to the brain lesions listed in Table 1. Inhomogeneous echogenicity was defined as areas within the periventricular white matter with inhomogeneous echogenicity, the echogenicity being equal to or exceeding that of the choroid plexus [20]. Scans were classified by three investigators (VB, MKR and GvWM) using Clinical Assistant (version 6.1; RVC Medical IT BV, Baarn, the Netherlands). The cUS investigators were blinded to the MRI findings.

2.3.2. MRI-protocol

MRI was performed during natural sleep, <1 h after the TEA-cUS. Infants were fed shortly before scanning, swaddled and placed in a vacuum-bag immobilizer (MedVac® bag, CFI Medical Solutions/Contour Fabricators, Fenton, Michigan, USA). Noise protection consisted of MiniMuffs (Natus Medical Incorporated, Foster City, California, USA), a headphone (EMS for kids, Hornchurch, UK), and a polystyrene noise-insulating coil cover. Infants were video-monitored. Heart rate and oxygen saturation were continuously measured (Invivo Precess MRI-compatible monitor, Invivo corporation, Orlando, FL, USA).

A 3 T Philips Ingenia MR system (Philips Medical Systems, Best, The Netherlands) was used. Three-dimensional T1- (slice thickness: 2 mm), coronal and transverse T2- (slice thickness 2 mm) weighted images, Diffusion Weighted Imaging (DWI; slice thickness: 3 mm), and Susceptibility Weighted Imaging (SWI; slice thickness: 1 mm) were performed.

Immediately after the procedure, the scans were assessed by MFB, a radiologist with >11 years of experience in pediatric imaging, checking for lesions with likely clinical consequences that might need medical intervention. Subsequently, three investigators (VB, GvWM and JN; the latter is a radiologist with >3 years of experience) evaluated the MRI scans by consensus. Investigators were unaware of (JN and MFB) or blinded to (VB, GvWM) the clinical course and cUS findings of the infants. The MRI scans were assessed with special attention to the brain lesions mentioned in Table 1. Diffuse white matter signal changes were defined as inhomogeneous and/or increased signal intensity within the white matter on T2-weighted images [21].

SWI and DWI are part of the standard scanning protocol for neonatal neuroimaging in our institution and support the accuracy of detection and investigation of brain injury. A distinction was made between hemorrhagic and ischemic punctate lesions using the SWI and DWI sequences. SWI was used to confirm hemorrhagic lesions, especially punctate lesions and the DWI sequence to determine timing of onset of ischemic lesions.

2.4. Classification of brain lesions

The following brain lesions were considered moderate-severe: IVH grade III [14], post-hemorrhagic ventricular dilatation [16], limited or massive cerebellar hemorrhage (CBH) [17], cystic white matter lesions, ≥ 6 punctate white matter lesions (PWML) [23], periventricular hemorrhagic infarction, arterial infarction, moderate-severe ex-vacuo ventricular dilatation, moderate-severe deep gray matter lesions. All other lesions mentioned in Table 1 were considered mild.

2.5. Statistics

Data-analyses were performed using SPSS software (version 26.0; SPSS inc, Chicago, Illinois, USA). Mean and SD were reported for normally distributed continuous variables. Differences in GA, birthweight

Table 1
Assessment cUS and MRI.

cUS	MRI
Hemorrhages	Hemorrhages
- Intraventricular hemorrhage (IVH) grade I-III according to Volpe et al. [14].	- (Remnants of) intraventricular hemorrhage (IVH)
Complications of IVH	Defined as presence of hemosiderin deposits at the level of the germinal matrix and/or in the lateral ventricular wall and/or the occipital horn of the lateral ventricles.
- Periventricular hemorrhagic infarction	Complications of IVH
Defined as an area of increased echogenicity adjacent to the lateral ventricle, co-occurring with and complicating IVH, evolving into a porencephalic cyst or several smaller cysts over a variable period of time (1−3 weeks) (15).	- Periventricular hemorrhagic infarction
	Defined as an area of abnormal signal intensity and/or cystic degeneration adjacent to or communicating with the lateral ventricle, co-existing with IVH or remnants of IVH [15].
- Post-hemorrhagic ventricular dilatation	- Post-hemorrhagic ventricular dilatation adapted for MRI from Brouwer et al. [16].
Defined as ventricular index > P97 for PMA and/or anterior horn width > 6 mm [16].	
- Choroid plexus hemorrhage	- Choroid plexus hemorrhage
Defined as a focal area of increased echogenicity within the choroid plexus.	Defined as presence of hemosiderin deposits within the choroid plexus.
- Cerebellar hemorrhage (CBH)	- Cerebellar hemorrhage (CBH)
Defined as increased echogenicity within the cerebellar parenchyma, categorized as 1) Punctate CBH: small lesions ≤ 4 mm; 2) Limited CBH: lesions > 4 mm but smaller than 1/3 of the cerebellar hemisphere; 3) Extensive CBH: lesions involving > 1/3 of the cerebellar hemisphere, according to Meijler en Steggerda [13].	Defined as hemosiderin deposits within the cerebellar parenchyma, categorized as 1) Punctate CBH: small lesions ≤ 4 mm 2) Limited CBH: lesions > 4 mm but smaller than 1/3 of the cerebellar hemisphere; 3) Extensive/massive CBH: lesions involving > 1/3 of the cerebellar hemisphere [17].
- Subdural hemorrhage	- Subdural hemorrhage
White matter	White matter
- Cystic white matter lesions	- Cystic white matter lesions
according to de Vries et al. [18].	according to Kidokoro et al. [19].
- Inhomogeneous echogenicity Defined as inhomogeneous areas within the periventricular white matter with echogenicity equal to or exceeding that of the choroid plexus, adapted from Van Wezel-Meijler et al. [20].	- Diffuse white matter signal changes
	Defined as inhomogeneous and/or increased signal intensity within the white matter on T2-weighted images, adapted from De Bruïne et al. [21].
- Suspected punctate white matter lesions (PWML) – only at cUS-TEA Defined as small, focal echogenic spots within the white matter [22].	- Punctate white matter lesions (PWML)
	Defined as focal areas of increased signal intensity within the brain white matter on T1-weighted images (adapted from Martinez-Biarge et al. [23]).
Arterial Infarction	Arterial Infarction
Defined as an area of focal or more diffusely increased echogenicity within the cerebral hemispheres in the territory of (branches of) one of the major cerebral arteries, followed by cystic evolution [24].	Defined as an area of focal abnormal signal intensity and/or volume loss within the cerebral hemispheres in the territory of (branches of) one of the major cerebral arteries [24].
Deep gray matter lesions	Deep gray matter lesions
Defined as inhomogeneous increased and/or focal echogenicity within the basal ganglia and /or thalami, not indicating arterial infarction (see above), subdivided in small focal abnormality (mild) or moderate-serious abnormality (moderate-severe).	Defined as abnormal signal intensity in the basal ganglia and /or thalami, not indicating arterial infarction (see above), subdivided in small focal abnormality (mild) or moderate-serious abnormality (moderate-severe).
Miscellaneous	Miscellaneous
- Choroid plexus cysts ≥ 6 mm [25].	- Choroid plexus cysts ≥ 6 mm [25].
- Germinolytic/subependymal cysts ≥ 6 mm [25].	- Germinolytic/subependymal cysts ≥ 6 mm [25].
- Lenticulostriate vasculopathy (LSV)	
Defined as thick and hyperechogenic lines within the basal ganglia and/or thalamus around the lenticulostriate vessels on coronal and parasagittal views (category D according to Sisman et al [26]).	
Signs suggestive of brain atrophy due to white matter injury	Signs suggestive of brain atrophy due to white matter injury
- Ex-vacuo ventricular dilatation	- Ex-vacuo ventricular dilatation
Mild dilatation: defined as uni- or bilateral ventricular index 13–15 mm; Moderate-severe dilatation: defined as uni- or bilateral ventricular index > 15 mm. The ventricular index was measured in the coronal plane at the level of the foramen of Monro. [27].	Mild dilatation: defined as uni- or bilateral ventricular index 13–15 mm; Moderate-severe dilatation: defined as uni- or bilateral ventricular index > 15 mm. The ventricular index was measured on a coronal T2-weighted scan at the level of the foramen Monro. Adapted for MRI [28].
- Irregular shape of the lateral ventricles See Fig. 2-I and and Leijser et al. [12], the shape was best assessed on sagittal images.	- Irregular shape of the lateral ventricles see Fig. 4-H and Leijser et al. [12].
- Widened interhemispheric fissure defined as interhemispheric fissure > 3 mm. The interhemispheric fissure was measured as the maximum width between the hemispheres from the surface of opposite gyri, in the coronal plane at the level of the foramen of Monro [27].	- Widened interhemispheric fissure defined as interhemispheric fissure > 3 mm. The interhemispheric fissure was measured as the maximum width between the hemispheres from the surface of opposite gyri, on a coronal T2-weighted image at the level of the foramen of Monro. Adapted for MRI [27].
	Delayed maturation
	- Delayed myelination of the posterior limb of the internal capsule defined as absence or insufficient myelination of the posterior 1/3 part of the posterior limb of the internal capsule on T1-weighted images [29].
	- Delayed gyration defined as visually assessed delayed gyration on T1- and T2-weighted images as compared to normal reference images [29].

