Imaging the preterm infant's brain

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Imaging the preterm infant's brain

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Part I

Introduction

Chapter 1

General introduction and Outline of the thesis

General introduction

Preterm birth and the immature brain

Preterm birth is an important public health problem. In the Netherlands, each year approximately 14,000 infants are born prematurely at a gestational age (GA) of less than 37 weeks. This represents about 8.0% of all live births. Approximately 2,500 (1.4% of all live births in 2005) of these preterm infants are born very prematurely, at a GA of less than 32 weeks. The incidence of preterm birth has risen over the past decades and is still rising, partly because of the increase in some of the risk factors for preterm birth, including increased maternal age at first birth, more widespread application of fertility treatments, and more multiple pregnancies (1).

Important advances in the care of newborn infants during the past decades have greatly improved the survival and outcome of very preterm infants (GA < 32 weeks). Despite these advances, very preterm infants are still at risk of health problems, both during the neonatal period and later in life. One of the major complications of preterm birth is injury to the brain.

In very preterm infants, important maturational processes of the brain still need to take place after birth (2-9). Very preterm infants spend a long, for brain development critical, period in an incubator on a neonatal intensive- or high-care unit, where undesirable visual and auditory stimuli are superfluous and intense. The clinical condition of most of these infants is unstable, requiring intensive respiratory and/or circulatory support. In addition, they frequently undergo stressful and painful medical and nursing procedures. Many infants need analgesic and/or sedative medication. All these factors may influence and destabilize cerebral blood flow and oxygenation, and thereby increase the risk of brain injury and deviant growth and development.

Brain injury in very preterm infants forms an important problem, not only for the infants but also for the parents, health care and society in general. This is partly related to the large number of these infants who survive with serious neurodevelopmental disability, including cognitive, behavioral, attention or socialization deficits in 25-50% and major motor deficits in 5-10% (8-13). In many very preterm neonates neurological development is delayed and suboptimal in comparison with full-term neonates, even if their age is corrected for prematurity and/or without overt brain injury (14-20).

Neuro-imaging

Imaging the preterm brain during the neonatal period has become an essential, basic part of the modern care of very preterm infants. The two most commonly used and valuable techniques to image the newborn infant's brain are cranial ultrasonography (cUS) and magnetic resonance imaging (MRI). Computed tomography (CT) is nowadays only used under rare circumstances, especially as the radiation dose involved in CT scanning is significant and in most cases it has little or no additional diagnostic value compared to high-quality cUS.

Cranial ultrasonography

cUS was introduced into neonatology as a diagnostic tool in the late 1970s. In short, ultrasound makes use of high-frequency sound waves that are sent into the body by the transducer. The sound waves are reflected at sites of density changes between and within tissues, e.g. between brain white matter (WM) and cerebrospinal fluid. The reflections of the sound waves are returned to the transducer, and processed and transformed into images by the ultrasound machine and software.

Advances in technology over the past decades have improved the quality of cUS imaging, and it is now the preferred technique for imaging the newborn infant's brain throughout the neonatal period and thereafter until closure of the fontanels. cUS can be initiated at a very early stage, shortly after birth, and is the most readily available and easily repeatable tool. It is safe, non-invasive, and can be done at the bedside with little disturbance to the infant. In addition, it is reliable for detecting congenital and perinatally acquired anomalies of the brain and for following brain growth and development (8,14,21-24) (Chapters 2 and 3).

For detailed descriptions on the main aims of cUS imaging in newborn infants, performing a standard high-quality cUS examination through the anterior fontanel, use of additional acoustic windows, and recommendations on timing, see Chapters 2 and 3 of this thesis and the practical guide to 'Neonatal Cranial Ultrasonography' by van Wezel-Meijler (8).

Although the advantages of cUS are numerous and widely appreciated, it also has several limitations that need to be acknowledged. These include that evaluation of superficial structures is often difficult, it is not always possible to precisely define

abnormalities in the cerebellum and posterior fossa, more diffuse and subtle changes may not be well detected, myelination cannot be visualized, and image quality can be affected by small acoustic windows and fluid and/or thick black hair between the transducer and brain. Consequently, there are several indications for (additional) MR imaging in neonates (8) (Chapter 4).

Magnetic resonance imaging

MRI is a relatively new technique that has been used for medical imaging of the structure and function of the body for just over 30 years. It provides detailed images of the body, including its organs and tissues, in different planes. In short, MRI uses a powerful magnetic field to align the hydrogen protons in water molecules, of which the human body mainly consists, in the direction of the field. A radiofrequency pulse is then used to systematically alter the alignment of this magnetization, causing the hydrogen protons to produce a rotating magnetic field that is detectable by the MR scanner. This signal can be manipulated by additional magnetic field pulses to build up enough information to construct an image of (part of) the body.

Since MRI was first introduced into neonatology for imaging the newborn infant's brain, it has greatly contributed to our understanding of brain injury and maturation, and the prediction of neurodevelopmental outcome in both preterm and full-term neonates. Nowadays, MRI is becoming more widely available for clinical imaging, and higher field strength MR systems (1.5 and 3 Tesla), providing higher resolution images, are being used. Consequently, neonatal MR imaging has become increasingly important as a diagnostic tool (4,25-29) (Chapter 4).

MR imaging has several advantages over cUS imaging. MRI demonstrates maturational processes of the brain, and changes therein, in great detail, and is more sensitive for assessing the exact site and extent and the origin of lesions. It thereby helps to define pathological processes and contributes to accurate prediction of outcome in newborn infants. MRI may (additionally) detect abnormalities in areas that are difficult to visualize with cUS, and is generally considered better for detecting diffuse and subtle injury (3-8,24,30-37). Modern MRI techniques, including diffusion-weighted and diffusion-tensor imaging, allow assessment of both the macro- and microstructure of brain structures and tissues, quantification of brain growth and development, and very early

detection of hypoxic-ischaemic injury. In addition, quantitative volumetric analysis, either manually or (semi-)automatically, enable volume measurements of different structures and tissues, including the deep and cortical grey matter (GM), myelinated and unmyelinated WM, and cerebrospinal fluid spaces (32,38-47).

However, although safe, MRI is a more burdening neuro-imaging technique to the sick, very preterm infant than cUS; the infant needs to be transported to and from the MR unit and mostly cannot stay in its own incubator during the examination. This poses challenges regarding patient preparation, monitoring, temperature regulation and safety. Very early imaging, within a few hours of birth, is therefore difficult to realize and, unlike sequential cUS, repetitive MR examinations, particularly to follow brain maturation and the evolution of injury throughout the neonatal period, are undesirable in these vulnerable patients (Chapter 4). Neonatal MR imaging also poses challenges with regard to optimal timing and sequence optimization, partly because of the very high water content of the immature neonatal brain that decreases with ongoing maturation (4,8,29,35,48) (Chapter 4). In addition, some brain findings, including lenticulostriate vasculopathy (LSV), calcification, germinolytic cysts and abnormality of the choroid plexus, are better or only visualized by cUS (33,49).

For all these reasons, cUS and MRI are nowadays mostly considered to be complementary neuro-imaging tools. In very preterm infants, we rely on sequential cUS throughout the neonatal period and a single MRI examination, preferably performed around term equivalent age (TEA). In our hospital, all neonatal MRI examinations are performed according to standard protocols for imaging the newborn infant's brain, which can be adjusted in individual cases based on the infant's clinical course and cUS findings (8) (Chapter 4).

Brain growth and development

Important maturational processes of the brain, including gyration, myelination, cell migration, germinal matrix involution and increase in volume, weight and surface area, take place during the late fetal period and early infancy. As mentioned above, in very preterm infants these processes, normally almost completely (gyration, cell migration) or partially (myelination, brain growth) occurring antenatally, need to take place after birth (2-7).

The maturational processes can be visualized with modern neuro-imaging techniques and show as (age-)specific phenomena on cUS and MRI, changing continuously with age. To distinguish these processes from pathology, it is important for those performing cUS and MRI, and particularly for those assessing the images, to be well informed on normal brain growth and development, on phenomena reflecting maturational processes on cUS and MRI, and on (gestational) age-related patterns of brain injury. In very preterm neonates, this not only includes signal changes on cUS and MRI in brain tissues such as the WM and deep GM and changes in size and structure of the brain over time, but also alterations in brain size and structure in comparison with full-term neonates at equivalent postmenstrual age.

Gyration starts very early, in the second trimester of pregnancy, and continues in an orderly and predictable way, proceeding from the posterior to the anterior parts of the brain. In infants born extremely prematurely (24-26 weeks' GA), the surface of the brain is still very smooth and has a lissencephalic appearance. Gyration is normally completed around term age, when the brain surface has an almost mature appearance. Consequently, in very preterm infants the brain surface before TEA, as depicted by neuro-imaging, differs substantially from that around TEA (4,6,8-9,41,50-55). (Quantitative) MRI studies have shown that very preterm neonates around TEA have less complexity of cortical gyration and reduced cortical GM volumes compared with full-term neonates (38,43,45,47,52).

Like gyration, myelination starts during the second trimester of pregnancy and progresses in an orderly and predictable way, proceeding from the central to the peripheral parts and from the posterior to the anterior parts of the brain. The posterior brainstem is the first structure to become myelinated, while the anterior brainstem, internal capsule and cerebral hemispheres do not start to myelinate until the mid-third trimester. Myelination proceeds rapidly during the late fetal period and infancy, and continues until early adolescence. In very preterm infants, myelination largely takes place after birth (2-5,7-9,41,50,52-53,56). Although myelination is only depicted by MRI and not by cUS, myelination, cell migration and germinal matrix involution do result in changes in the WM that are shown on cUS (8,24).

The germinal matrix is a highly cellular and vascular structure producing neuroblasts and glioblasts. It lines the entire wall of the lateral and 3rd ventricles during early

gestation, and regresses from 24 to 26 weeks onwards. After 34 weeks' gestation, remnants only remain in the caudo-thalamic notch and temporal horns of the lateral ventricles. In very preterm infants before TEA, the germinal matrix can be detected on cUS as small areas of high echogenicity, mostly only around the caudo-thalamic notch, while on T_1- and T_2-weighted MR images it is clearly visible as a respectively high and low signal intensity zone in the ventricular wall (4,8-9,24,41,50,57).

From the first trimester of pregnancy onwards, neurons and glial cells migrate through the WM, from the germinal matrix towards the immature cortex. Neuronal cell migration is complete around 20 weeks' gestation, while migration of glial cells continues until late gestation (second and third trimester) (4,9,57-59). In very preterm infants during the early preterm period, glial cell migration is visible on conventional MR images as bands of alternating signal intensity (4,24,35,41,50,57-62). On cUS, this process may be represented by bilateral, symmetrical areas of subtle increased echogenicity in the frontal and parietal periventricular WM (8,24).

In fetuses and in very preterm infants during the early preterm period, the extracerebral spaces are often wide and the lateral ventricles wide and asymmetrical (predominantly left-sided and occipital horns). Due to brain growth and fluid loss during the first few postnatal days, these spaces gradually become smaller with age (4,8). However, in most preterm neonates around TEA, cerebrospinal fluid spaces are wider in comparison with full-term neonates (9,40,43,45,47,62).

Brain injury

As in very preterm infants brain maturation largely takes place after birth, their brains are vulnerable to injury and deviant growth and development. Brain injury is a major cause of neurological handicaps in very preterm infants (8-13). In addition, in many very preterm infants neurological development is suboptimal, even if corrected for prematurity and/or without overt brain injury (14-20). It can therefore be hypothesized that some forms of cerebral pathology are overlooked or not demonstrated by currently used imaging techniques, that brain growth and/or development is disturbed, and/or that certain phenomena are incorrectly considered normal because they frequently occur in this age-group (32,38,41,43,63).

In newborn infants, the pattern of brain injury varies, depending not only on the origin (i.e. traumatic, ischaemic, hypoglycaemic, inflammatory and/or haemorrhagic) and severity of the insult, but also on the postmenstrual age at the time of the insult. In very preterm infants, the periventricular WM and germinal matrix are the most vulnerable to injury during the perinatal period (9,64).

Early neuro-imaging studies in very preterm infants were mainly directed at the detection of peri- and intraventricular haemorrhage, periventricular haemorrhagic infarction, post-haemorrhagic ventricular dilatation and cystic periventricular leukomalacia (PVL) (27,65-74) (Chapter 2). Over the past decades, the incidence of these abnormalities has decreased and the distribution of WM injury has shifted from cystic and focal lesions to more diffuse and/or subtle changes (9,25,30-31,33,36-37,43,63,75-79). In very preterm infants around TEA, dilatation of the lateral ventricles, widening of extracerebral spaces and decreased complexity of gyration are nowadays frequently reported (9,38,40,42-43,45,47,62). In addition, cUS and MR imaging have improved considerably. Recent studies describing the incidence and evolution of various brain imaging findings in very preterm infants, as detected with modern, high-quality cUS and MRI, are limited.

Identification of risk factors for brain abnormalities in very preterm infants may contribute to appreciating the infants at risk and to early detection and intervention. It may even contribute to prevention of brain injury and neurological sequelae. Previous studies have described risk factors for different forms of injury occurring in the preterm infant's brain (31,77,80-95). However, neonatal care has advanced and the relation between more diffuse and/or subtle forms of WM injury and clinical data is still largely unknown. Recent studies on risk factors for brain abnormalities in very preterm infants throughout the neonatal period are scarce.

White matter

The WM of the cerebral hemispheres predominantly consists of fibres of the cortico-spinal tracts, including descending motor fibres, association fibres and optic radiations. It plays an important role in many functions, including motor control, cognition, behavioural and attention functions, and vision. Injury to and/or deviant growth and development of the WM may therefore lead to significant neurological sequelae, such as spastic motor disorders, cognitive deficits, behavioural and attention deficits, and visual impairment (9).

In the preterm infant's brain, the periventricular WM is largely unmyelinated and has a very high water content. Myelination of the WM starts in the mid-third trimester of pregnancy, and progresses at a high rate until the first months after term age. During the early preterm period, glial cells are still migrating through the WM. In addition, up to the first months after TEA, the volume of the WM increases considerably. Consequently, in preterm infants, the WM changes almost continuously from birth until early infancy (2-5,7-9,41,50,52-53,56-59).

MRI shows these maturational processes in the WM in detail (2-5,7-9,24,41,50,53,57-62). As cUS is the preferred and usually the initial technique for sequential imaging of the preterm infant's brain (8,14,21), it is important to define phenomena that represent normal maturational processes as visualized on cUS.

Bilateral, symmetrical areas of increased echogenicity are frequently encountered on cUS scans of apparently well preterm infants. The areas are mainly located in the frontal and parietal periventricular WM, are less echogenic than the choroid plexus, and do not evolve into obvious lesions. They usually have a linear or smoothly rounded shape. Some of the areas have been correlated anatomically with areas of glial cell migration in the preterm brain before TEA (8,24). It can therefore be hypothesized that these bilateral, symmetrical echogenic areas reflect maturational processes of the immature WM on cUS, comparable to areas of altered signal intensity in the periventricular WM, previously suggested to represent maturational processes, on MRI (4,24,41,50,57-58,60-62).

As mentioned above, in very preterm infants, the distribution of WM injury has shifted from cystic and focal lesions, such as cystic PVL and periventricular haemorrhagic infarction, to more diffuse and/or subtle changes, such as periventricular echodensities (PVE) on cUS and punctate WM lesions (PWML) and diffuse and excessive high signal intensity in the WM (DEHSI) on MRI. Recent studies have focused on the detection and implications of these latter WM changes (9,15,24,30-31,33-34,36-37,62-64,75-79,84,96-99).

Echodensities in the periventricular WM (PVE), also referred to as periventricular flaring, are frequently encountered on cUS scans of very preterm infants, and may represent ischaemic and/or inflammatory damage (9,22,64). PVE are transient, persisting for a variable period of time, and can subsequently resolve or evolve into cystic lesions

(22,24,36). When persisting for more than 7 days, PVE are considered the first stage of PVL (22). PVL often leads to neuronal/axonal injury, affecting not only the WM but also the deep and cortical GM, cerebellum and brainstem (9,64). In preterm infants, cystic forms of PVL have been associated with reduced WM and deep and cortical GM volumes and increased volumes of cerebrospinal fluid spaces around TEA (42-43,47). They often lead to neurological impairment and are mostly well detected by cUS (15,63,100). If long-lasting, milder forms of PVE, not evolving into cysts, may also be associated with suboptimal or deviant neurological development, especially when combined with changes in size and/or shape of lateral ventricles (15,19,33,76,97,99,101). It is important for clinicians to distinguish pathological PVE, especially those leading to neurological sequelae, from phenomena representing maturational processes in the immature WM on cUS (24,102).