and sex between participating and non-participating eligible infants were explored using the unpaired T-test or Chi-squared test. The incidences of brain lesions on cUS and MRI were calculated, including asymptotic continuity-corrected 95 % confidence intervals (CI). For both serial-cUS and MRI, the incidences of mild and moderate brain lesions were compared per GA week using the Chi-squared test. Furthermore, for each lesion we recorded whether it was seen on TEA-cUS and TEA-MRI, only/more on TEA-cUS or only/more on TEA-MRI. The level of significance was 5 %. Bias due to missing data for presence of lesions on cUS-discharge and to evaluate differences between infants with and without MRI was investigated using the Chi-squared test.

3. Results

3.1. Participants

During the study period, 404 MLPT infants were admitted to the neonatal ward (n = 298) or neonatal intensive care unit (n = 106). Consent was obtained from parents of 167 infants (Fig. 1). One infant was excluded after informed consent (chromosomal disorder apparent at

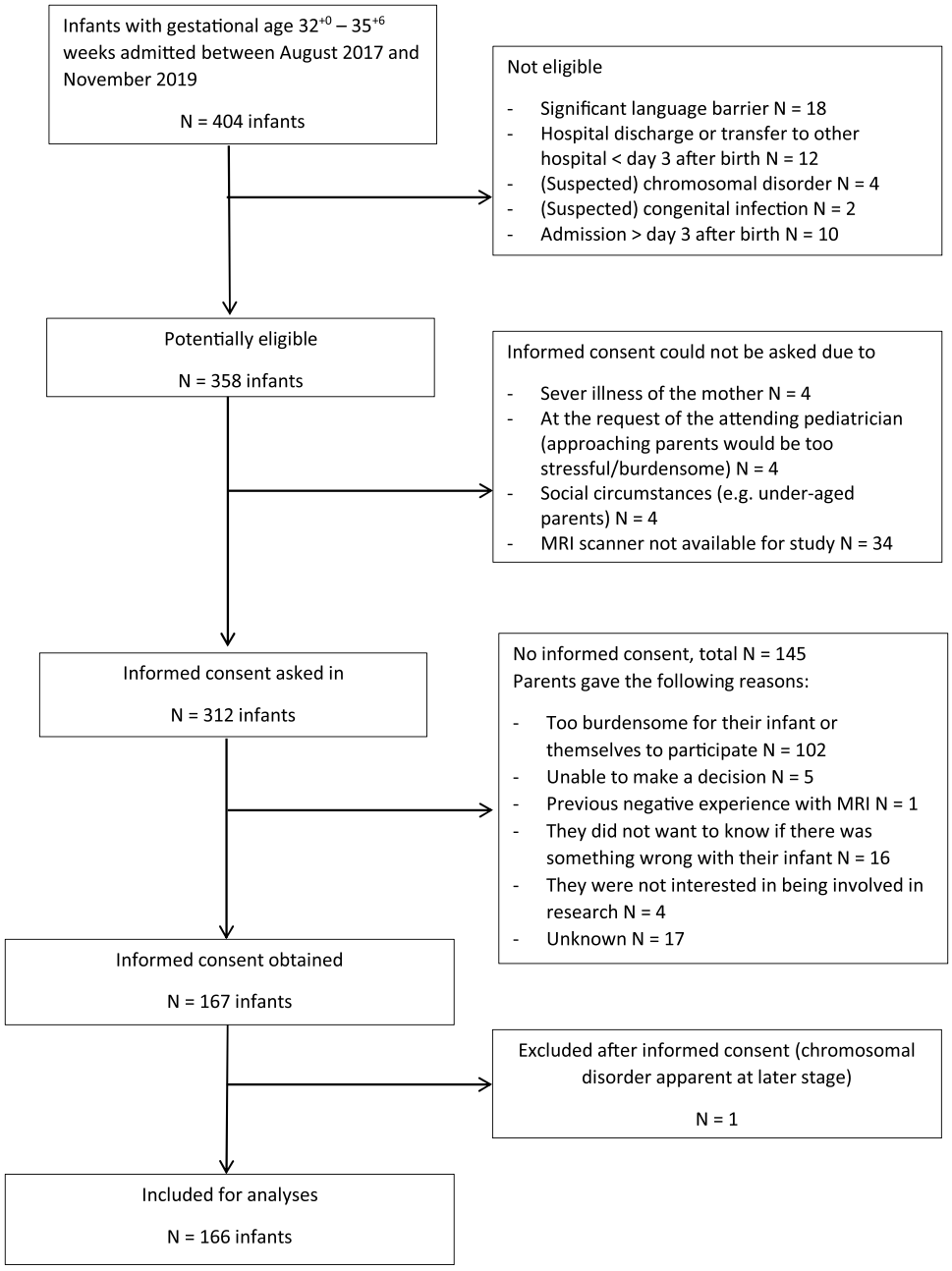

Fig. 1. Flow-chart.

Table 2
Characteristics of participants.

Variables	N = 166
GA in weeks, mean (SD)	34.2 (1.1)
Number of infants per GA week:	
32 weeks, n (%)	27
33 weeks, n (%)	38
34 weeks, n (%)	48
35 weeks, n (%)	53
Birth weight in grams, mean (SD)	2237 (476)
Man, n (%)	90 (54.2 %)
Singleton, n (%)	117 (70.5 %)
Twin, n (%)	46 (27.7 %)
Triplet, n (%)	3 (1.8 %)
Admission to the neonatal ward, n (%)	126 (75.9 %)
Admission to the neonatal intensive care unit, n (%)	40 (24.1 %)

GA = gestational age.

later stage). There were no significant differences in GA, sex and birth weight between participating and non-participating infants. See Table 2 for general characteristics of included infants.

3.2. Neuro-imaging

One or more brain lesion(s) were present on cUS and/or MRI in 125/166 infants (75.3 %; 95 % CI 67.9–81.5 %). In 119 infants these were considered mild (71.7 %; 95 % CI 64.1–78.3 %) and in six moderate-severe (3.6 %; 95 % CI 1.5–8.1 %).

3.2.1. Early-cUS

Imaging quality was insufficient in two infants. Therefore, early-cUS was assessed of 164 infants (median: 4 days; range: 2–6 days). Of these, 109 (66.5 %; 95 % CI 58.6–73.5 %) had no brain lesions, 48 (29.3 %; 95 % CI 22.6–37.0 %) one lesion, and seven (4.3 %; 95 % CI 1.9–8.9 %) two

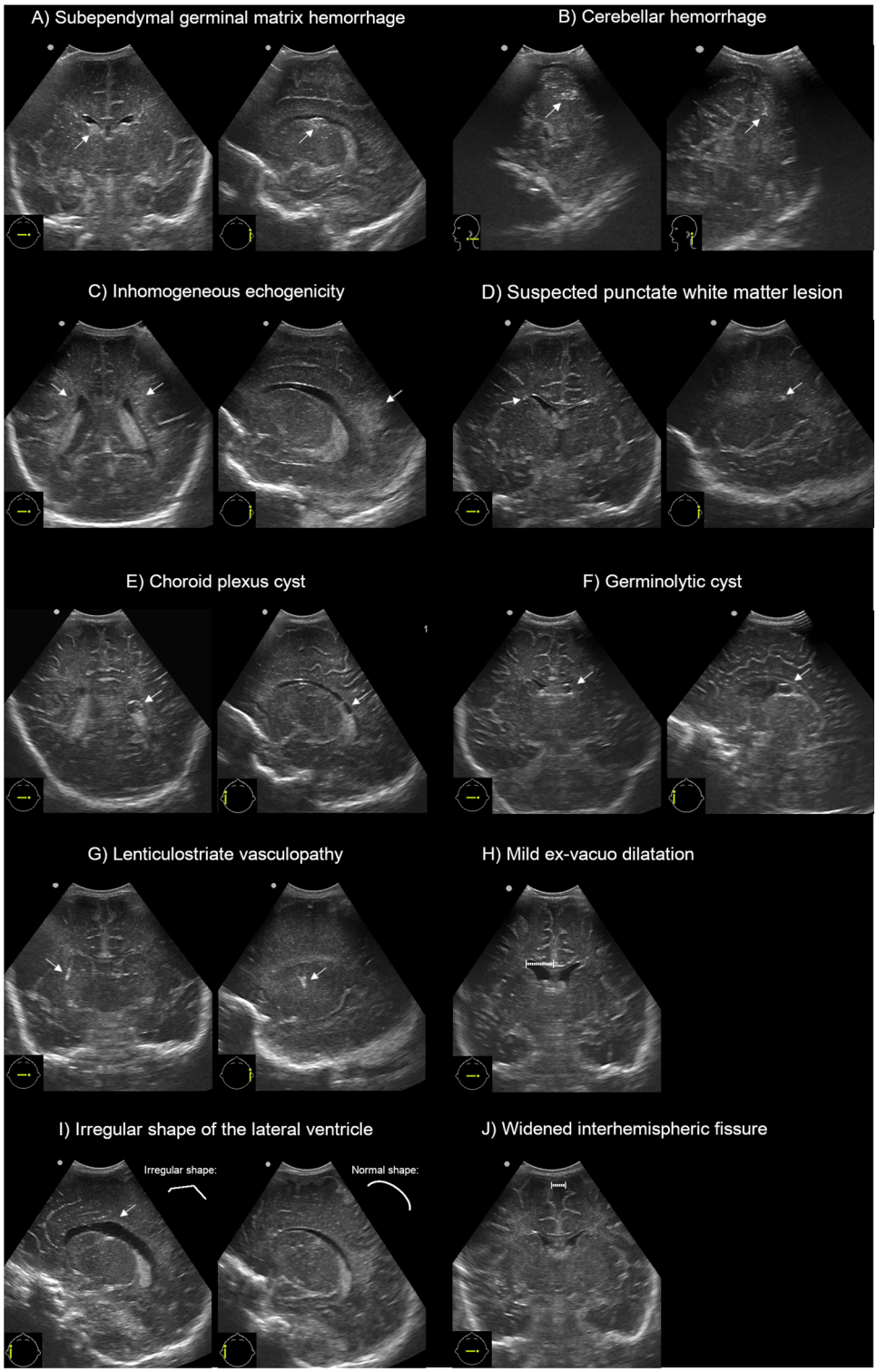

Fig. 2. Coronal and sagittal/axial images of mild brain lesions on cUS in MLPT infants.
A) Subependymal germinal matrix hemorrhage (arrow); B) Punctate cerebellar hemorrhage (arrow); C) Bilateral inhomogeneous periventricular echogenicity (arrows); D) Small punctate echogenic lesion (arrow) suspected for a punctate white matter lesion; E) Choroid plexus cyst (arrow); F) Germinolytic cyst (arrow); G) Lenticulostriate vasculopathy; H) Mild ex-vacuo dilatation, dashed line = measurement of ventricular index; I) Irregular shape (angular instead of round) of the lateral ventricle (arrow), for comparison an image of a normally shaped ventricle is added; J) Widened interhemispheric fissure, dashed line = measurement of interhemispheric fissure.

or more brain lesions. All lesions were considered mild (Fig. 2).