Concerns have been raised that cUS is not a good tool for detecting subtle and/or diffuse WM injury, particularly as seen on MRI of very preterm infants around TEA, such as PWML and DEHSI (9,30-31,33,36,62-63,75-76,78-79,98,100,103). PWML show as small areas of high signal on T_1- and low signal on T_2-weighted MR images. They are mostly isolated or linearly in organization and located in the periventricular WM at the level of the centrum semiovale and/or adjacent to the optic radiation (31,75,98). DEHSI shows as areas of excessive high signal intensity diffusely distributed within the periventricular and/or subcortical WM on T_2-weighted MR images (33). These subtle and/or diffuse forms of WM injury have been associated with changes in diffusivity in the WM, with deviant brain growth and development, and with decreased WM and deep and cortical GM volumes and increased volumes of cerebrospinal fluid spaces (25,31,42-43,47,62,80,98). Several authors have attempted to find cUS-correlates for PWML and DEHSI, but so far these have not been established (30,33,36,63,75-76,78-79,100). Although the clinical importance of subtle and/or diffuse WM injury on MRI has not fully been elucidated, preterm infants with this finding seem to be at risk of motor and mental impairment (9,30-31,33,63-64,96-98). The low sensitivity of cUS for subtle and/or diffuse WM injury has prompted several authors to suggest a standard MRI examination in all very preterm infants (63,76,78,100). Recent studies on WM injury in very preterm infants using frequent, sequential high-quality cUS throughout the neonatal period and/or assessing not only changes within the WM but also other brain changes thought to be related to WM injury (such as ventricular dilatation) are limited.

Deep grey matter

The deep GM, i.e. the basal ganglia and thalami (BGT), is important in the guidance of signals to and from other brain structures; all information to and from the cortical GM is guided through and modulated by the thalamus (9,64). Consequently, the deep GM plays an important role in many functions, including motor control, cognition, affective functions and vision. Injury to and/or deviant growth and development of the deep GM may therefore lead to significant neurological sequelae, such as motor problems, cognitive deficits, affective deficits and visual impairment (9).

The basal ganglia consist of the caudate nucleus and lentiform nucleus, which is subdivided into the globus pallidus and putamen. The caudate nucleus, lentiform nucleus and thalamus are separated by the anterior and posterior limbs of the internal capsule (104). Myelination of the deep GM starts early, at the beginning of the third trimester of pregnancy. It then progresses rapidly throughout the different areas of the deep GM until 3 months post-term. Consequently, in preterm infants, the deep GM changes almost continuously from birth until maturation is complete (2,4-5,7,56).

MRI shows the maturational processes in the deep GM in detail, as has been described by several authors (2-5,7,61). However, albeit less detailed, cUS may also show maturational processes in these structures in very preterm infants (72,105). Although, so far, this has received little attention, it is important to define phenomena that represent normal maturational processes of the immature deep GM as visualized on cUS in very preterm infants, and to distinguish these from pathological processes.

Echogenicity of the BGT region (EG-BGT) is frequently encountered on cUS scans of very preterm infants and fetuses. EG-BGT is mostly seen as bilateral, subtle and diffusely increased echogenicity in the BGT region in comparison with surrounding tissue. Its origin and clinical significance in both preterm infants and fetuses are largely unclear (72,105-106). It can be hypothesized that EG-BGT, like the bilateral, symmetrical echogenic areas in the frontal and parietal periventricular WM mentioned above (24,102), represents a normal maturational phenomenon of the immature deep GM. However, like mostly more distinct, demarcated and often more inhomogeneous echodensities in the BGT in (near) full-term neonates (107-109), it may also reflect ischaemic and/or inflammatory damage and be of clinical importance.

Injury to the deep GM seems relatively infrequent in very preterm infants. The main forms of injury to the BGT include localized lesions that are unilateral or bilateral and mostly reflect infarction of the lenticulostriate branches of the middle cerebral artery and haemorrhage. They have been associated with suboptimal neurodevelopmental outcome (19,110-114). The incidence of these focal lesions in preterm infants seems low, with incidences reported up to 5% for cUS and up to 8% for MRI, and they appear to resolve before TEA (19,31,33,105-106,111,115-117).

Another, more frequent localized finding in the deep GM of very preterm infants is LSV. LSV is depicted by cUS as an unilateral or bilateral punctate, linear or branching echogenic structure in the distribution of the thalamo-striatal vessels. It has been associated with a wide variety of clinical conditions of the fetus and neonate, including congenital (e.g. TORCH) and acquired neonatal infections, chromosomal abnormalities, congenital heart disease, other congenital malformations, hypoxic-ischaemic events, and metabolic disorders (23,49,118-135). In addition, it occurs more often in infants of multiple pregnancies, particularly monochorionic twin pregnancies, than of singleton pregnancies and in full-term neonates than in preterm neonates (123,126,136-138). However, the incidence, aetiology and clinical significance of LSV in very preterm infants are largely unclear, and so far no MRI-correlate has been established (121,123,127).

Finally, recent studies have described visually and quantitatively assessed reductions in deep GM volumes in preterm neonates around TEA in comparison with full-term neonates, being more prominent in case of WM injury (31,39,43,46,64,115,139-141). However, neuro-imaging data on growth and development of the deep GM, and their relation with WM injury, in very preterm infants are limited (43,46,115).

Outline of the thesis

The general aim of this thesis is to study and describe brain imaging findings in very preterm infants, including normal maturational phenomena as well as pathological changes, using modern, high-quality imaging techniques.

This thesis reports the results of 11 reviews and original studies on neuro-imaging in (very preterm) neonates and is divided into six parts. Except for the study in Chapter

7, which was performed at the Hammersmith Hospital, London (United Kingdom), all studies were performed at the tertiary neonatal referral centre of the Leiden University Medical Center, Leiden (the Netherlands), and restricted to the population of infants born very prematurely (GA < 32 weeks). We selected this population as very preterm infants are the most at risk of experiencing brain injury, and are a relatively homogeneous group with respect to the occurrence of brain injury and severity of illness. Besides the studies reported in Chapters 8 and 10, all studies had a prospective design and were performed in large (consecutive) cohorts of very preterm infants.

Part II reviews the techniques used to image and follow the newborn infant's brain during the neonatal period.
Chapters 2 and 3 discuss our experience on neonatal cUS imaging and address issues on technical aspects, appropriate timing and protocols, diagnostic accuracy, safety, and optimizing its performance.
Chapter 4 discusses our experience on neonatal MR imaging and addresses its indications, technical aspects and sequences, appropriate timing and protocols, safety, and patient preparation and transportation.

Part III gives an overview of brain imaging findings in very preterm infants.
Chapter 5 describes the incidence and evolution of brain imaging findings, assessed with frequent, sequential cUS throughout the neonatal period and MRI around TEA. The accuracy of both techniques is compared for findings seen around TEA.
Chapter 6 reports the relation between frequent and/or clinically relevant brain imaging findings during the early neonatal period and around TEA and several potential perinatal risk factors. It is evaluated whether risk factors have changed over recent decades.

Part IV focuses on imaging of the WM in very preterm infants.
Chapter 7 describes the incidence and origin of bilateral, symmetrical and subtle echogenic areas in the frontal and parietal periventricular WM, frequently seen on cUS scans of apparently well preterm infants. cUS scans are compared with contemporaneous T_2-weighted MR images to identify MR-correlates for these cUS phenomena.

Chapter 8 assesses the value of sequential, neonatal cUS and MRI within the first 3 months after birth for detecting WM changes, and for predicting short-term neurodevelopmental outcome based on WM changes.
Chapter 9 evaluates the reliability of a classification system for grading WM injury, based on a combination of findings in the WM and abnormality of lateral ventricles on frequent, sequential cUS throughout the neonatal period, using a MRI classification system as reference standard.

Part V focuses on imaging of the deep GM in very preterm infants.
Chapter 10 assesses the incidence, clinical significance and origin of bilateral, subtle and diffusely increased echogenicity in the basal ganglia and thalami (EG-BGT), frequently seen on cUS scans of very preterm infants. EG-BGT is related to findings in the deep GM on MRI and to short-term neurological outcome.
Chapter 11 systematically describes imaging findings of the deep GM, and their relation with age and WM injury, assessed with sequential, neonatal cUS and MRI around TEA. The incidence and characteristics of EG-BGT and its relation with other brain imaging findings and quantitative measurements of the deep GM are studied. Additionally, the relation between quantitative measurements of the deep GM, indicative of growth and development, and age and WM injury is assessed.
Chapter 12 studies the incidence, evolution and clinical significance of LSV, as seen on frequent, sequential cUS throughout the neonatal period. LSV is related to perinatal clinical parameters, previously associated with brain injury in preterm infants, and to findings in the deep GM on MRI.

Part VI
Chapter 13 gives an overview of the main findings and conclusions of the reviews and original studies reported in this thesis, and discusses future perspectives and proposals for further research.
A summary in English is presented in **Chapter 14**, and a summary in Dutch in **Chapter 15**.

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Part II

Neuro-imaging techniques

Chapter 2

Using cerebral ultrasound effectively in the newborn infant

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Abstract

Cranial ultrasound is the most available and easily repeatable technique for imaging the neonatal brain. Its quality and diagnostic accuracy depends on various factors; the suitability of the ultrasound machine for neonatal cranial work, the use of optimal settings and probes, appropriate scanning protocols, the use of a variety of acoustic windows and, not least, the scanning experience of the examiner. Knowledge of normal anatomy and the echogenicities of different tissues in normal and pathological situations as well as familiarity with the physiological and pathological processes likely to be encountered is vital. This paper assesses the value and appropriate use, safety and diagnostic accuracy of modern, high-quality ultrasound in evaluating the brain of the preterm and term-born infant. Issues of concern regarding teaching, supervision and experience of the examiner are also addressed.

Introduction

Cranial ultrasound (cUS) is the most readily available and easily repeatable technique for imaging the neonatal brain. In contrast to other neuro-imaging tools such as magnetic resonance imaging (MRI) and computed tomography (CT), it can be done bedside with little disturbance to the infant. Neonatal cUS has been used for over 25 years and early studies on intraventricular (IVH) and parenchymal haemorrhage (HPI), post-haemorrhagic ventricular dilatation and cystic periventricular leukomalacia (PVL) have helped greatly our understanding of risk factors for neurodevelopmental abnormalities. Advances in technology have improved the quality of cUS imaging such that it can be a reliable tool for following brain development and showing the most frequently occurring forms of cerebral injury in the preterm and term-born infant brain. The range of cUS diagnoses has increased with the recognition of more subtle patterns of injury and the appreciation of features suggestive of developmental, metabolic and infectious disorders.

In recent years concerns have been raised that cUS is not able to detect more subtle abnormality in the preterm infant (1-4) and that it is not reliable for detecting lesions in the term infant with hypoxic-ischaemic encephalopathy (HIE) and focal infarction. The arrival of MRI with its multislice coverage of the whole brain and large range of sequences has led a very negative press as far as cUS is concerned. This negativity is not well supported by comparative studies where both techniques receive the same time and expertise regarding image acquisition and analysis (5-6).

The quality of cUS imaging and its diagnostic accuracy, as with any other imaging technique, depends on many factors. These include not only the suitability of the equipment for neonatal cranial work and the use of appropriate settings and probes, but also scanning at appropriate times depending on the pathology being sought, the use of different acoustic windows and not least the experience and expertise of the examiner.

This review assesses the value of appropriate timing of modern, high-quality cUS in evaluating both the preterm and term-born infant brain and highlights the current areas of emphasis in this important field of neonatal medicine.

Scanning protocols

There are some technical guidelines on scanning quality and image acquisition (7) but there is no universal agreement about optimal timing for neonatal cUS. Scanning protocols vary considerably between different neonatal units. This variability reflects the different purposes for scanning which include diagnosis, assessing aetiology and predicting outcome, and the population of infants examined, imaging skills and interest of the examiner, the availability of an ultrasound scanner on the neonatal unit and experienced staff, cost-effectiveness and potential hazards.

Preterm infants

Preterm infants have a high risk of hypoxic, haemorrhagic and inflammatory cerebral lesions, mainly IVH, HPI, cystic and non-cystic PVL and more diffuse white matter (WM) injury. Cerebellar abnormality is probably more common than realized (8-11). These findings are of clinical importance, making the use of appropriately timed screening protocols necessary.

Perlman et al. (12) recommended that preterm infants of birth weight < 1000 grams should be scanned between days 3 and 5, 10 and 14, around day 28 and pre-discharge; that those between 1000 and 1250 grams are scanned between days 3 and 5, day 28 and pre-discharge and those between 1250 and 1500 grams between days 3 and 5 and pre-discharge. This recommendation was based on data obtained using this protocol in about 250 preterm neonates. 65% of IVH was detected in the first week after birth, the remaining in the second or third week. Cystic PVL occurred in larger, more mature infants and was not always preceded by increased periventricular echogenicity (PVE). In two out of nine infants it was only detected on the pre-discharge scan. Ventriculomegaly was detected on the initial scan in 50% but only after day 28 in 33%. Significant lesions were detected on the pre-discharge examination in nine infants for the first time. In this study 13% of neonates died in the first 24 hours and were not scanned.

The American Academy of Neurology in 2001 reviewed neuro-imaging strategies for evaluating preterm and encephalopathic term-born infants (13) and recommended practice parameters for imaging of the newborn infant brain. They suggested that in preterm infants < 30 weeks' gestational age (GA), routine cUS should be performed

once between 7 and 14 days of age and optimally repeated between 36 and 40 weeks' postmenstrual age. They argued that with this strategy lesions that influence clinical care (e.g. IVH) and provide information about long-term outcome (e.g. PVL and ventriculomegaly) would be detected.

Both these scanning protocols give rise to concern. Neither recommends scanning on admission, which is essential for detecting lesions of antenatal onset (14). Their recommendations were based on their existing protocol and thus they do not know whether a more extensive protocol would have detected more abnormalities. The protocol by Ment et al. (13) is limited to preterm infants < 30 weeks' gestation with no recommendations for older preterm infants.

Pierrat et al. (15) used frequent cUS examinations and compared the evolution of localized and extensive cystic PVL with neurodevelopmental outcome. Localized cysts developed after the first month from birth in more than half of the infants and were often no longer visible around term equivalent age (TEA). De Vries et al. (16) in a tertiary unit setting, used high-resolution, sequential cUS in preterm infants for predicting cerebral palsy (CP). Infants were divided into those < 32 weeks' GA and those between 33 and 36 weeks' GA, and scanned weekly until discharge and once more at TEA. cUS detected abnormalities in the majority (94%) of children in whom CP was evident by 2 years. The risk for CP was the same for both groups of infants. Infants of 33 to 36 weeks' GA are a population of increasing neurodevelopmental concern that frequently are not scanned at all in the UK. In 29% of infants < 32 weeks' GA cystic PVL, the most predictive marker for CP, was only detected after 28 days. This data gives evidence that cUS can detect most lesions leading to CP if scanning is performed frequently until discharge and again around TEA and supports the need for scanning all gestation preterm infants admitted to a neonatal unit.

Evidence of suboptimal brain growth or atrophy is frequently present in preterm infants, particularly around TEA. Horsch et al. (17) related signs of brain atrophy (enlarged extracerebral spaces (ECS), widened interhemispheric fissure (IHF), reduced complexity of gyral folding) on sequential cUS of preterm infants with neurodevelopmental outcome at 3 years of age. Infants without major lesions but with signs of atrophy at discharge had significantly poorer neurocognitive outcomes. A recent paper by Anderson et al. (18) measuring the length of the corpus callosum and cerebellar vermis

has shown early changes that inform the timing of the effects of preterm birth on brain development – information that would be difficult to obtain by other imaging means in such a large group.

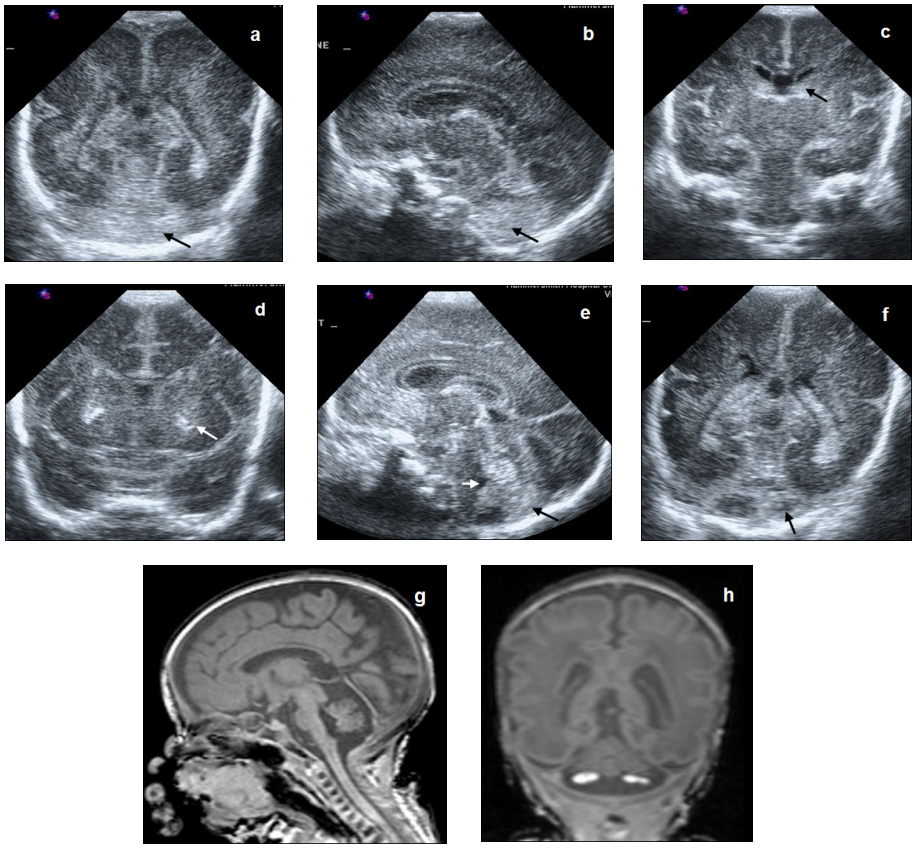
Based on these studies and the population admitted to our tertiary neonatal unit, we developed a scanning protocol for preterm infants (Table 1). All infants admitted to the unit have a cUS scan done by the paediatric specialist registrars (middle grade staff) and reviewed the next day on the ward round. The purpose of this admission scan is to ascertain that neurodevelopmental anatomy looks normal, there are no features to suggest congenital infection, metabolic disease or long-standing brain injury and also to identify recently evolving problems such as haemorrhage or WM echogenicity. Equally important is to note that the scan appears normal at this time.

Table 1. cUS scanning protocol for preterm infants used at the neonatal unit of the Hammersmith and Queen Charlotte's Hospital, London – a tertiary referral centre

	Gestational age at birth (weeks)			
	23-26	27-29	29-32	32-35
Postnatal age at which cUS should be performed	1, 2 and 3 days	Day 1	Day 1	Day 1
	1 week	1 week	1 week	1 week
	2 weeks	2 weeks		
	Weekly to 31 weeks	Weekly to 31 weeks	3 weeks	3 weeks
	Alternating weeks to 36 weeks	At 36 weeks		
	Term	Term	Term	Term

On the early cUS scans special attention should be paid to the presence of IVH and periventricular flaring, while the later cUS scans identify evolving parenchymal lesions (cystic PVL or HPI), the development and progression of post-haemorrhagic ventricular dilatation and signs of atrophy (enlarged lateral or 3rd ventricles especially without evidence of IVH, irregular ventricular margins, a thinned rim of WM around the lateral ventricles, a thin corpus callosum and widened IHF and ECS and changes in the cerebellum) (Figure 1). When assessing the significance of enlarged ventricles and ECS it is necessary to measure the head circumference (HC) and review the pattern of head growth. A small group of infants develop an enlarged ECS associated with increased HC centiles and these children are of less concern.

Figure 1. Series of ultrasound images from a 24-week intrauterine growth restricted infant. Parts a and b: Day 2 showing abnormal echogenicity and loss of definition of the cerebellum suggestive of haemorrhage (arrows); parts c and d: 4- to 6-week scans showing the development of echogenicity in the caudo-thalamic notch (c, arrow) and lenticulostriate vasculopathy (d, arrow); parts e and f: 8-week scans showing a widened 4th ventricle (short arrow) and persisting abnormal echogenicity behind the cerebellum (e, long arrow) and areas of low echogenicity within small cerebellar hemispheres (f, arrow).
MRI scans (parts g and h) at term equivalent age showing an obvious 4th ventricle, small vermis and cerebellar hemispheres with haemorrhage and also an increased interhemispheric fissure and widened extracerebral space (also seen on cUS, images not shown). All the abnormality that is seen on the MRI was seen on cUS. Additionally the cUS showed the development of echogenicity in the caudo-thalamic notch and the lenticulostriate vasculopathy not seen on the term MRI.



In addition to detecting lesions, assessing their site and extent is important for accurate prediction of outcome. In preterm infants, unilateral HPI located at the trigone is associated with a less favourable outcome than lesions in the fronto-parietal region (19). Multiple PVL cysts in the (parieto-)occipital but not the frontal regions are highly predictive of adverse motor outcome (20). Even when cUS is performed optimally, unexpected cases of CP occur. This may in part be due to cerebellar lesions (21) which can be difficult to detect or to subtle injury that has occurred antenatally; awareness of the importance of assessing the posterior fossa structures and scanning through acoustic windows other than the anterior fontanel may be needed (see below).

Stroke occurs in preterm infants (22-23), often affecting the central grey matter, and may only be detected by careful sequential scanning. It is more common in those with congenital heart disease and twins (particularly with twin-to-twin transfusion syndrome), a high risk group that should all have a postnatal cUS scan. It is also important to scan sequentially preterms who become sick or have unexpected postnatal events and also to scan prior to surgery in case of complications (Table 2). Unusual patterns of WM echogenicity and the appearance of cysts may reflect infections in the central nervous system. These include fungal infections, viruses (24-25) and a range of bacterial infections (26). These data apply both to preterm and term-born infants.

Table 2. Clinical indications for additional scans to a standard protocol (CSF, cerebrospinal fluid)

A sudden deterioration in clinical state
A sudden increase in the need for ventilatory support
Necrotizing enterocolitis
Repeated episodes of apneas and/or bradycardias
A sharp fall in haemoglobin level
Onset of seizures or change in neurological status
Increasing ventricular dilatation
Abnormal head growth
Before and after lumbar puncture and for drainage of CSF
Before and after surgery

Term-born infants

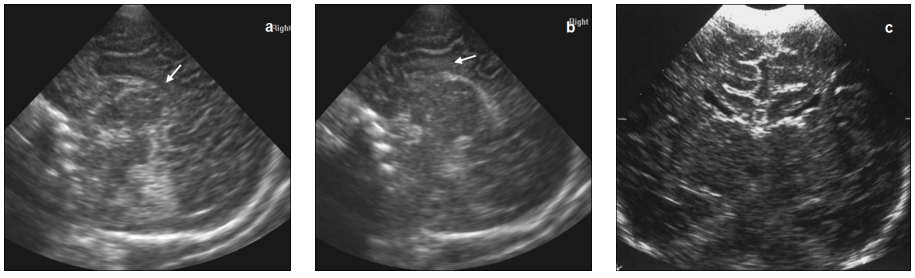
In term-born infants, HIE and stroke are still the major causes of, respectively, diffuse and focal brain injury and neurological morbidity.

Hypoxic-ischaemic encephalopathy

cUS is often considered not very helpful in detecting lesions occurring with HIE or predicting outcome, as the initial swelling makes focal lesions difficult to detect and precisely locate. The American Academy of Neurology (13) recommended that in encephalopathic term infants a CT should be performed to detect haemorrhagic lesions and if findings are inconclusive, MRI should be performed between days 2 and 8 to assess the location and extent of injury. They give no data supporting the diagnostic value of cUS in HIE.

cUS in term-born infants with suspected HIE has several roles. Scanning as part of the admission procedure identifies congenital structural cerebral abnormalities, detects evidence for long-standing or more recently established injury initiated prior to the onset of labour, and detects abnormalities characteristic of non-HIE causes of encephalopathy, e.g. a hypoplastic corpus callosum suggesting a diagnosis of non-ketotic hyperglycinaemia (Figure 2) and germinolytic cysts suggesting mitochondrial or peroxisomal disorders or congenital infection. This information is clearly important for early diagnosis and management. Additionally, with cUS, the evolution of intrapartum injury can be followed and apart from clinical implications this information is very important in medicolegal issues.

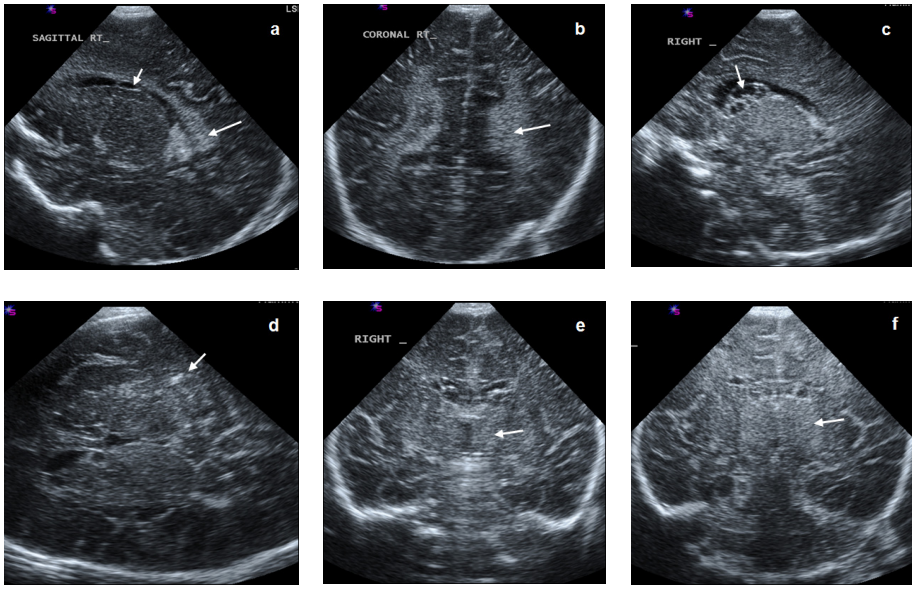
Figure 2. Hypoplastic corpus callosum (a, arrow) and mildly echogenic white matter (b, arrow) in an encephalopathic term infant with non-ketotic hyperglycinaemia. Typical widely spaced ventricles from another patient with non-ketotic hyperglycinaemia (c).



Our protocol for scanning infants with suspected HIE is that a scan should be performed on admission, at 24 hours after birth, days 3 to 4, days 7 and 14, and once again in clinic at 4 to 6 weeks.

The initial cUS, mainly performed to exclude other causes of encephalopathy, by identifying any abnormal anatomy, evidence for established damage (e.g. presence of calcium, marked echogenicity and parenchymal echolucency), lenticulostriate vasculopathy, germinal matrix cysts, diffuse WM echogenicity (Figure 3) or signs of recent haemorrhage. In our experience, haemorrhage is well seen on cUS and the need for CT is restricted to infants with a traumatic assisted delivery, where a midline shift is seen on cUS and neurological intervention is considered. Data from Eken et al. (27) show that the majority of cUS scans in the first 6 hours are normal in HIE but if they are already abnormal the outcome is poor.

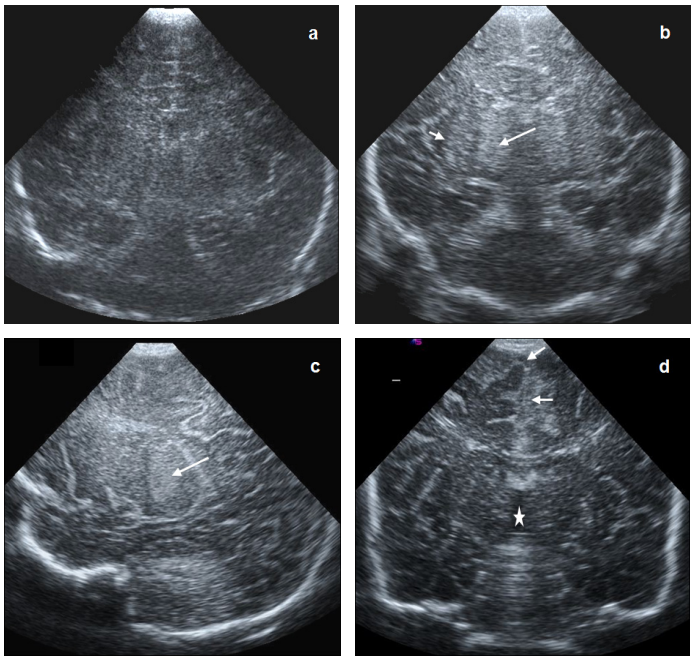
Figure 3. Term infant with evidence of acute asphyxia, retroplacental clot and severe encephalopathy. Initial cUS scans showed small germinolytic cysts (a, short arrow) and an unusual pattern of periventricular white matter echogenicity (a and b, long arrows). Scans at 10 days show enlarging cysts (c, arrow), and specks of calcification (shown on the axial view taken via the mastoid window) (d, arrow). Evolving acute lesions typical of hypoxic-ischaemia particularly to the basal ganglia are seen in parts e and f (arrows). There was a history of an acute gastro-intestinal illness associated with eating uncooked foods in France at 33 weeks' gestational age. No evidence of a viral or metabolic disorder was confirmed; the clinical course is that of a dystonic spastic quadriplegia consistent with the basal ganglia lesions seen in parts e and f.



Acute changes on cUS suggestive of HIE may include diffuse brain swelling on days 1 to 2 (Figure 4, part a), though for infants with only a relatively short hypoxic insult swelling may not be seen. There follows a loss of normal tissue differentiation and increasing echogenicity of basal ganglia (BG) and thalami and WM over the next 3 to 4 days. The cortex often appears very echolucent compared to the adjacent hyperechogenic WM and sulci (Figure 4, part c) in the first days but later may become hyperechogenic if severely damaged (Figure 4, part b). BG and thalamic echogenicity typical of an acute hypoxic-ischaemic insult is usually bilateral, increases daily and has a characteristic appearance (Figure 4, parts b and c). Generalized bilateral WM echogenicity is suggestive of a more long-standing subacute insult; both central grey matter and WM are involved in more severe acute or mixed insults when additionally the cortex appears abnormal. Milder changes can be subtle and are often not seen before 7 days after the insult. With severe widespread injury, the WM becomes increasingly echogenic and then breaks down into cysts. In a recent study by our own group reviewing sequential early cUS of 139 term-born infants with mild-severe HIE (unpublished data), we found that the presence of abnormal echogenicity in the BG and the visualization of the internal capsule, seen as an echolucent line running through the BG region (Figure 4, parts b and c), were highly predictive of an abnormal motor outcome.

Late cUS findings after focal BG lesions include persisting echogenicity in the deep grey matter and dilatation of the 3rd ventricle, signs significant for motor outcome (Figure 4, part d). Widening of the IHF suggest poor hemispheric growth and is associated with poor cognitive outcome. These signs present on later scans are of concern despite apparent clinical improvement in the first few weeks after birth.

Figure 4. Part a (coronal cUS scan): Acute swelling with loss of grey-white matter differentiation. Parts b and c (coronal and parasagittal cUS scans, respectively): Evolving abnormality in the lentiform nucleus (short arrow) and the thalamus (long arrow) with a line of low signal indicating the site of the internal capsule. Part d (coronal cUS scan): Widening of the 3rd ventricle (asterisk), and enlargement of the interhemispheric fissure and the extracerebral space (arrows) at 6 weeks.