3.2.2. *Discharge-cUS*

Forty-four infants did not have discharge-cUS: 37 were transferred to another hospital or discharged home within three days after early-cUS, in five infants discharge-cUS was not performed (missed cases) and in two cases image quality was insufficient. Altogether, discharge-cUS was performed in 122 infants. Mean PMA was 36.0 (SD 1.1) weeks. On discharge-cUS 88 infants (72.1 %; 95 % CI 63.2–79.7 %) had no, 29 (23.8 %; 95 % CI 16.7–32.5 %) had one, and five (4.1 %; 95 % CI 1.5–9.8 %) had two or more brain lesion(s). All lesions were considered mild (Fig. 2).

3.2.3. *TEA-cUS*

Parents of eighteen infants considered the TEA-visit too burdensome. Therefore, 148/166 infants underwent TEA-cUS. Mean PMA was 41.3 (SD 2.0) weeks. On TEA-cUS, 71 infants (48.0 %; 95 % CI 39.8–56.3 %) had no, 44 (29.7 %; 95 % CI 22.7–37.9 %) had one, and 33 (22.3 %; 95 %

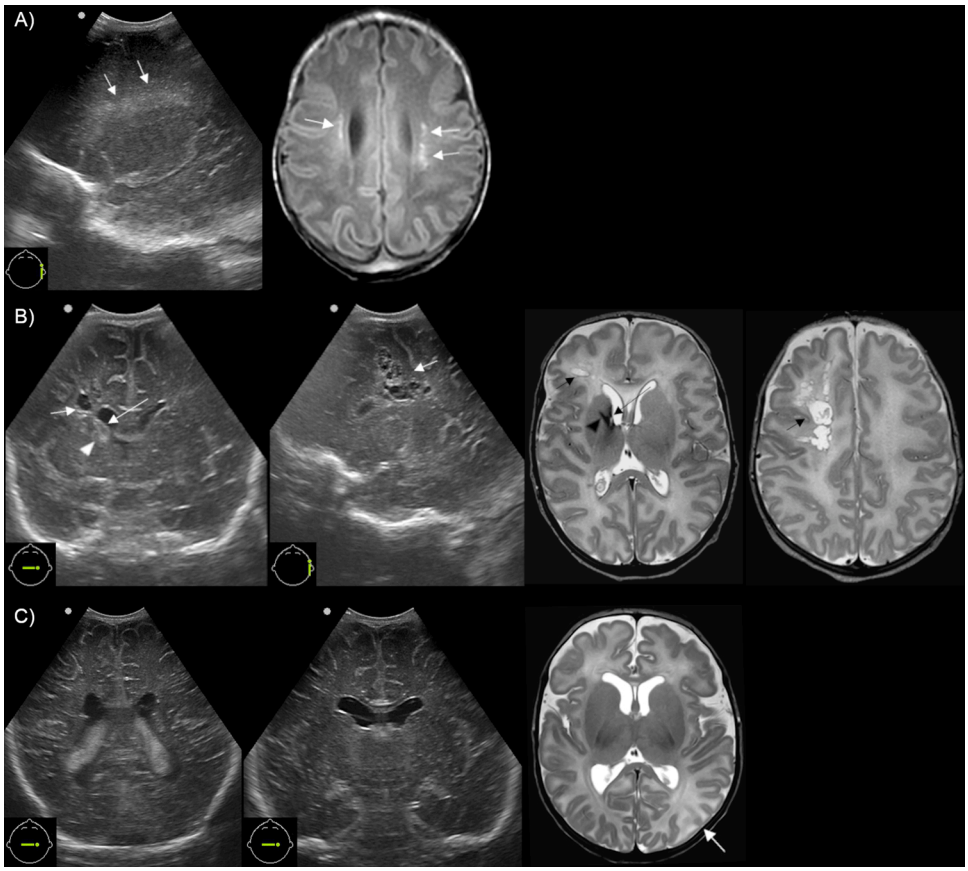

Fig. 3. Cases with moderate-severe brain lesions.
A) cUS and MRI of an infant (GA 32^{+3} weeks) scanned at PMA 38^{+6} weeks with sagittal cUS-TEA showing inhomogeneous echogenicity (arrows) and T1-weighted MRI showing clusters of PWML (arrows); B) Coronal and sagittal view of TEA-cUS and T2-weighted transverse MRI of an infant (GA 33^{+4} weeks) performed at PMA 39^{+6} weeks showing remnants of IVH (long arrow) with cystic sequelae of PHVI (short arrow) and focal echogenicity in the caudate nucleus (arrowhead), corresponding with abnormal signal intensity on MRI (long arrow). C) Coronal view of TEA-cUS and transverse MRI of an infant (GA 35^{+6} weeks) performed at PMA 42^{+5} weeks. TEA-cUS shows moderate-severe ex-vacuo dilatation (ventricular index > 15 mm), but no clear signs of a posterior cerebral arterial infarction. On the transverse T2-weighted MRI a high intensity signal and some loss of grey-white matter differentiation (arrow) is seen in the territory of the left posterior cerebral artery, suggesting a posterior cerebral arterial infarction. No acute signs of diffusion restriction were seen on diffusion weighted imaging, we therefore assume the infarction developed around birth (> 1 week before the MRI was performed).

CI 16.1–30.0 %) had two or more brain lesion(s). In three infants (2.0 %; 95 % CI 0.5–6.3 %) lesions were considered moderate-severe (i.e. one with periventricular hemorrhagic infarction, two with ex-vacuo ventricular dilatation) (Fig. 3). The infant with periventricular hemorrhagic infarction had a normal early-cUS and unfortunately discharge-cUS was not performed due to an unexpected early discharge (one of the missed cases mentioned above).

3.2.4. Serial-cUS

Serial-cUS was available of 146 infants (36 infants with two and 110 infants with three cUS examinations). Of these, 43 infants (29.5 %; 95 % CI 22.4–37.7 %) had no, 59 (40.4 %; 95 % CI 32.5–48.9 %) had one, and 44 (30.1 %; 95 % CI 23.0–38.4 %) had two or more brain lesion(s). In three infants (2.1 %; 95 % CI 0.5–6.4 %) lesions were considered moderate-severe (the same as mentioned under TEA-cUS). Table 3 shows the incidences and characteristics of brain lesions on early-, discharge- and TEA-cUS.