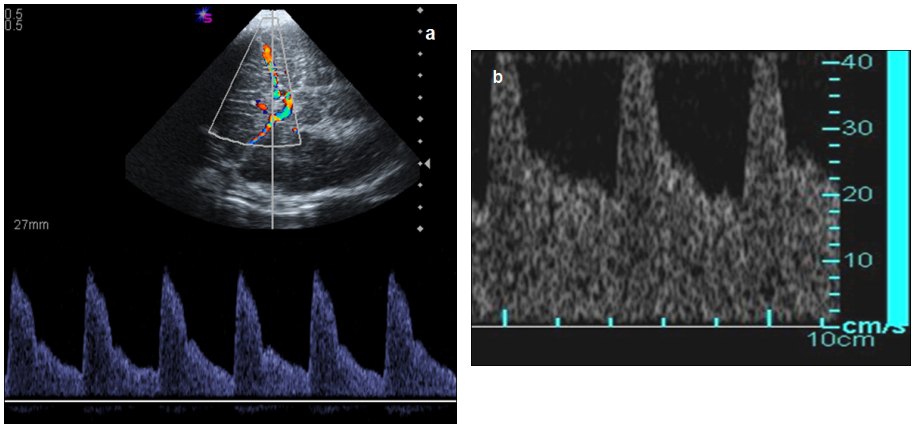


Doppler ultrasound gives useful information in HIE (28). Measurements can be made at the time of the cUS imaging; it is not critical which intracerebral vessel is used – usually the anterior cerebral artery via the anterior fontanel or the middle cerebral artery via the temporal window (Figure 5, part a). Two parameters can be assessed, the total flow velocity (CBFV) and the pulsatility index (PI) (confusingly referred to as the resistance index (RI) in obstetric papers). Normal values for the PI are between 0.65 and 0.85.

$$PI = \frac{\text{peak systolic velocity – the end-diastolic velocity}}{\text{peak systolic velocity}}$$

Abnormal values < 0.55 occur in severe HIE usually between days 2 and 4 after birth (Table 3) (Figure 5, part b). The outcome of infants with abnormal values in the first 6 hours after birth is very poor and suggests a prolonged insult either intrapartum or 1 to 2 days prior to delivery (27). The absolute flow velocities are more difficult to assess as they require the angle of insonation on the vessel to be near to zero and the values vary with the vessel measured on. However, high values carry a poor prognosis and are associated with a low PI.

Figure 5. Part a: View through the temporal window enabling visualization of the middle cerebral artery; below are normal Doppler spectra with a pulsatility index of 0.8. Part b: Abnormal Doppler spectra in hypoxic-ischaemic encephalopathy with a pulsatility index of 0.5.



Doppler measurements are useful in assessing venous flow especially in the straight sinus in suspected venous thrombosis (often associated with IVH or thalamic haemorrhage) (29) and to document abnormal velocity patterns in suspected vascular malformations.

We find cUS, both imaging and Doppler, of great use in excluding non-HIE diagnoses and in following the timing and evolution of acute injury. cUS together with electrophysiological data and clinical progress often allow early prognosis and appropriate clinical management in a situation where it is not possible to obtain a MRI scan. However, there is no doubt that a MRI in the first 1 to 3 weeks is superior for defining lesions and giving more precise long-term prognosis in HIE but the value of

cUS should not be underestimated in the first days after birth and for monitoring at 4 to 6 weeks when a normal cUS scan, clinical examination and head growth are good prognostic indicators.

Table 3. The predictive value of the pulsatility index and cerebral blood flow velocities for adverse neurological outcome in hypoxic-ischaemic encephalopathy in term-born infants (CBFV, cerebral blood flow velocities; PI, pulsatility index; PPV, positive predictive value)

Measurements made 2-4 days after birth - Levene et al. (28)		
	Abnormal CBFV	Low PI < 0.55
Sensitivity	57%	60%
Specificity	88%	63%
PPV	94%	83%

Early (< 6 hours) measurements - Eken et al. (27)		
	Sensitivity	Specificity
Ultrasound	42.1%	60%
Doppler	23.5%	100%

Infant with seizures

Term infants with early neonatal seizures who had fairly normal Apgar scores and were not acidotic at birth are most likely to have had a neonatal stroke; other more common diagnoses are parasagittal infarction and focal haemorrhage. Neonatal stroke has an estimated prevalence of at least 1 / 4000 live births. It is an important cause of hemiplegic CP and other neurological disabilities. cUS is often said to have a poor sensitivity for detecting focal infarction. We found that early cUS (days 1-3) showed abnormalities suggestive of infarction in 68% of cases and in 87% when cUS was performed after day 4 (5). Infants whose late cUS scans remained normal had relatively small, mostly posterior infarcts; none of these infants developed a hemiplegia. Thus, neonatal cUS does allow the detection of abnormality suggestive of focal ischaemic lesions, particularly those likely to lead to hemiplegia.

We perform cUS scans on infants presenting with seizures on admission and then at 2 days, 5 to 7 days and 2 weeks after the onset of seizures. Special attention should be paid to presence of subtle asymmetrical parenchymal echogenicity, a wedge-shaped echogenic area suggestive of middle cerebral artery (MCA) infarction (Figure 6), a

rounded very echogenic lesion suggestive of haemorrhage (Figure 7) and any abnormal structural development suggestive of a developmental abnormality. We suggest however that any infant with seizures a neonatal MRI examination is performed; precise detail of lesion size, location and prognosis are better defined on MRI (30-31) allowing more precise prognosis.

Figure 6. Full-term infant with neonatal seizures. Large wedge-shaped area of echogenicity on the right including the basal ganglia (arrows) is shown (a, b and c, parasagittal cUS scans), typical of a middle cerebral artery territory stroke. MRI confirms the diagnosis; T_1-weighted (d), diffusion-weighted (e) and follow-up (f) scans.

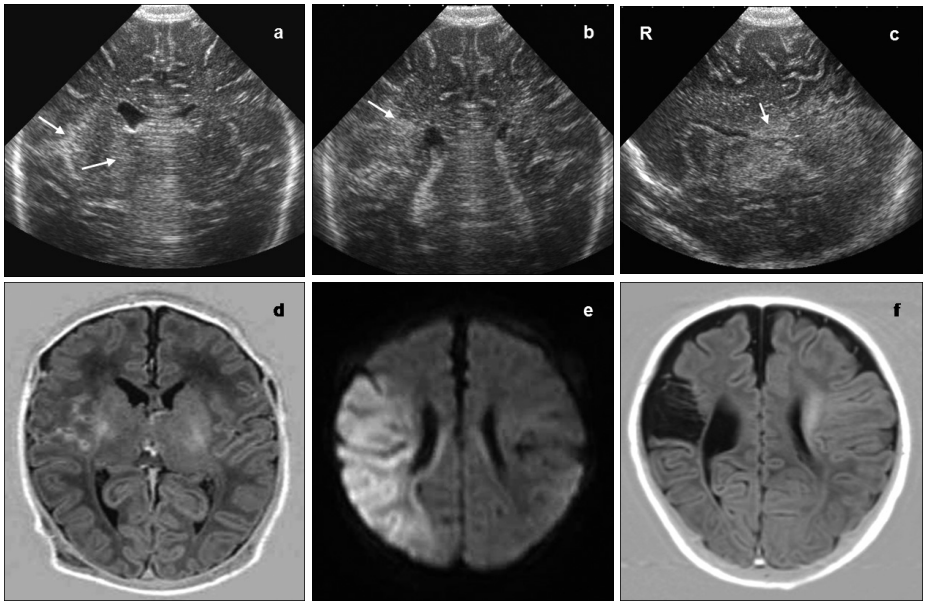
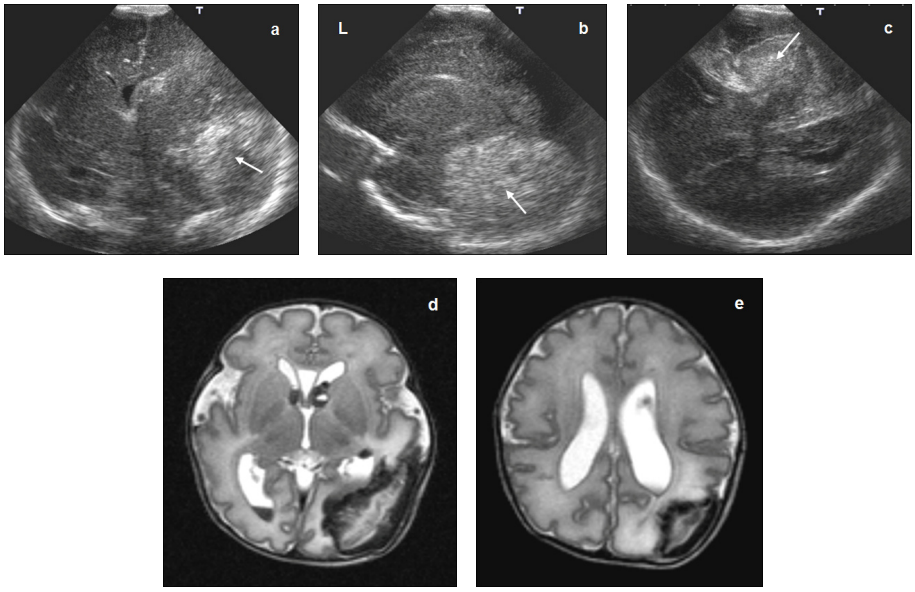


Figure 7. cUS in coronal (a), parasagittal (b) and mastoid view (c) from a 31-week infant with low platelets showing a large recent focal haematoma (long arrows) with a midline shift (a, short arrow). 20 cm^3 of blood was removed by subdural drainage. MRI (d and e) following tap.



The dysmorphic or floppy infant and those with metabolic disorders

Dysmorphic features and the floppy infant syndrome can be indicators of developmental disorders and congenital infection, genetic/chromosomal syndromes, congenital or acquired disorders of the central nervous system and neuromuscular and metabolic disorders (32). The diagnostic work up is often complex and recognition of characteristic cUS findings may aid the diagnostic process. When evaluating the cUS scans attention should be paid to signs of abnormal anatomy, calcification, germinolytic cysts and established injury; ventriculomegaly is common in myotonic dystrophy. As outlined in the section on HIE, term symptomatic infants with germinolytic cysts, lenticulostriate vasculopathy, unusual gyral patterns, abnormal appearances to the cerebellum, diffuse mild increase in WM echogenicity, hypoplasia of the corpus callosum should be investigated for metabolic disorders.

Acoustic windows

The standard acoustic window used for imaging the neonatal brain is the anterior fontanel. However, the cerebellum, brainstem and posterior subcortical WM may be poorly visualized using this approach. The detection of cerebellar abnormality via the anterior fontanel is complicated by the echogenic appearance of the tentorium and cerebellar vermis. The cerebellum is increasingly recognized as an important structure not only for motor control but also for cognitive and behavioural development. Abnormalities due to haemorrhage and infarction and poor growth (8-10) have gone under-recognized. Scanning through the posterior fontanel (junction of the lambdoid and sagittal sutures) and mastoid fontanels (junction of the posterior parietal, temporal and occipital bones) can help to detect lesions and structural malformations in these areas (Figure 7) (19,21,33-34). Imaging through the temporal window allows good views of the mesencephalon and brainstem.

Safety

Although sequential cUS is clearly very important, its potential hazards and burden for the often sick and unstable newborn infant should be kept in mind. These include extra handling, applying pressure and cold gel to the fontanel, the risk of dislodging tubes or lines or introducing infection from equipment that is not kept clean or from the operator. Most of these issues are relatively easy to prevent when appropriate safety and hygienic precautions are taken. All ultrasound equipment for use on a neonatal unit must be kept regularly cleaned, the probes wiped with a damp cloth. We also use hard surface wipes that contain some alcohol but these are not suitable for all probes and the manufacturers should be consulted.

There are also concerns about potential hazards of the ultrasound waves. To date no adverse effects have been shown to result from the sequential use of ultrasound in newborn infants or fetuses, although a slightly increased risk of delayed speech (35), left handedness (36) and intrauterine growth restriction (37) after multiple fetal examinations has been reported. However, ultrasound waves, especially when used

for colour Doppler imaging, may induce temperature elevations in human tissue over time that have the potential to cause damage. It is important to keep the duration of exposure as short as possible. The British Medical Ultrasound Society (BMUS) has published guidelines for diagnostic ultrasound (www.bmus.org). The power used should be kept within the guidelines with the default setting as low as possible compatible with obtaining diagnostic images.

Teaching and experience and accuracy of cUS

Many studies have cast doubt on the accuracy of cUS for detecting cerebral abnormalities predictive of unfavourable outcome. Some have suggested that only in 40-50% of preterm infants with CP (38-39), lesions were detectable on cUS though this contention is not supported by the study of de Vries et al. (14). Few studies have assessed the skills of the examiner and interpreter. In a study comparing cUS and MRI (4), no major lesions were missed on cUS (1-3) though subtle WM change on cUS and MRI were not consistent; the clinical significance of both observations is still not fully understood.

In a survey in the Greater London area in 2000, 56% of those interpreting neonatal cUS were middle grade neonatal registrars, only 44% of whom had any formal training in cUS (40). Assessing the abilities of the doctors in this survey, including consultants, to interpret important cerebral abnormalities on high-resolution cUS images, the mean accurate identification of abnormality was only 59%. In a study in the West Midlands evaluating the training of paediatric specialist registrars in cUS, 26% had never carried out supervised scans; 51% lacked confidence in performance and 57% in interpreting scans (41). Harris et al. (42) recently compared the cUS findings of three reviewers with previously reported rates of WM damage by six neonatal units in New Zealand. They showed that there was only moderate agreement between the reviewers' reports and those of the neonatal units and between the reviewers; the reviewers reported 3 to 6 times more WM damage.

These studies highlight the need for more widespread formal training in scanning techniques and that teaching of cerebral anatomy, the appearance of normal structures,

an understanding of normal growth as well as knowledge of the appearances and evolution of different pathologies are essential for those responsible for acquiring and interpreting cUS scans. These skills need to be assessed and competencies maintained. Increased collaboration between neonatologists, radiographers and radiologists with an interest in neonatal scanning and prognosis is needed in order to improve and rationalise the use of this valuable technique.

Conclusions

Current evidence is that cUS imaging using modern machines, probes, a variety of acoustic windows and sequential scanning at optimal times gives high-quality images that are diagnostically accurate. Issues of teaching, supervision and experience for both paediatric and radiological staff need to be addressed and collaboration between paediatric and radiology departments is needed to improve protocols, image quality and interpretation. Whilst MRI does have advantages over cUS and clear clinical indications, especially in the term-born infant, cUS facilitates early bedside diagnosis and monitoring of pathology in a way that is relatively easy and not disturbing and safe for the newborn infant. Awareness of the timing of injury and its manifestation on cUS are vital and routine scanning must be of high-quality with maximal coverage of the whole brain, and appropriate to the population of infants under review.

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Chapter 3

Neonatal cranial ultrasonography: how to optimize its performance

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Abstract

Cranial ultrasonography (cUS) is an excellent and non-invasive tool for brain imaging during the neonatal period. It is traditionally performed through the anterior fontanel. Although the advantages of cUS are numerous, there are also diagnostic limitations. Alternative imaging techniques including the use of different transducer types and frequencies and of additional acoustic windows can improve image quality and the diagnostic accuracy of cUS. This review will focus on techniques to be applied for optimizing the performance of cUS in the newborn infant.

Introduction

Cranial ultrasonography (cUS) is an essential part of the routine standard of care in high-risk neonates. Its major advantages are that it is safe, relatively inexpensive, and can be performed at the bedside, with little disturbance to the infant. It can be initiated at an early stage and repeated as often as necessary, making it the most suitable tool for serial imaging of the neonatal brain (1).

Since the introduction in the late 1970s, image quality has significantly improved and with optimal settings cUS has become a reliable tool for detecting congenital and acquired brain anomalies and assessing brain maturation in both preterm and full-term neonates.

Although the advantages of cUS are numerous, there are some limitations. cUS is routinely performed through the anterior fontanel (AF). If settings are optimized for neonatal brain imaging, this provides an excellent view of most supratentorial structures, but evaluation of the most peripheral and superficial structures located at the convexity of the cerebral hemispheres may remain difficult. Visualization of structures located far away from the transducer, such as the cerebellum, may also be less optimal (1).

Adapting focus and transducer frequency and using different transducers may overcome some of these limitations. Furthermore, the use of supplemental acoustic windows, such as the mastoid fontanels (MF), the posterior fontanel (PF) and the temporal windows (TW), enables a better view of structures located further away from the AF and a better visualization of the posterior fossa, brainstem, and the occipital regions of the brain (1-6).

This review will focus on different techniques that can optimize the performance of cUS in the newborn infant and covers the following issues:

1. General technical considerations
2. Standard cUS views through the AF
3. Adapting transducer frequency and focus
4. The use of different transducer types
5. The use of alternative acoustic windows
    a. MF
    b. PF
    c. TW

General technical considerations

Neonatal cUS should be performed at the bedside, by an experienced sonographer who is aware of the needs of the sick newborn infant and who is familiar with normal ultrasound anatomy, brain maturation, and frequently encountered anomalies of the newborn brain (1).

A high-resolution, real-time, 2D ultrasound machine should be equipped with special settings for the newborn infant´s brain and with a multifrequency transducer or different frequency transducers (5, 7.5 and 10 MHz). The transducer should be small enough to fit the AF of the (preterm) neonate.

It is essential to record the images for patient archives and teaching purposes. Images can be printed and kept with the patients' files, but facilities for centralized digital image storage are preferred.

Standard cUS views through the anterior fontanel

Images through the AF should be recorded in at least six coronal and five sagittal planes as described by van Wezel-Meijler (1). Anterior coronal views should include the frontal lobes and frontal horns of the lateral ventricles, anterior parts of the parietal and temporal lobes, the basal ganglia and the body of the lateral ventricles. Posterior coronal views should include posterior parts of the parietal and temporal lobes, the occipital lobes, the occipital horns of the ventricular system and the posterior fossa (7). The transducer can be angled laterally for visualization of superficial structures at the convexity of the cerebral hemispheres. A midline sagittal view should include the corpus callosum, cavum septum pellucidum, 3rd and 4th ventricle, aqueduct, pons, mesencephalon, cerebellar vermis and cisterna magna. Parasagittal views should include the right and left lateral ventricles, choroid plexus, periventricular white matter (WM), thalamus and basal ganglia. The angulation of the probe should be sufficient to include the Sylvian fissure and insula on each side (7).

In addition to the standard planes, the whole brain should be scanned to obtain an overview of its appearance and to allow detection of possible abnormalities. Any suspected lesion should be visualized in both planes (1).

Adapting transducer frequency and focus

In neonatal cUS, most brain structures are located close to the transducer. This allows the use of high frequency transducers with a high resolution. Usually, good quality images can be obtained using a transducer frequency of 7.5 MHz. This enables detailed visualization of the ventricular system and periventricular WM, while penetration is still sufficient for visualization of the deep grey matter structures. However, in some cases more detailed assessment of superficial structures located at the convexity of the cerebral hemispheres, including the subarachnoid spaces, cortex, and subcortical WM, is necessary. In these cases, additional scanning with a higher frequency of 10 MHz provides more detailed information. This is, for example, indicated in (near) term neonates with (suspected) hypoxic-ischaemic brain injury. While in preterm infants brain injury is often confined to the (peri)ventricular areas and/or WM, in (near) term infants the cortical and subcortical areas may be involved (8-9). Additional scanning with a higher frequency is also indicated in neonates with suspicion of focal infarction or WM injury in the peripheral regions of the brain (Figure 1). cUS is not the optimal imaging modality for the detection of extracerebral haemorrhage and abnormalities in cortical development, such as cortical dysplasia. However, when higher transducer frequencies are applied, such abnormalities can sometimes be detected. In very small premature neonates with a very small distance between the brain structures and the transducer, a frequency of 10 MHz can further optimize image quality.

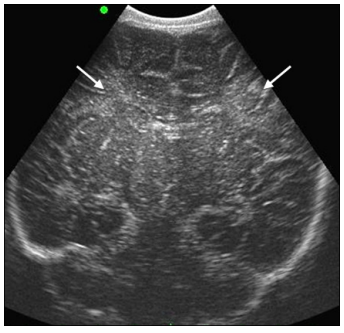
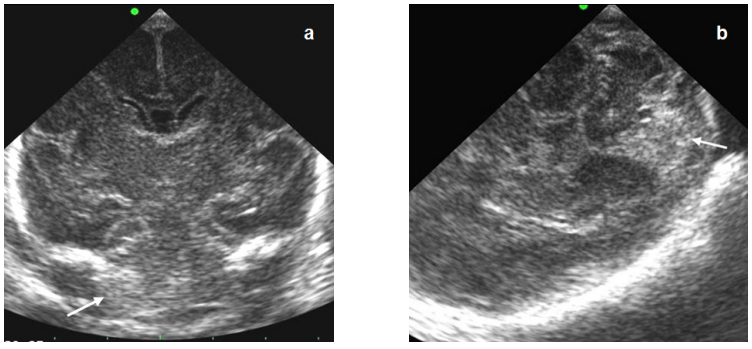


Figure 1. Coronal cUS scan at the level of the bodies of the lateral ventricles, performed through the anterior fontanel with a convex probe and transducer frequency of 10 MHz, showing increased echogenicity in the periventricular and subcortical white matter (arrows) in a term-born infant with parechovirus meningo-encephalitis.

A limitation of using a high frequency transducer is the loss of penetration. A lower transducer frequency allows better penetration and a better view of deeper structures such as the deep grey matter, the temporal lobes, and the posterior fossa. When abnormalities in these areas are suspected, additional scanning at a lower frequency of 5 MHz is helpful. In the (near) term-born asphyxiated infant this can improve visualization of the thalami and basal ganglia, areas that are vulnerable to hypoxic-ischaemic injury in this age group (8-9). In preterm infants, using a lower transducer frequency can help to detect cerebellar injury while scanning through the AF (Figure 2, part a) (10). In addition, in large full-term neonates and in infants with thick hair a transducer frequency of 5 MHz is often necessary to obtain enough penetration for sufficient image quality (1).

A disadvantage of using a lower transducer frequency is the loss of resolution. In addition to changing transducer frequency, the focus can be adapted to improve image quality. At the depth of the focus point, the ultrasound beam has the narrowest width. This improves resolution and allows more detailed images of the area of interest. Alternatively, two focus points can be applied, that can be adapted to the location of interest, allowing detailed visualization of the area between these points.

Figure 2. Coronal cUS scan at the level of the bodies of the lateral ventricles (a), performed through the anterior fontanel with a phased array probe and transducer frequency of 5 MHz in a preterm infant, showing an echodensity in the right cerebellar hemisphere (arrow) suspect for haemorrhage. Coronal cUS scan of the posterior fossa at a superior anterior level (b), performed through the left mastoid fontanel with a phased array probe and transducer frequency of 7.5 MHz in the same infant, clearly demonstrating haemorrhage in the right cerebellar hemisphere (arrow).



The use of different transducer types

Ultrasound transducers are available in many shapes and sizes. The length of the array of the transducer determines its number of crystal elements, the shape determines its field of view. The neonatal cUS transducer should have a small footprint to match the size of the AF. In small preterm infants a paediatric phased array (PA) transducer may be small enough to fit the AF, while still providing a sufficiently large acoustic window. The ultrasound beam starts at one point and diverges; therefore the far field resolution of this probe is limited. If the size of the fontanel allows the use of a larger convex (CV) transducer, this improves image quality as the size of the acoustic window becomes larger, enabling visualization of the more peripheral and superficial brain structures (Figure 3). In addition, a CV probe provides sharper images and enables better near field resolution. The ultrasound beam is divergent, leading to some loss of far field resolution. However, the far field resolution of the CV probe remains superior as compared to the PA probe (Figure 4). In infants with ventricular dilatation, the use of a CV probe with a larger scan area is essential. In these neonates, when using the PA probe, visualization of brain structures is limited as the small field of view is often taken up by the dilated ventricles (Figure 5).

In the linear array (LA) transducer, the crystal elements are arranged along a line, resulting in a parallel arrangement of the ultrasound beam. This provides optimal image quality. The very high scanning frequency is useful for Doppler sonography of the superior sagittal sinus and for detailed visualization of superficial structures. However, because of its large size, this transducer is not suitable for routine neonatal cUS procedures.

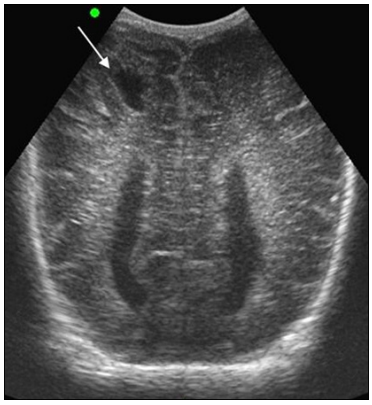


Figure 3. Coronal cUS scan at the level of the trigone of the lateral ventricles, performed through the anterior fontanel with a convex probe and transducer frequency of 7.5 MHz in a preterm infant, showing a large cystic lesion in the subcortical white matter on the right side (arrow).

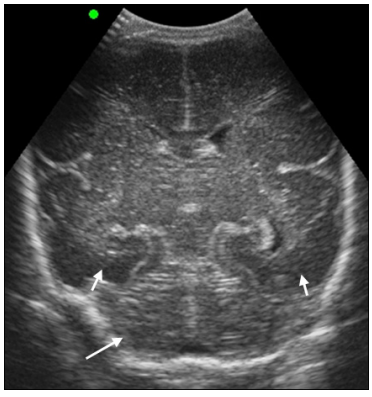


Figure 4. Normal coronal cUS (anterior fontanel view) in a preterm infant at the level of the bodies of the lateral ventricles, with transducer frequency set at 7.5 MHz. The far field resolution of the convex probe is sufficient to give a clear view of the temporal lobes (short arrows) and posterior fossa (long arrow).

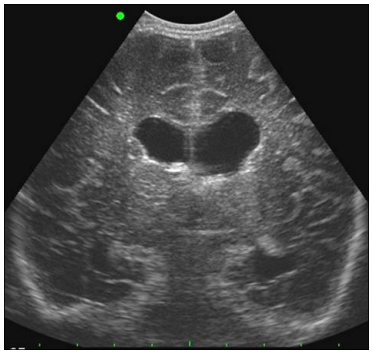


Figure 5. Coronal cUS scan at the level of the bodies of the lateral ventricles, performed through the anterior fontanel with a convex probe and transducer frequency of 10 MHz in a preterm infant with severe post-haemorrhagic ventricular dilatation, with sufficient size of the acoustic window to enable visualization of the periventricular white matter.

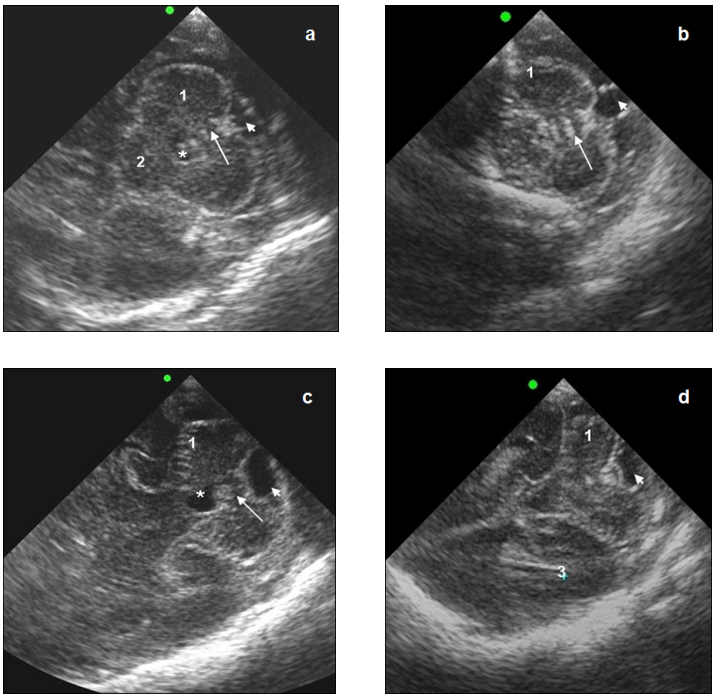
The use of alternative acoustic windows

Mastoid fontanels (MF)

The AF is an excellent acoustic cUS window to obtain good views of supratentorial structures, but visualization of infratentorial structures is less optimal because of their location further away from the transducer. Decreasing transducer frequency and directing focus on the posterior fossa can improve penetration but at the expense of resolution. In addition, the echogenic tentorium and vermis impede detailed imaging. When additionally using the MF (also known as posterolateral fontanel), the transducer is closer to the posterior fossa structures, allowing the use of higher transducer frequencies with better resolution. The structures can be approached at different angle, avoiding the echogenic tentorium.

The MF is located at the junction of the posterior parietal, temporal and occipital bones (1-3). The infant is positioned with the head to one side, and the transducer is placed over the MF, behind the helix of the ear, just above the tragus and then moved slightly, using real-time imaging until an appropriate view of the posterior fossa is obtained. Images can be performed in axial and coronal planes. Axial images are obtained with the transducer almost parallel to the orbitomeatal plane. Coronal views are obtained with the transducer placed along the coronal suture (1,4). Superior axial views include the cerebral peduncles, perimesencephalic and quadrigeminal cisterns, aqueduct and superior vermis. Middle axial views include the vermis, 4th ventricle, cerebellar hemispheres and cisterna magna. Inferior axial views include the inferior part of both cerebellar hemispheres and the inferior vermis (Figure 6, parts a and b). Superior anterior coronal views include the temporal horns, tentorium, 4th ventricle, vermis, cerebellar hemispheres and cisterna magna. Inferior posterior coronal views include the lateral ventricles, tentorium, cerebellar hemispheres and cisterna magna (Figure 6, parts c and d).

Figure 6. Middle (a) and inferior (b) axial cUS scans, and superior anterior (c) and inferior posterior (d) coronal cUS scans of the posterior fossa, performed through the mastoid fontanel with a phased array probe and transducer frequency of 7.5 MHz in a preterm infant, showing cerebellar hemispheres (1), pons (2), lateral ventricles (3), 4th ventricle (asterisk), vermis (long arrows) and cisterna magna (short arrows).



Intraventricular haemorrhage and post-haemorrhagic ventricular dilatation

Germinal matrix haemorrhage and intraventricular haemorrhage extending into the frontal horn and body of the lateral ventricle is usually well seen while using the AF, but haemorrhage extending into the 4th ventricle, cisterna magna and subdural spaces is more difficult to detect by this approach. The MF approach provides a better visualization of haemorrhage in these structures. This may have clinical consequences, as infants with posterior fossa haemorrhage are at increased risk of developing post-haemorrhagic ventricular dilatation and require intensive cUS examinations (11). In addition, scanning through the MF gives a better overview of the entire ventricular system and can help distinguishing between obstructive and communicating forms of hydrocephalus (Figure 7). In infants with unexplained ventricular dilatation, imaging

through the MF should be performed to look for posterior fossa abnormalities, including haemorrhage and posterior fossa malformations (1,4).

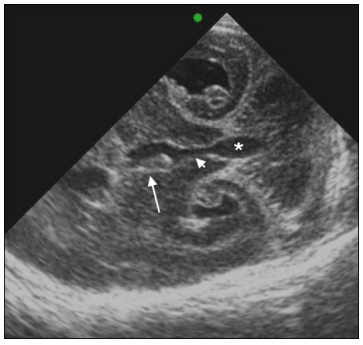


Figure 7. Coronal cUS scan of the posterior fossa, performed through the mastoid fontanel with a phased array probe and transducer frequency of 7.5 MHz in a preterm infant with post-haemorrhagic ventricular dilatation, showing blood residue in 3rd ventricle (long arrow), connecting via dilated aqueduct (short head) with a dilated 4th ventricle (asterisk).

Acquired cerebellar lesions

Cerebellar haemorrhage and abscesses are the most commonly described acquired cerebellar lesions in newborns. Cerebellar haemorrhage can occur in association with supratentorial haemorrhage, but can also be an isolated finding with a clinically silent presentation. The exact incidence is unknown, but recent neuro-imaging studies have shown that experienced sonographists can detect cerebellar haemorrhage in 19% of very preterm infants (birth weight < 750 grams) by using the MF approach (12). Merrill et al. showed that consistent imaging via the MF can demonstrate cerebellar haemorrhage missed by the AF approach (5). In infants in whom cerebellar haemorrhage is detected using the AF, the MF view usually improves visualization of the lesion (Figure 2, part b) (6). Reliable detection of cerebellar haemorrhage in preterm neonates is of importance, since it can have major impact on neurodevelopmental outcome (13-14).

Cerebellar abscesses can occur in both preterm and full-term neonates, secondary to systemic fungal or bacterial infection. Most cases have been studied by CT or MRI, but abscesses can also be detected by cUS, in particular when scanning is done through the MF (4). Early detection and appropriate treatment is of importance.

Congenital malformations

MF sonography is also a valuable tool for imaging of congenital posterior fossa anomalies, such as a mega cisterna magna, arachnoid cyst, cerebellar vermis agenesis or hypoplasia, cerebellar hypoplasia, and Dandy Walker malformation or variants (Figure 8).

However, one should be aware of a pitfall of MF fontanel ultrasonography: under certain angles the normal communication between the 4th ventricle and the cisterna magna via the foramina of Luschka and Magendie can give a false impression of inferior vermis agenesis. Imaging at different angles in axial and coronal planes through the MF, in combination with a good quality midline sagittal image obtained through the AF, is usually sufficient to distinguish between normal structures and a true Dandy Walker variant (6).