3.2.5. MRI

In addition to the eighteen infants lost for TEA-visit, parents of 21 infants did not consent to MRI, resulting in 127 infants with MRI. PMA at MRI was 41.5 (SD 2.0) weeks. MRI quality was excellent in 102/127 infants. In 25/127 infants not all brain lesions (described in Table 1) could be scored due to movement artefacts or missing MRI sequences. SWI was available of 117/127 infants. The incidences of brain lesions including delayed brain maturation are shown in Table 4. Of 127 infants, 34 had no lesion (26.8 %; 95 % CI 19.5–35.5%), 43 (33.9 %; 95 % CI 25.9–42.9 %) had one, and 50 (39.4 %; 95 % CI 30.9–48.5 %) had two or more lesion(s). Fig. 4 shows examples of mild brain lesions including delayed brain maturation. Six infants (4.7 %; 95 % CI 1.9–10.4 %) had moderate-severe brain lesions (i.e. one periventricular hemorrhagic infarction, one posterior cerebral artery infarction and ex-vacuo ventricular dilatation, one isolated ex-vacuo dilatation, and three ≥ 6 PWML) (Fig. 3).

3.2.6. Comparison serial cUS and MRI per gestational age week

In infants born at 32 weeks' gestation we found the highest incidence of mild brain lesions on serial cUS and MRI, but differences with other GA groups were small and not significant ($p = 0.39$ and $p = 0.08$ respectively). Three out of the six moderate-severe lesions were seen in the 35 weeks GA group (Table 5).

3.2.7. Comparison cUS TEA and MRI per brain lesion

One hundred and twenty-seven infants had TEA-cUS and MRI. There were no significant differences between infants with and without MRI in number of brain lesions on early- ($p = 0.55$), TEA- ($p = 0.66$) or serial-cUS ($p = 0.92$). Table 4 shows whether brain lesions were found on both TEA-cUS and MRI, only/more on TEA-cUS or only/more on MRI.

In three infants, moderate-severe lesions were found on both TEA-cUS and MRI (periventricular hemorrhagic infarction in one, moderate-severe ex-vacuo ventricular dilatation in two). One of the infants with ex-vacuo dilatation also had an arterial infarction, which was missed on TEA-cUS (Fig. 3). Additionally, in three infants ≥ 6 PWML were detected with MRI.

Remnants of IVH were seen in four infants on TEA-cUS, and confirmed with SWI in three infants. In one infant with remnants of IVH on TEA-cUS, a small plexus hemorrhage was seen on MRI. In nine additional infants, hemorrhages undetected with cUS were encountered on MRI (remnants of IVH in five, choroid plexus hemorrhages in four infants; Fig. 5). Except for one infant, punctate CBH was only seen on MRI.

Inhomogeneous echogenicity was seen in 47/127 infants on serial-cUS. In 12/47 infants this was still present at TEA. At TEA-cUS this corresponded with diffuse white matter signal changes on MRI in 6/12

Table 3
Incidences of brain lesions on cUS.

Brain lesions		Early-cUS N = 164 n (%; 95 % CI)	Discharge-cUS N = 122 n (%; 95 % CI)	TEA-cUS N = 148 n (%; 95 % CI)
Hemorrhages				
IVH	Total	8 (4.9; 2.3–9.7)	10 (8.2; 4.2–14.9)	7 (4.7; 2.1–9.9)
	Grade I	6 (3.7; 1.5–8.2)	8 (6.6; 3.1–12.9)	6[a]
	Grade II	2 (1.2; 0.2–4.8)	2 (1.6; 0.3–6.4)	1[a]
	Grade III	0	0	0
Periventricular hemorrhagic infarction		0	0	1 (0.7; 0.04–4.3)
Post-hemorrhagic ventricular dilatation		0	0	0
Choroid plexus hemorrhage		0	0	0
CBH[‡] Punctate		0	0	1 (0.7; 0.04–4.2)
Limited		0	0	0
Extensive/Massive		0	0	0
Subdural hemorrhage		0	0	0
White matter				
Cystic white matter lesions		0	0	0
Inhomogeneous echogenicity		50 (30.5; 23.7–38.2)	23 (18.9; 12.6–27.2)	12 (8.1; 4.5–14.1)
Suspected PWML		NA	NA	7 (4.7 %; 2.1–9.9)
Infarction				
Arterial infarction		0	0	0
Deep gray matter lesions[‡]		0	0	1 (0.7; 0.04–4.3)
Small focal lesion		0	0	1 (0.7; 0.04–4.3)
Moderate-severe lesion		0	0	0
Miscellaneous				
Choroid plexus cyst ≥ 6 mm		1 (0.6; 0.03–3.9)	1 (0.8; 0.04–5.2)	3 (2.0; 0.5–6.3)
Germinolytic or subependymal cyst ≥ 6 mm		4 (2.4; 0.8–6.5)	4 (3.3; 1.1–8.7)	11 (7.4; 4.0–13.2)
Lenticulostriate vasculopathy[‡]		0	1 (0.8; 0.04–5.2)	1 (0.7; 0.04–4.3)
Signs suggestive of brain atrophy due to injury				
Ex-vacuo ventricular dilatation*				
Mild (13–15 mm)		NA	NA	34 (23.1; 16.8–30.9)
Moderate-severe (> 15 mm)		NA	NA	2 (1.4; 0.2–5.3)
Irregular shape of the lateral ventricles*		NA	NA	23 (15.6; 10.4–22.8)
Widened interhemispheric fissure*		NA	NA	24 (16.3; 10.9–23.5)

Percentages were adjusted for number of missing data.
CBH = cerebellar hemorrhage; IVH = intraventricular hemorrhage; NA = not assessable; PWML = punctate white matter lesions.
[a] Considered as 'remnants of IVH' at TEA. In one infant both (remmants of) IVH and a germinolytic cyst were present. [‡] CBH, echogenicity in the basal ganglia and/or thalami and lenticulostriate vasculopathy and could not be assessed due to poor imaging quality in 3 infants on early-cUS and in 1 infant on discharge-cUS. * Ex-vacuo ventricular dilatation, irregular shape of the lateral ventricles and widened interhemispheric fissure at TEA could not be determined in one infant due to poor imaging quality.

infants. Diffuse white matter signal changes were encountered in 21 additional infants without signs of inhomogeneous echogenicity on TEA-cUS. Fifteen of those had never experienced inhomogeneous echogenicity on serial cUS.

PWML were seen in 20 infants on MRI and suspected in seven on TEA-cUS (Fig. 5). Of these 20 infants, nine had inhomogeneous echogenicity on TEA-cUS. Fourteen of these 20 infants experienced inhomogeneous echogenicity on serial-cUS.

Choroid plexus cysts (> 6 mm) were seen on TEA-cUS in two infants, while not on MRI (Fig. 5). LSV was seen in one infant on TEA-cUS, but not on MRI. Signs suggestive of brain atrophy were more frequently seen on MRI.

4. Discussion

Performing cranial ultrasound (cUS) and magnetic resonance imaging (MRI) in a cohort of moderate-late preterm (MLPT) infants, has demonstrated a high incidence of brain lesions in this population. Most of these lesions were considered mild. Six infants (3.6 %) had moderate-severe brain lesions.

The incidences of moderate-severe lesions are comparable to those reported by others. Fumagalli et al. found venous and arterial infarction in respectively 0.17 % and 0.34 % in a cohort of 1172 late preterm infants (GA 34^{+0} -36^{+6} weeks) [9]. Walsh et al. found extensive/linear PWML in 10/199 (5 %) MLPT infants [30]. Our and their incidences were, as expected, much lower than those found in very preterm infants [12,19]. This is probably related to several factors: MLPT infants are generally vitally stable, the vast majority not needing respiratory support, and their brains are more mature and thus less vulnerable than the brains of very preterm infants [31].

The reported incidences of several types of hemorrhages in our MLPT cohort are different from incidences reported in very preterm and full-term cohorts. The incidence of (remnants of) IVH in our cohort was higher than that reported in full-term infants (range: 2.2 %–5.2 %) [32,33], but in contrast to very preterm infants, severe IVH was rare. None of the MLPT infants in our cohort experienced post-hemorrhagic ventricular dilatation. Contrary to the low incidence of IVH, the incidence of CBH (12.6 % in our cohort) was similar to reported incidences in very preterm populations [34]. Furthermore, subdural hemorrhage was not detected in our cohort, while this is the most often reported hemorrhage in otherwise healthy full-term infants [32,35]. These differences with very preterm and full-term infants underpin that MLPT infants should be seen as a different group.

White matter injury or signs suggestive of white matter injury were most frequently seen in our cohort. The incidence of inhomogeneous echogenicity was relatively high, respectively 30.5 % at early-cUS and 8.1 % at TEA-cUS. Fumagalli et al. reported an incidence of 19.6 % at early-cUS and 1.8 % at cUS performed five weeks after birth in a cohort of 1172 late preterm infants (GA 34^{+0} – 36^{+6} weeks) [9]. More than half of their cohort consisted of "more mature" infants born at GA 36^{+0} – 36^{+6} weeks. These "more mature" preterm infants were not included in our study, which may explain our higher incidence of inhomogeneous echogenicity. We also found a high incidence of diffuse white matter signal change on MRI. This was not previously reported for MLPT infants, while in very preterm infants it is frequently observed [12]. It is suggested that diffuse white matter signal changes may represent mild white matter injury or delayed white matter maturation [36]. However, neurodevelopmental consequences are unclear as available studies on

Table 4
Incidences of brain lesions including delayed maturation on TEA-cUS and MRI and comparison between both techniques.

Brain lesions	TEA-cUS (N = 127) n (%; 95 % CI)	MRI (N = 127) n (%; 95 % CI)	Both cUS and MRI	Only/ more on cUS	Only/ more on MRI
Hemorrhages					
Remnants of IVH‡	4 (3.2; 1.0–8.4)	8 (6.3; 3.0–12.4)	3	2	5
Periventricular hemorrhagic infarction	1 (0.8; 0.04–5.0)	1 (0.8; 0.04–5.0)	1	0	0
Post-hemorrhagic ventricular dilatation	0	0	0	0	0
Choroid plexus hemorrhage‡	0	5 (3.9; 1.5–9.4)	0	0	5
CBH Punctate	1 (0.8; 0.04–5.0)	16 (12.6; 7.6–19.9)	1	0	15
Limited	0	0	0	0	0
Extensive/Massive	0	0	0	0	0
White matter					
Cystic white matter lesions	0	0	0	0	0
Inhomogeneous echogenicity (cUS)/diffuse white matter signal changes (MRI)	12 (9.4)	27 (23.5; 16.3–32.5) *(N = 115)*	6	5	21
Total (suspected) PWML#	7 (5.6; 2.5–11.6)	20 (16.4; 10.5–24.4)			
< 6 PWML	NA	17 (13.9; 8.6–21.7)	7	0	13
≥ 6 PWML	NA *(N = 125)*	3 (2.5; 0.6–7.6) *(N = 122)*			
Infarction					
Arterial infarction	0	1 (0.8; 0.04–5.0)	0	0	1
Deep gray matter lesions¤	1 (0.8; 0.04–5.0)	1 (0.8; 0.04–5.0)	1	0	0
Small focal lesion	1 (0.8; 0.04–5.0)	1 (0.8; 0.04–5.0)	1	0	0
Moderate-severe lesion	0	0 *(N = 126)*	0	0	0
Miscellaneous					
Subdural hemorrhage	0	0	0	0	0
Choroid plexus cyst ≥ 6 mm	2 (1.6; 0.3–6.1)	0	0	2	0
Germinolytic or subependymal cyst ≥ 6 mm	10 (7.9; 4.1–14.4)	9 (7.1; 3.5–13.4)	8	2	1
Lenticulostriate vasculopathy	1 (0.8; 0.04–5.0)	0	0	1	0
Signs suggestive of brain atrophy due to injury					
Ex-vacuo ventricular dilatationβ					
Mild (13–15 mm)	30 (23.8; 16.9–32.4)	34 (28.8; 21.0–38.0)	20	7	14
Moderate-severe (> 15 mm)	2 (1.6; 0.3–6.2) *(N = 126)*	2 (1.7; 0.3–6.6) *(N = 118)*	2	0	0
Irregular shape of the lateral ventricles¤	22 (17.3; 11.4–25.3)	20 (15.9; 10.2–23.7) *(N = 126)*	15	7	5
Widened interhemispheric fissure¥	20 (15.9; 10.2–23.7) *(N = 126)*	29 (24.6; 17.3–33.5) *(N = 118)*	17	1	12
Delayed brain maturation* Total	NA	17 (14.5; 8.9–22.5) *(N = 117)*	NA	NA	17
Myelination of the posterior Unilateral	NA	6 (5.1; 2.1–11.3)	NA	NA	3
limb of internal capsule < 1/3* Bilateral	NA	5 (4.3; 1.6–10.2) *(N = 117)*	NA	NA	6
Delayed gyration	NA	6 (4.7; 1.9–10.4)	NA	NA	6