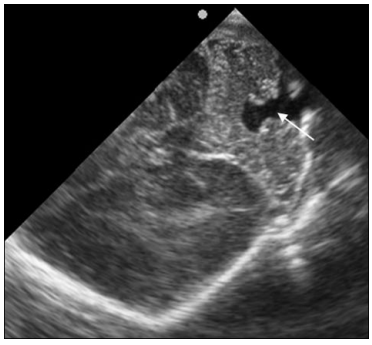


Figure 8. Coronal cUS scan of the posterior fossa, performed through the mastoid fontanel with a phased array probe and transducer frequency of 7.5 MHz in a preterm infant with a Dandy-Walker variant. The arrow indicates the vermian hypoplasia and abnormal connection between 4th ventricle and cisterna magna.

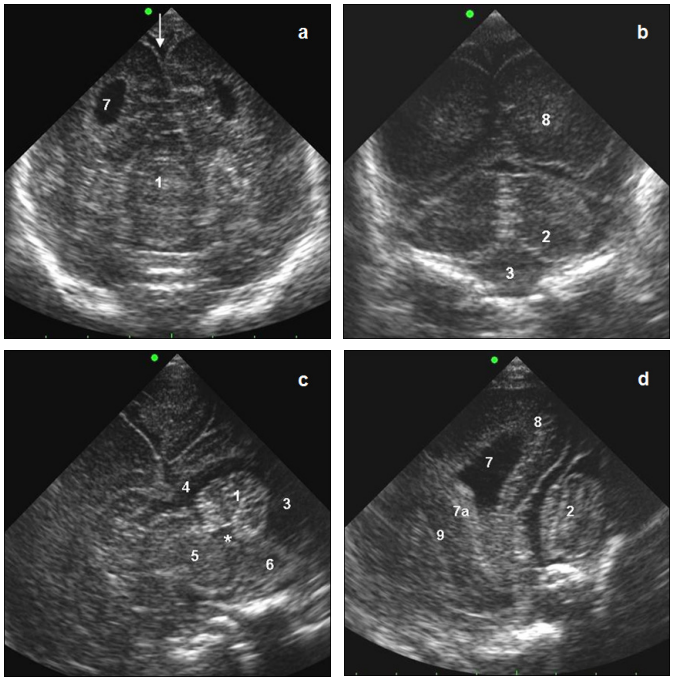
Sinovenous thrombosis

Sinovenous thrombosis is a severe condition that can affect the newborn infant. Risk factors are sepsis/meningitis, perinatal hypoxic-ischaemic events and polycythemia. Colour Doppler sonography can be used to identify the presence of flow in the venous system, but the deeper venous structures are difficult to visualize through the AF. Venous flow in the transverse and sigmoid sinuses can be detected by colour Doppler using the MF.

Posterior fontanel (PF)

The PF is located at the junction of the lambdoid and sagittal suture (2-3). Compared to the AF, it provides a more detailed view of the occipital regions of the brain and the posterior fossa. The transducer is positioned in the middle of the PF. To facilitate transducer movement, the infant's head can be slightly rotated and lifted by placing it on a folded blanket. Images can be obtained in three coronal and five sagittal planes (1-2). The most superior coronal view includes the lateral ventricles with the choroid plexus and parts of the parietal and occipital lobes. The middle and inferior coronal views show the occipital horns, occipital lobes, tentorium, vermis and cerebellar hemispheres (Figure 9, parts a and b). The midline sagittal view gives a detailed image of the vermis, 4th ventricle, pericerebellar cisterns, pons and medulla. The parasagittal views show the thalamus, the choroid plexus, the entire occipital horns of the lateral ventricles and the occipital periventricular WM (Figure 9, parts c and d).

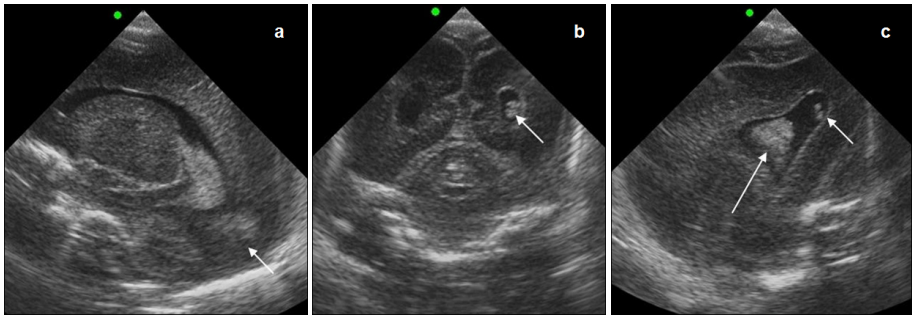
Figure 9. Middle (a) and inferior (b) coronal cUS scans, and mid- (c) and para- (d) sagittal cUS scans performed through the posterior fontanel with a phased array probe and transducer frequency of 7.5 MHz in a preterm infant, showing cerebellar vermis (1) and hemispheres (2), cisterna magna (3), pericerebellar cistern (4), pons (5), medulla oblongata (6), occipital horn of lateral ventricle (7) with choroid plexus (7a), occipital periventricular white matter (8), thalamus (9), 4th ventricle (asterisk) and interhemispheric fissure (arrow).



Intraventricular haemorrhage

Small amounts of blood in the occipital horns are difficult to detect with the AF approach, especially in the absence of germinal matrix haemorrhage. According to the classification of Volpe, grade 2 intraventricular haemorrhage is defined as a haemorrhage with less than 50% filling of the lateral ventricle, without ventricular dilatation (15). As in these cases haemorrhage is often only present in the occipital horns, the most important contribution of PF sonography in addition to AF sonography is the diagnosis of grade 2 intraventricular haemorrhage (Figure 10) (2-3).

Figure 10. Parasaggital cUS scan through the left lateral ventricle (a), performed through the anterior fontanel with a phased array probe and transducer frequency of 7.5 MHz in a preterm infant, showing an echogenic lesion in the occipital horn of the lateral ventricle, suspect for haemorrhage (arrow). Coronal (b) and parasagittal (c) cUS scans, performed through the posterior fontanel with a phased array probe and transducer frequency of 7.5 MHz in the same infant, clearly demonstrating the grade 2 intraventricular haemorrhage with blood in the occipital horn of the left lateral ventricle (short arrows) and choroid plexus in body of the lateral ventricle (long arrow).



Posterior fossa abnormalities

Compared to the AF, the PF is located closer to the posterior fossa structures. A midline sagittal view can give more detailed information on the size and shape of the cerebellar vermis, 4th ventricle and cisterna magna. This can be helpful in diagnosing congenital malformations of the posterior fossa, although in our experience the MF approach is better for this purpose. On the coronal and parasagittal views, the cerebellar hemispheres can be visualized and abnormal echodensities including haemorrhage can be detected. However, the MF approach is more reliable for the detection of cerebellar haemorrhages.

Temporal window (TW)

The TW allows a detailed transverse view of the brainstem area. The transducer is placed in a horizontal position, above the ear, approximately 1 cm above and anterior to the external auditory meatus. The transducer is then moved slightly, using real-time imaging until an appropriate image is obtained (1). The anatomic structures that can be recognized are the mesencephalon and pons, the perimesencephalic cistern, the 3rd ventricle, aqueduct and the temporal lobes (1). This can be helpful to detect structural abnormalities of the brainstem and brainstem haemorrhage. Furthermore, scanning through the TW window allows Doppler sonography and flow measurement within the circle of Willis (1).

Conclusions

cUS is an excellent and non-invasive tool for brain imaging during the neonatal period. Traditionally, it is performed through the AF. The use of additional acoustic windows including the MF, PF and TW can significantly improve its diagnostic abilities and help to define abnormalities in regions that are difficult to visualize with routine cUS views. Using different transducer frequencies and several transducer types, and adapting focus points can optimize image quality and improve the diagnostic performance of cUS.

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Chapter 4

Magnetic resonance imaging of the brain in newborn infants: practical aspects

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Abstract

Magnetic resonance imaging is becoming more widely available and increasingly important for imaging the neonatal brain. In newborn infants it poses challenges regarding patient preparation, safety, optimal timing, and sequence optimization. These issues are addressed in this paper and indications for performing neonatal magnetic resonance imaging are presented.

Introduction

Cranial ultrasound (cUS) is a reliable and safe tool to demonstrate cerebral injury and to follow brain development in preterm neonates and in full-term neonates with increased risk of brain injury or with suspected congenital malformations (1). Magnetic resonance imaging (MRI) demonstrates the site and extent of abnormalities more precisely and shows maturational processes in detail (2-8). MR imaging of the neonatal brain has become increasingly important over the past several years, especially as higher field strength MRI systems (1.5 and 3 Tesla), providing high-quality images, are becoming more widely available for clinical imaging (3-4,7,9-12).

However, although MRI as such is a safe technique, the procedure can be burdening to the infant and, if not performed under optimal circumstances, a hazardous procedure in sick, instable neonates. In each case the indication for MRI examination should be well considered, and the timing of the examination depends not only on the information expected from MRI, but also on the clinical condition of the infant.

During the last 3 years, more than 300 neonates, admitted to our tertiary neonatal unit, underwent a cerebral MRI procedure, using 1.5 or 3 Tesla Philips MR systems. In this paper we share our experience on neonatal MRI and address the following issues:

1. Indications and timing
2. Safety
3. Patient preparation and transportation
4. Feeding and sedation
5. Technical aspects, sequences, and scan protocols

Indications and timing for neonatal MRI

Preterm neonates

In preterm neonates, MRI performed during the neonatal period before term equivalent age (TEA), poses special challenges in terms of safety (including temperature regulation, maintaining of vital functions, and monitoring). If performed around TEA, MRI provides essential information on brain growth and maturation (7-8,13). Therefore, unless MRI is

needed to confirm possible life-threatening conditions, or to make important medical decisions, including continuation or withdrawal of intensive care treatment, we do not recommend MRI in preterm infants before TEA (2).

Diffuse and/or subtle white matter injury can be detected by MRI but is possibly not as reliably detected by cUS (2,14-16). Involvement of white matter tracts in parenchymal brain injury is of importance for neurological outcome and is not reliably demonstrated by cUS (9,13). In cases of (severe) post-haemorrhagic ventricular dilatation, the field of view of cUS is often largely taken up by the dilated ventricular system and cUS may fail to demonstrate additional white matter injury. Cerebellar injury, an increasingly recognized serious complication of prematurity, can be accurately diagnosed by cUS, especially if the mastoid fontanels are used as acoustic windows, but even then small haemorrhages and hypoxic-ischaemic injury may remain beyond the scope of cUS (1,17-18). Abnormalities at the brain's convexity, such as subdural and subarachnoidal haemorrhages, may also be difficult to detect with cUS (1,18). Therefore, MRI is indicated in infants born very prematurely and in preterm infants with (suspicion of) the abovementioned conditions.

Full-term neonates

While in preterm neonates injury is often located in and/or around the ventricular system, brain injury in full-term neonates is more often located in the deep grey matter and/or the cortical and subcortical regions (7,19-21). These areas are more difficult to visualize with cUS. In addition, arterial infarction is not always reliably detected with cUS (22). Therefore, MRI is often indicated in full-term neonates with seizures, other neurological symptoms, and/or suspicion of brain injury (1).

In some conditions, timing of the MR examination is of great importance. In suspected hypoxic-ischaemic or hypoglycaemic brain injury, optimal timing is probably 4 to 7 days after the incident. Shortly after the incident, conventional T_1- and T_2-weighted images may underestimate hypoxic-ischaemic injury, while diffusion-weighted imaging (DWI) may already "pseudonormalize" at 6 to 10 days after the incident (7,11,23-24).

We recommend to perform MRI in the following conditions (1):

- Prematurity, < 30 weeks' gestational age
- Hypoxic-ischaemic encephalopathy (HIE) stage 2 or 3 in (near) full-term neonates (25)

- cUS diagnosis of significant parenchymal brain injury, such as inhomogeneous periventicular echodensities, cystic periventricular leukomalacia, periventricular haemorrhagic infarction, and arterial infarction
- cUS diagnosis of severe post-haemorrhagic ventricular dilatation
- Traumatic delivery
- Clinical or cUS suspicion of abnormalities in the posterior fossa
- Clinical or cUS suspicion of abnormalities at the brain's convexity
- Severe and/or symptomatic hypoglycaemia
- (Suspected) metabolic disease
- Clinical or cUS suspicion of brain inflammation (meningitis, encephalitis, brain abscess)
- Congenital malformations with possible involvement of the brain
- Neurological symptoms such as seizures, abnormal consciousness, and/or asymmetry, not sufficiently explained by cUS findings

Safety

MRI does not involve radiation and is therefore relatively safe. However, the strong magnetic field needed for high-quality images and the need to transport patients to and from the MR department necessitate several precautions. Newborn infants are prone to hypothermia, may be haemodynamically unstable, and/or may require respiratory support. In each case, it needs to be considered when the MRI is best performed. This largely depends on the optimal timing of the MR examination in order to obtain the most valuable information (see above), presence and severity of neurological symptoms, cUS findings, clinical condition of the infant, and consequences of MR findings with respect to clinical decision-making and treatment.

Safety during sedation, transportation and scanning is essential (26). Presence of a physician and/or nurse experienced in neonatal resuscitation during transportation and throughout the MR procedure is needed, as are close communication and cooperation between neonatal and MR staff. During the scanning procedure, monitoring devices can be checked from the control room either through a window between the control room and the scanner room, or directly if the monitor is positioned in the control room. The infant can be seen on a television screen (Figure 1).

Figure 1. MRI control room, the television screen shows a neonate in the MR scanner. Also showing the neonatal ventilator.

Metal

As the MR system generates a strong magnetic field, metal containing objects should be kept out of the scanner room. Therefore, the number of people in the scanner room needs to be kept to a minimum and before entering the scanner room, the infant and others present during the MR procedure need to be checked thoroughly for metal inside the body (i.e. clips, implants, shunts) and on or close to the skin (i.e. watches, jewellery, hair wear, clothes with metal buttons or poppers, etc.). Special metal-free t-shirts are available for infants.

Maintenance of body temperature

Temperature can be maintained by swaddling the infant in blankets, and by covering it with warm hotpacks or 'gel bags' (3M Nederland B.V., Zoeterwoude, the Netherlands) (Figure 2). The temperature in the MR scanner room should be timely increased.

Figure 2. Ventilated neonate undergoing preparations for MRI examination. The infant is covered with a warm "hot pack" and will be swaddled in warm blankets. The infant's ears are covered with neonatal earmuffs. The MR-compatible, fibre-optic probe with lead of the pulse oximeter is attached to the right foot.

Monitoring

The infant's heart rate and oxygen saturation need to be monitored throughout the procedure, including transportation. During transportation, a portable saturation monitor can be used. These monitors are generally not MR-compatible. At the MRI department, the saturation monitor should be changed to a MR-compatible monitoring device (Nonin 8600FO pulse oximeter with fibre-optic sensor and lead; PT Medical B.V.,

Leek, the Netherlands) (Figure 3). Most MR-compatible monitoring devices have not yet been tested for 3 Tesla field strengths. Therefore, if a 3 Tesla MR system is used, the monitor can be placed in the control room and the fibre-optic lead with probe, which is guided to the scanner room via a hole in the wall between control and scanner room, is connected to the MR-compatible monitor (Figure 4). To prevent possible skin burns caused by these wires in rapidly changing magnetic fields, it is best to attach the sensor of the pulse oximeter to the infant's foot, outside and away from the coil (Figure 2). In addition, it can then be easily reached and readjusted without bothering or moving the infant.

Heart rate and oxygen saturation, and the proper functioning of the monitor need to be checked before the infant is positioned in the scanner.

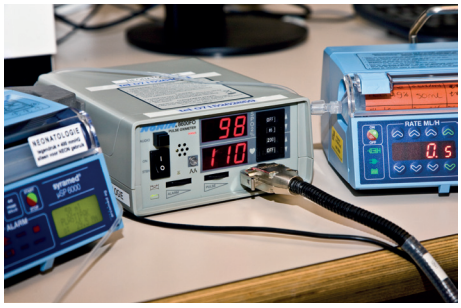


Figure 3. MR-compatible pulse oximeter with fibre-optic lead, positioned in the control room of the 3 Tesla MR unit. Also showing standard (not MR-compatible) intravenous pumps.