Percentages were adjusted for number of missing data.
‡ In one infant, remnants of IVH on cUS turned out to be a choroid plexus hemorrhage on MRI. MRI assessment of diffuse white matter signal changes was missing in 12 infants due to poor imaging quality. One of these infants had inhomogeneous echogenicity on TEA-cUS. # Assessment of suspected PWML was missing in 1 infant on cUS and in 5 infants on MRI due to poor imaging quality. ¤ MRI assessment of deep gray matter and irregular shape of the lateral ventricles was missing in 1 infant due to poor imaging quality. β cUS measurement was missing in 1 infant and MRI measurement was missing in 9 infants due to poor imaging quality. In three infants with mild ex-vacuo ventricular dilatation on cUS, the lateral ventricles could not be measured on MRI, due to missing MRI sequences. ¥ cUS measurement was missing in 1 infant, MRI measurement was missing in 9 infants due to poor imaging quality. Two infants with a widened interhemispheric fissure (> 3 mm) on cUS, had no coronal MRI to compare with.
*Missing in 10 infants due to poor imaging quality on MRI.
CBH = cerebellar hemorrhage; IVH = intraventricular hemorrhage; NA = not assessable; PWML = punctate white matter lesions.

the association with neurodevelopmental outcome are inconsistent [37].

Signs suggestive of brain atrophy due to injury, i.e. irregular shape of the lateral ventricles, ex-vacuo ventricular dilatation and a widened interhemispheric fissure, were frequently seen in our cohort. In very preterm infants these signs were associated with lower scores on neurodevelopmental outcome at preschool age [2,22]. It may thus also be of clinical relevance in MLPT infants. The same may be applicable to delayed myelination and/or gyration. Especially delayed myelination may be a sequel of white matter injury and thus be of clinical importance [31].

In agreement with previous studies, small hemorrhages such as remnants of small IVH, plexus hemorrhages and punctate CBH were more frequently detected by MRI than by cUS [12,38]. As expected, the incidence of PWML was higher on MRI. However, we suspected punctate lesions in the periventricular white matter on cUS in seven infants who had obvious PWML on MRI. Furthermore, of the 12 infants with inhomogeneous echogenicity at TEA-cUS, nine infants had PWML on MRI, suggesting that inhomogeneous PVE on cUS may represent PWML on MRI. In agreement with others [22,39], we have demonstrated that in some cases cUS does depict PWML, and that non-cystic white matter injury is not an exclusive MRI finding.

Strengths of our study are the serial cUS examinations, combining cUS and MRI around TEA, using SWI, and the special classification of - and attention for subtle lesions. However, some limitations also need to be addressed. Firstly, infants with a GA 36^{+0}–36^{+6} weeks were not included because they are not routinely admitted at our hospital. Secondly, some data is missing: not all infants underwent cUS-discharge or MRI, and some infants were lost to TEA-visit. Although we found no significant differences in the number of brain lesions between these infants and infants who underwent all cUS and MRI examinations, this may have influenced our results.

Our study is the first to give a detailed overview of brain lesions detected on both cUS and MRI in a cohort of MLPT infants and to compare cUS and MRI in this population. Frequently encountered brain lesions were signs suggestive of white matter injury, small hemorrhages and delayed brain maturation. The reported brain lesions were mainly mild and some may be considered incidental findings. The majority of

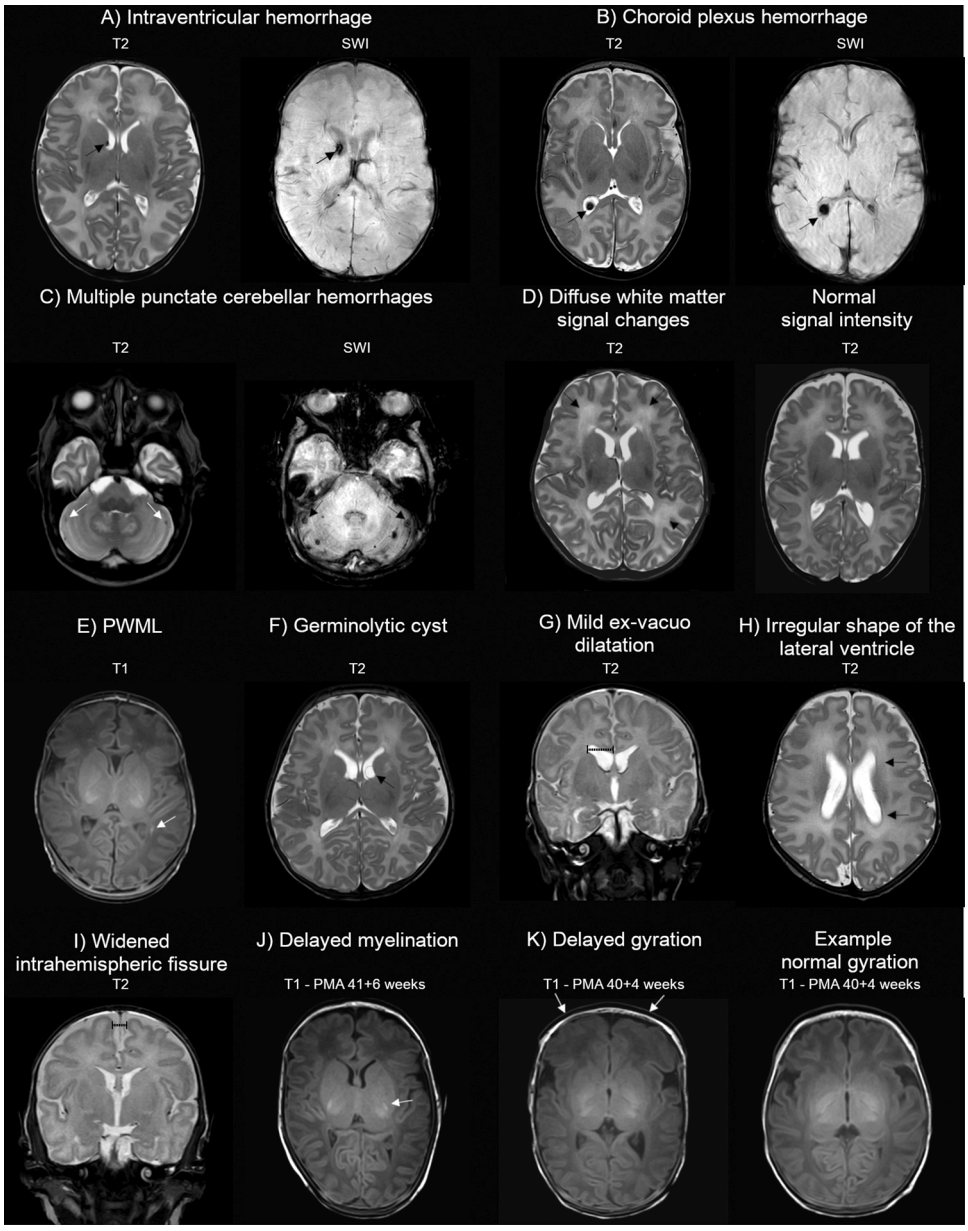

Fig. 4. MRI images of mild brain lesions in MLPT infants A) Subependymal hemorrhage/ intraventricular hemorrhage grade I (arrow); B) Choriod plexus hemorrhage (arrow); C) Multiple punctate cerebellar hemorrhages; D) Diffuse white matter signal changes (arrows), for comparison a T2-weighted image with normal signal intensity is added; E) Small PWML (arrow); F) Germynolitic cyst (> 6 mm) (arrow); G) Mild ex-vacuo dilatation, dashed line = measurement of ventricular index H) Irregular shape of the lateral ventricle (arrows); I) Widened interhemispheric fissure, dashed line = measurement of interhemispheric fissure. J) Delayed myelination of the posterior limb of the internal capsule (arrow) in an infant scanned at PMA 41 + 6 weeks; K) T1-weighted image showing delayed gyration, especially in the frontal lobes (arrows), as compared to normal gyration reference images of Barkovich and Mukherjee [29]. For comparison a T1-weighted image showing normal gyration in another infant, scanned at the same PMA.
PMA = postmenstrual age; SWI = susceptibility weigthed imaging

Table 5
Overview of infants with none, mild or moderate severe brain lesions on serial cUS and MRI per GA group.

GA group	32 weeks N = 27		33 weeks N = 38		34 weeks N = 48		35 weeks N = 53	
	Serial cUS	MRI	Serial cUS	MRI	Serial cUS	MRI	Serial cUS	MRI
None, n (%) (95 % CI)	7 (25.9 %) (11.8–46.6)	6 (22.2 %) (9.4–42.7)	9 (23.7 %) (12.0–40.6)	3 (7.9 %) (2.1–22.5)	18 (37.5 %) (24.3–52.7)	15 (31.3 %) (19.1–46.4)	9 (17.0 %) (8.5–30.3)	10 (18.9 %) (9.9–32.4)
Mild, n (%) (95 % CI)	17 (63.0 %) (42.5–79.9)	16 (59.3 %) (39.0–77.0)	22 (57.9 %) (12.0–40.6)	18 (47.4 %) (31.3–34.0)	27 (56.3 %) (41.3–70.2)	25 (52.1 %) (37.4–66.5)	33 (62.3 %) (47.9–74.9)	28 (52.8 %) (38.7–66.5)
Moderate – severe, n (%) (95 % CI)	0	1 (3.7 %) (0.2–20.8)	1 (2.6 %) (0.1–15.4)	1 (2.6 %) (0.1–15.4)	1 (2.1 %) (0.1–12.5)	1 (2.1 %) (0.1–12.5)	2 (3.8 %) (6.5–14.1)	3 (5.7 %) (1.5–16.6)
Missing data, n (%) (95 % CI)	3 (11.1 %) (2.9–3.0)	4 (14.8 %) (4.9–34.6)	6 (15.8 %) 6.6–31.9)	16 (42.1 %) (26.7–59.1)	2 (4.2 %) (0.7–15.4)	7 (14.6 %) (6.5–28.4)	9 (17.0 %) (8.5–30.3)	12 (22.6 %) (12.7–36.6)

these lesions may not influence neurodevelopmental outcome, but long-term follow-up is needed to assess the clinical relevance.

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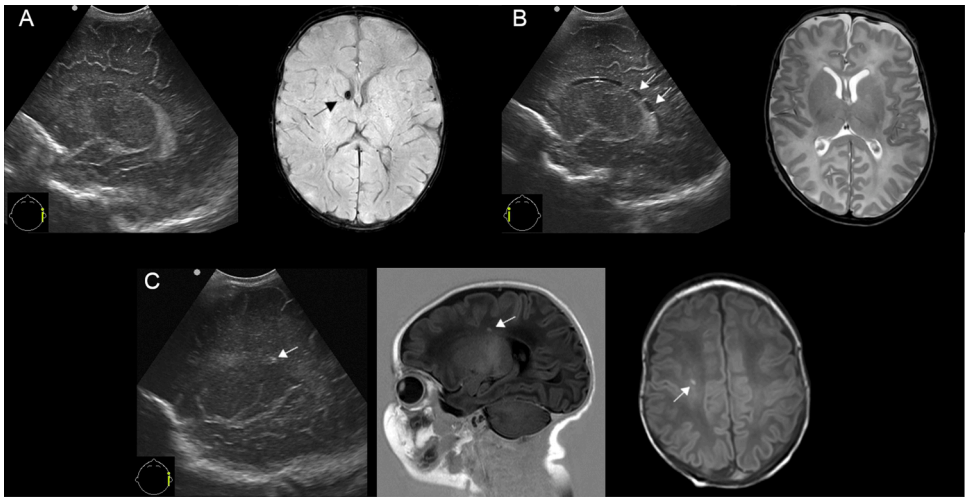

Fig. 5. Comparisons between cUS and MRI. A) Sagittal view of a TEA-cUS with no signs of IVH, while SWI shows a low signal intensity, representing remnants of an IVH. B) Several choroid plexus cysts are seen on the sagittal view of the TEA-cUS, while this is not depicted by T2-weighted MRI. C) A small punctate inhomogeneous lesion suspected for a PWML is seen in the frontal lobe on the sagittal view of the TEA-cUS, corresponding to a high signal on the sagittal inversion recovery T1-weighted image and transverse T1 weighted image.

and interpretation of the data, or in the preparation, review, approval of the manuscript, or decision to submit the manuscript for publication.

6. Declaration of Competing Interest

None.

CRediT authorship contribution statement

Vivian Boswinkel: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Martine F. Krüse-Ruijter:** Conceptualization, Methodology, Validation, Investigation, Data curation, Writing - review & editing, Project administration. **Jacqueline Nijboer - Oosterveld:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing. **Ingrid M. Nijholt:** Conceptualization, Methodology, Validation, Formal analysis, Writing - review & editing. **Mireille A. Edens:** Conceptualization, Methodology, Validation, Formal analysis, Writing - review & editing. **Susanne M. Mulder - de Tollenaer:** Conceptualization, Methodology, Writing - review & editing. **Mei-Nga Smit - Wu:** Conceptualization, Methodology, Writing - review & editing. **Martijn F. Boomsma:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision. **Linda S. de Vries:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision. **Gerda van Wezel - Meijler:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision.

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