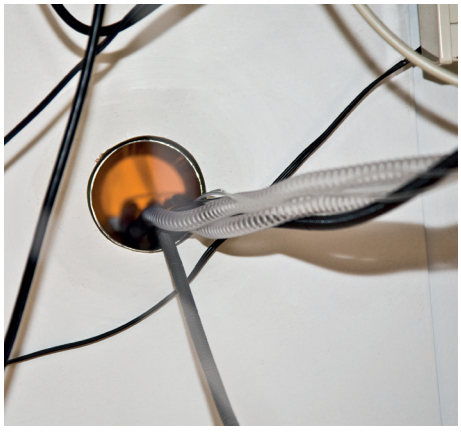


Figure 4. Ventilation hoses, intravenous lines and fibre-optic lead, guided from scanner room to MR control room through a hole in the wall.

Incubator

Special MR-compatible incubators are available (LMT Lammers Medical Technology, Lübeck, Germany). These can be combined with MR-compatible transport trolleys, monitors, ventilators, intravenous (iv) pumps, and gas cylinders, and with neonatal head coils (Figure 5). These systems are suitable for transporting babies up to 4.5 kg and 55 cm and can stay in the scanner room. At the neonatal unit, before transportation, the baby is installed in the incubator and head coil, connected to the monitor and, if ventilated, to the ventilator (Figure 5). Iv lines are connected to the MR-compatible iv pumps. After arrival at the MR unit, before the scanning procedure starts, the incubator itself is tilted from the trolley. Scanning is performed while the infant is in the incubator and continuously connected to the same monitor, ventilator, and iv pumps (Figure 6). Consequently, transportation and the scanning procedure as such are less burdening for the newborn and less time-consuming for the attending staff. However, these incubators are expensive and may not be compatible with all field strengths and MR systems. Alternatively, standard transport incubators can be used. As these are not MR-compatible, the infant needs to be taken out of the incubator in a room adjacent to the scanner room, and subsequently installed on the scanning table (Figures 2, 7 and 8).

Figure 5. Neonate installed in MR-compatible incubator and head coil. The baby is snugly swaddled in blankets and in supine position, the nose facing the ceiling.

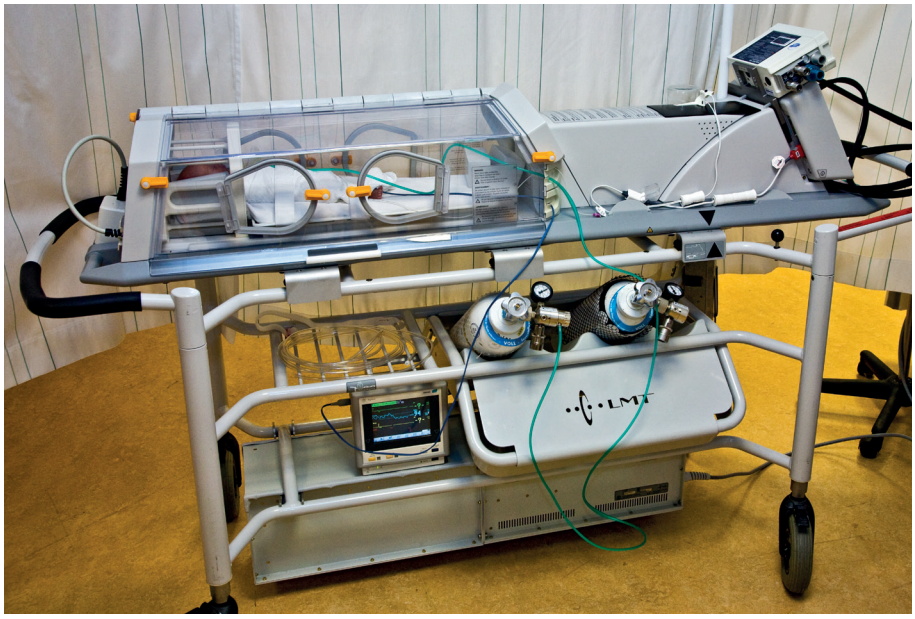


Figure 6. MRI incubator, removed from the trolley and installed on the MR table. Also showing the MR-compatible ventilator.

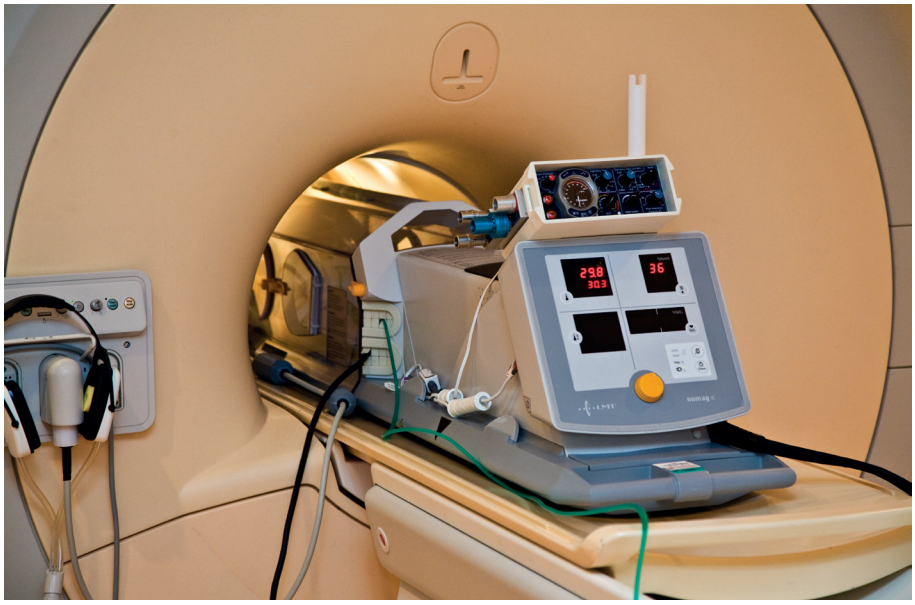
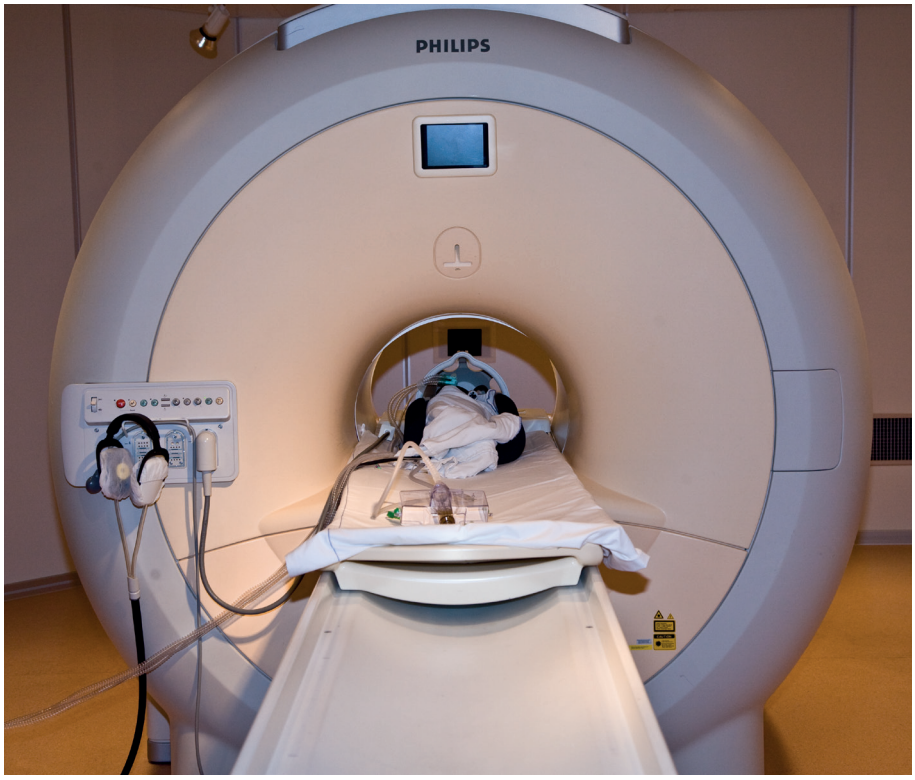


Figure 7. Ventilated neonate on the MR table, the head installed in the coil. Note the headphone covering the earmuffs and the moulded foam between the headphone and the coil. The infant is snugly swaddled in blankets and in supine position, the nose facing the ceiling.

Figure 8. The ventilated neonate is installed in the scanner. Note the extended ventilation hoses and intravenous lines guided to the hole in the wall.



Resuscitation equipment

Resuscitation equipment, appropriate for newborn infants, needs to be available during transportation and the scanning procedure. Minimal requirements for neonatal resuscitation equipment at the MRI department include a positive-pressure oxygen delivery system with flow meter, wall suction, and variously sized suction catheters, laryngoscopes, oral airways, and positive-pressure bags. In addition, back-up portable oxygen cylinders and suction equipment, an emergency medication box, and emergency telephone numbers should be close at hand. Since most items are not MR-compatible, the resuscitation equipment is kept outside the scanner room, in a magnetic field free space. In case of emergency, the infant is taken to an adjacent room for stabilization.

Ventilation equipment

For neonates requiring artificial ventilation or continuous positive airway pressure, special MR-compatible ventilators and gas cylinders are available (see paragraph on incubator). Alternatively, a standard neonatal ventilator with appropriately adapted ventilation circuits and extended hoses can be used. The ventilator is positioned in the control room and the extended hoses are guided to the scanner room and towards the infant through a hole in the wall between the rooms (Figures 3 and 4).

Intravenous pumps

MR-compatible iv pumps are available (see paragraph on incubator). Alternatively, regular iv pumps with extended lines, again guided through holes in the wall, can be used (Figures 3, 4 and 8).

Ear protection

Some MR pulse sequences are very noisy. To protect the infant from excessive noise, ear protection should be used (27). Neonatal earmuffs (Natus MiniMuffs; Natus Medical Inc, San Carlos, CA, USA) are placed over the ears (Figure 2). For additional protection, after installation on the MR table, the earmuffs are covered by headphones (Figure 7).

Patient preparation and transportation

In most hospitals, neonatal MR examinations are performed at the MRI department, at some distance from the neonatal unit. To avoid unnecessary waiting, the infant and attending staff should leave the neonatal unit or ambulatory ward only shortly prior to the planned MRI procedure. Timing of transportation is planned in close dialogue with the MR staff.

Ventilated and/or unstable neonates

MRI in sick, unstable, and/or ventilated newborns is a complicated and time-consuming procedure. It can be hazardous if safety precautions and/or patient preparations are insufficient. Intensive monitoring, maintenance of vital functions, and presence of staff experienced in neonatal resuscitation are of utmost importance. In

most hospitals, neonatal MRI examinations are conducted without the availability of MR-compatible incubators. If so, preparations need to start timely (i.e. about 1 hour) prior to transportation and the planned MR procedure. These necessary preparations subsequently include:

1. Iv catheters are removed from the infant's head in order to avoid signal distortions
2. The number of iv pumps is kept to a minimum. Generally, one pump with a glucose with mineral solution, and one or two pumps with essential medication is sufficient. If possible, other fluids and medication are temporarily discontinued during transportation and the scanning procedure
3. Iv lines and ventilation hoses are sufficiently extended (Figures 4 and 8)
4. Monitor electrodes are replaced by MR-compatible electrodes
5. Clothing containing metal parts is removed
6. If necessary, (additional) sedative medication is administrated (see chapter on sedation); Timing of sedation should be optimal and is planned in close dialogue with the MR staff
7. Neonatal earmuffs are applied (Figure 2)

After these necessary preparations, the infant can be positioned in the transport incubator and transported to the MR department, while ventilated with a mobile neonatal ventilator or mask and bag and closely monitored with a mobile saturation and ECG monitor. It is important that the MR department and staff are ready and available for the infant on arrival.

After arrival at the MR department:

1. The imaging staff performs a metal check on the infant and accompanying people before they enter the scanner room
2. The incubator, iv pumps and ventilator are positioned in the adjacent control room (Figures 1 and 3)
3. The infant is positioned on the MR table. In order to obtain the best image quality, we prefer a supine position, the nose facing the ceiling (Figures 5 and 7)
4. The extended iv lines and ventilation hoses are guided through holes in the wall between the control room and the scanner room and connected to the iv pumps and ventilator in the control room (Figures 3, 4 and 8)

5. The infant is connected to a MR-compatible saturation monitor or to a saturation monitor with extended fibre-optic lead (Figures 2 and 3). If necessary, the infant is also connected to an ECG monitor with extended leads
6. To prevent the infant from moving, waking up and/or cooling, it is snugly swaddled in pre-warmed blankets and covered with warm hot packs or 'gel bags' (Figures 2 and 7)
7. A headphone is placed over the ears and earmuffs (Figure 7)
8. The infant's head is immobilized in the coil by applying moulded foam between the headphone and the coil (Figure 7)
9. The coil is placed over the head (Figure 7)
10. As soon as these precautions and preparations are completed, and adequate monitoring, ventilation, and maintenance of vital functions are ensured, the actual MR procedure can start (Figure 8)

After the MR procedure, the infant is repositioned in the transport incubator, while maintaining ventilation and monitoring. The infant is then transported back to the neonatal unit.

Stable, non-ventilated neonates

If the infant was already discharged or transferred to another hospital, it needs to be readmitted on the day of the MRI examination. It is recommended that the infant and its caretakers arrive timely to allow a medical history and physical examination.

About 1 hour prior to the MRI examination, the following preparations need to be performed:

1. To make sure there are no contra-indications for sedation and/or MRI, a detailed medical history is taken. This includes previous operations, illnesses, and possible implants. Relative contra-indications for an elective MRI procedure under sedation include certain drugs (including anti-epileptic and/or sedative medication), respiratory disorders/distress, apneas, (suspicion of) increased intracranial pressure, seizures, increased risk of aspiration, metabolic deregulation, liver and kidney disorders, and muscular disorders. In these cases it is recommended to perform the MRI procedure while the infant is under general anaesthesia and supervised by an

anaesthesiologist. Contra-indications for the MRI examination as such include metal (containing) or electronically activated pacemakers. Nowadays, most implants, clips and shunts are MR-compatible

2. The infant and its caretakers are thoroughly checked for metal containing clothes or medical implants by taking a detailed clinical history (see above) and/or using metal check forms
3. A physical examination is performed
4. MR-compatible monitoring electrodes are applied
5. To prevent the infant from waking up and/or cooling during installation and scanning, it is snugly swaddled in pre-warmed blankets and earmuffs are applied
6. Sedation (see chapter on sedation) is administered 30 to 40 minutes prior to the planned MR procedure. This should be optimally timed and is planned in close dialogue with the MR staff
7. The infant's heart rate and oxygen saturation are monitored throughout the period of sedation
8. The infant can now be transported to the MR department, again in close dialogue with the MR staff

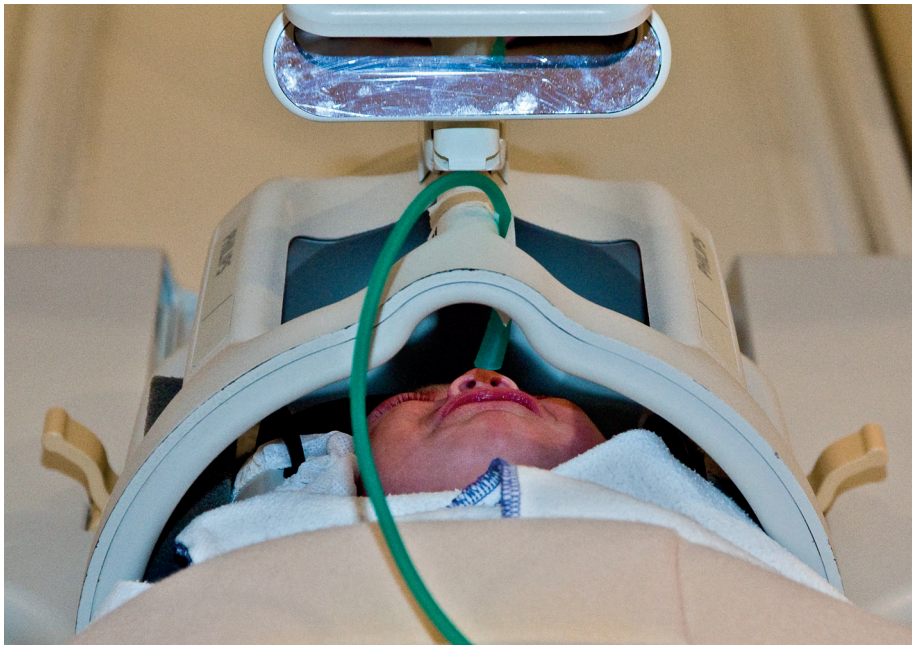
After arrival at the MR department:

1. The imaging staff performs a metal check on the infant and accompanying people before they enter the scanner room
2. The already swaddled infant is transferred from the cot to the MR table (the cot stays in the control room)
3. The infant is covered with warm hot packs or 'gel bags' (Figure 2)
4. The infant is preferably laid supine, its nose facing the ceiling (Figure 7). However, if the infant objects, it is better to allow it to settle into its preferred position. If so, in order to obtain straight MR images, imaging settings need to be adjusted with the survey images
5. The infant is connected to the MR-compatible saturation monitor (see above) and monitoring is maintained throughout the procedure (Figures 2 and 3)
6. Supplemental oxygen may be needed while the infant is sedated, especially if there is a history of chronic lung disease, prematurity, snoring, and/or apneas. During the

scanning procedure, this can be supplied using an extended oxygen hose. The hose is guided to the infant's face and securely kept in place by taping it onto the blanket or the head coil (Figure 9)

Subsequently, steps 7 to 10 as mentioned for 'Ventilated and/or unstable neonates' are carried out.

Figure 9. Infant installed in head coil. Supplemental oxygen is administered using an extended hose, positioned in front of the infant's face.



After the procedure, the infant needs to be continuously monitored until it is well awake (generally within 2 hours after scanning). Criteria for discharge after sedation include that the infant has returned to the baseline established prior to administering sedation, which depends on the level of development of the infant (26). We consider discharge safe when the infant is well awake and orientated with stable vital signs and has been drinking without problems. Before discharge, caretakers should get information on the sedation and MRI procedure, and telephone numbers to use in case of problems or questions.

Feeding and sedation

In most neonates anaesthesia is not necessary for a safe and effective MR procedure. In order to reduce movement artefacts we prefer "conscious sedation" using chloral hydrate (see below). However, other regimens may also be effective and in each individual case it should be decided whether sedation is necessary or not.

Ventilated and/or unstable neonates

Some very sick newborns are comatose due to their clinical condition (i.e. severe encephalopathy) and these infants may not need sedative medication. Many other ventilated and/or unstable newborns will be on sedative and/or anti-epileptic medication according to local protocols. In most of these cases, additional sedation is not necessary. If the infant is still uncomfortable or restless, sedation needs to be adapted by increasing the dosage of administered sedatives and/or by adding medication in accordance with local protocols.

Stable, non-ventilated neonates

In stable, non-ventilated infants up to 5 kg and/or 3 months post-term age we use the following regimen:

1. Last feed 4 hours prior to sedation
2. Chloral hydrate 50 to 55 mg/kg, administered orally 30 to 40 minutes prior to the MR procedure

Chloral hydrate is a frequently used drug in neonates for sedation during MRI procedures (28-29). It is widely available, easy to administer and has proven safe (29). It is best given on an empty stomach (dissolved in glucose 5% solution in a bottle, sprayed into the side of the infant's mouth, or administered via a naso-gastric tube). It is then rapidly absorbed and effective: most neonates fall asleep within 15 to 30 minutes, are well sedated throughout the procedure, and awake rapidly afterwards. If oral administration is undesirable, rectal administration is an alternative. Using this regimen we have only rarely encountered mild respiratory depression that was easily managed with supplemental oxygen (see paragraph on patient preparation).

If, despite this regimen, the infant does not sleep or lie still, we do not recommend additional sedation. In these cases oral sucrose is given and the infant is settled by staying patient and calm and by holding and rocking it to sleep. In our experience, abortion of the MR procedure is hardly ever necessary.

Technical aspects, scanning protocols, and sequences for 1.5 Tesla and 3 Tesla MR systems

MR systems and coils

At our hospital, 1.5 Tesla and 3 Tesla field strengths are available for neonates (Philips Intera 1.5 Tesla and Philips Achieva 3 Tesla; Philips Medical Systems, Best, the Netherlands). The higher the field strength, the better the signal-to-noise ratio (SNR) and/or the shorter the scan time. Therefore, except for very sick, unstable infants, needing more intensive monitoring, the 3 Tesla system is preferably used (10). For optimal SNR, properly sized, small head coils are needed. This can be a paediatric head coil or an adult knee coil (Figures 2, 5, 7 and 9).

Sequence optimization for imaging the neonatal brain

The water content of the neonatal brain is much higher than of the adult brain. Consequently, T_1 and T_2 values are higher and therefore echo times (TE) and repetition times (TR) need to be higher than in adult and paediatric patients (11,30-31). Due to ongoing maturational processes, including myelination, taking place in the immature brain, T_1 and T_2 values decrease significantly over the first few months after birth up to 2 years of age. This results in marked changes in T_1 and T_2 relaxation times (30). The small field of view to be used when scanning the newborn infant's brain reduces the SNR. Thus, specific and optimized protocols (accommodating the changes in T_1 and T_2 values) are needed for different field strengths. Fast and turbo imaging techniques are helpful to reduce artefacts due to movement of the infant.

Scan protocols

In our hospital, all neonatal MRI examinations are performed according to standard protocols for imaging the neonatal brain. These protocols have been thoroughly optimized over the past years for both preterm and full-term infants and for 1.5 Tesla as well as 3 Tesla MR systems. Protocols can be adjusted in individual cases based on clinical findings and the findings on cUS examinations.

As mentioned above (see chapter on indications and timing), prematurely born infants are preferably scanned around term corrected age. Scan protocols for preterm and full-term neonates include at least T_1-weighted 3 dimensional images, allowing reconstruction in every desired orientation, or T_1-weighted sagittal and axial images, and T_2-weighted images, DWI, and susceptibility-weighted images in the axial plane. If a field strength of 3 Tesla is used, two DWI scans are performed, with the water-fat shift in two different directions (anterior-posterior and left-right), to avert clinical misinterpretations caused by echo-planar distortions in the frontal lobe. We routinely perform susceptibility (T_2*) scans as small punctate lesions (such as calcifications and punctate haemorrhages) are more easily detected with this technique (32). For reliable detection of small lesions, slice-thickness is kept at a minimum with minimal (1.5 Tesla) or no (3 Tesla) interslice gaps. Because of the high water content of the immature brain, fluid-attenuated inversion recovery (FLAIR) images are of limited use in the first year after birth, and therefore we do not routinely perform these in neonates (11). In addition, it has recently been demonstrated that FLAIR and contrast enhanced images do not contribute to detection of hypoxic-ischaemic brain injury in (near) full-term neonates (33).

Details of the sequence parameters as used in our hospital for neonatal brain examinations are presented in Tables 1 and 2. Table 3 demonstrates the concise scan protocol used in sick full-term neonates with hypoxic-ischaemic encephalopathy for reliable detection of hypoxic-ischaemic brain injury (33).

Table 1. Standard protocol optimized for imaging the newborn infant's brain using a 1.5 Tesla MR system
(EPI, echo planar imaging; FFE, fast field echo; FOV, field of view; Max, maximum; min, minute; ms, millisecond; NSA, number of signal averages; s, second; Sag, sagittal; SE, spin echo; SPIR, spectral pre-saturation inversion recovery; TE, echo time; TFE, turbo field echo; TR, repetition time; Tra, transverse; TSE, turbo spin echo)

1.5 Tesla field strength					
Sequence	T_2	T_1 3D	T_2*	DWI	Sag T_1
Plane	Tra	Tra	Tra	Tra	Sag
Technique	TSE	TFE	FFE	SE-EPI	SE
b-value (s/mm^2)				1000	
FOV (mm)	180	200	220	220	200
Matrix	256	256	256	128	256
SENSE	No	No	No	No	No
Number of slices	22	80	22	22	16
Slice thickness (mm)	4	1.5	4	6	3
Gap (mm)	0.4	0	0.4	0.6	0.3
TE (ms)	120	12	48	74	20
Flip angle (°)	90	20	60	90	90
TR (ms)	5327	26	2604	3471	503
Turbo factor	13				
EPI factor			25	77	
Water/fat shift	Max	Max	Max	Max	2
Fat suppression			SPIR	SPIR	
NSA	3	1	2	1	2
Scan time (min,s)	4,05	5,45	0,41	0,24	3,01

Table 2. Standard protocol optimized for imaging the newborn infant's brain using a 3 Tesla MR system
(dir, directions; DTI, diffusion-tensor imaging; EPI, echo planar imaging; FFE, fast field echo; FOV, field of view; Max, maximum; min, minute; Min, minimum; ms, millisecond; NSA, number of signal averages; s, second; Sag, sagittal; SE, spin echo; SPIR, spectral pre-saturation inversion recovery; TE, echo time; TFE, turbo field echo; TR, repetition time; Tra, transverse; TSE, turbo spin echo)

3 Tesla field strength						
Sequence	T_2	T_1 3D	T_2*	DWI-P	DWI-A	DTI
Plane	Tra	Tra	Tra	Tra	Tra	Tra
Technique	TSE	TFE	FFE	SE-EPI	SE-EPI	SE-EPI
b-value (s/mm^2)				1000 (7 dir)	1000 (7 dir)	1000 (41 dir)
FOV (mm)	180	180	230	180	180	180
Matrix	336	192	256	96	96	128
SENSE	No	No	No	Yes	Yes	Yes
Number of slices	50	100	25	25	25	50
Slice thickness (mm)	2	1	4	4	4	2
Gap (mm)	0	0	0	0	0	0
TE (ms)	120	4.6	16	64	64	56
Flip angle (°)	90	8	18	90	90	90
TR (ms)	6269	9.7	735	2406	2406	10383
Turbo factor	18					
TFE factor		128				
EPI factor				37	37	56
Water/fat shift	Max	Max	2	Min	Min	Min
Fat suppression				SPIR	SPIR	SPIR
NSA	2	1	1	1	1	1
Scan time (min,s)	5.38	4.32	2.01	0.31	0.31	7.21

Table 3. Concise protocol for optimal detection of hypoxic-ischaemic brain injury in the early neonatal period in full-term infants with asphyxia
(DwSsh, diffusion-weighted single-shot; ms, millisecond; SE, spin echo; SPIR, spectral pre-saturation inversion recovery; TE, echo times; TR, repetition time; Tra, transverse)

1.5 Tesla field strength			
Sequence	T_1	T_2	DwSsh
Plane	Tra	Tra	Tra
Technique	SE	SE	SE
Slice thickness (mm)	4-5	4-5	6
Gap (mm)	0.4-0.5	0.4-0.5	0.4-0.5
TE (ms)	14-20	100-120	74
TR (ms)	550-560	5406-6883	5132

Summary and conclusions

MRI does not involve hazardous radiation. However, in neonates MR imaging can be challenging with respect to safety, temperature regulation, transportation, and image quality. It requires flexibility, patience, and close communication between neonatal and MR staff. Scan protocols need to be adapted to the immature neonatal brain. Special MR-compatible intensive care incubators facilitate the procedure for patients and staff. If these are not available, ventilation and monitoring equipment needs to be adapted for neonatal MRI and properly sized head coils need to be used.

If the necessary safety precautions are thoroughly followed, imaging is well timed, and appropriately sized head coils and proper scan protocols are used, MRI is a safe procedure and provides invaluable information on brain maturation and injury in (preterm) neonates.

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Part III

Brain imaging findings in very preterm infants throughout the neonatal period

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

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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).

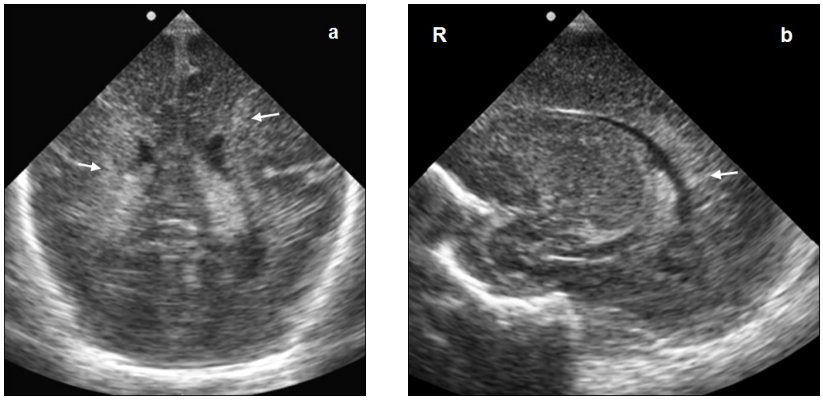
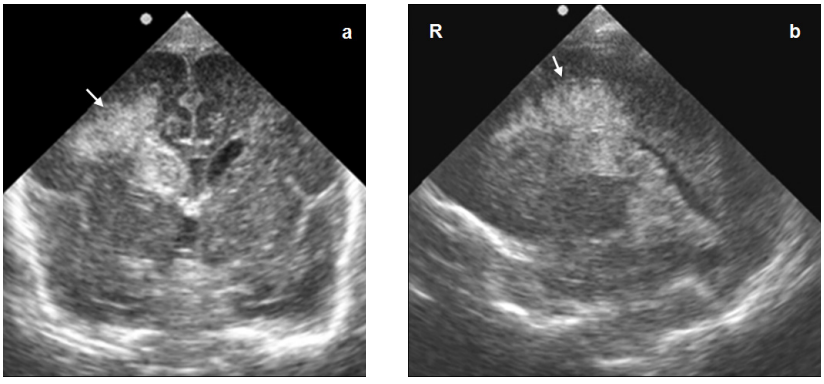


Figure 2. Coronal (a) and parasagittal (b) cUS scans of a preterm infant (gestational age 29.0 weeks) at a postmenstrual age of 29.7 weeks showing right-sided grade 3 intraventricular haemorrhage with co-existing ipsilateral intraparenchymal echodensity (periventricular haemorrhagic infarction) in the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

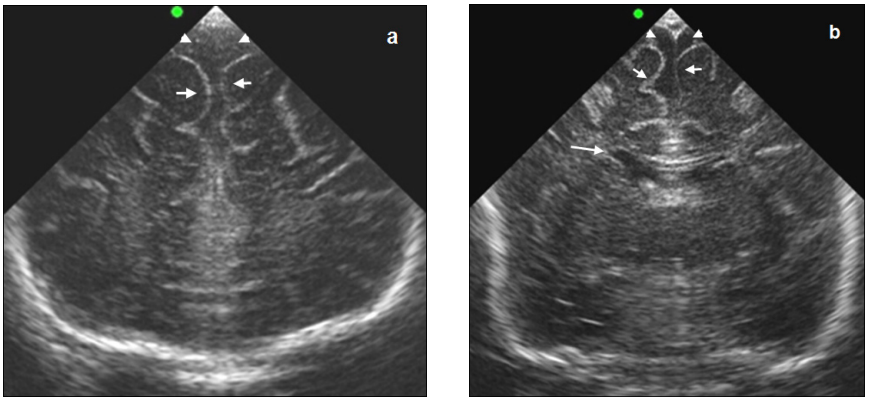


In addition, possible signs of atrophy, including ventricular dilatation (with the exception of PHVD), widened extracerebral spaces, and/or decreased complexity of gyration, were scored on the MRI-cUS (Figure 3) (8). The size and shape of the lateral ventricles and extracerebral spaces were scored visually 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).

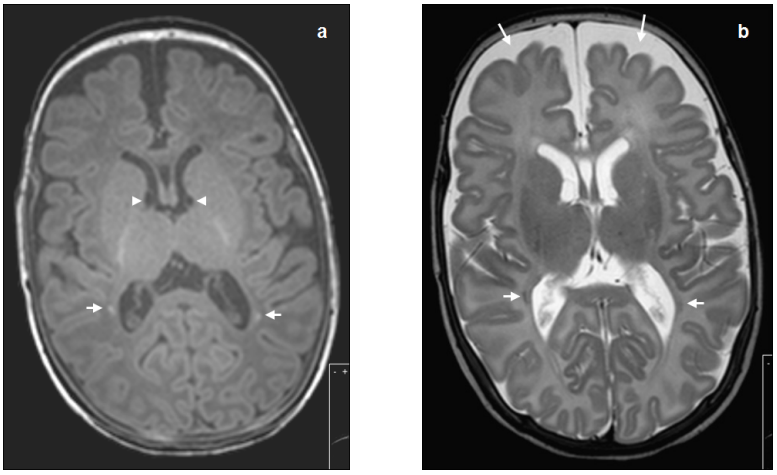
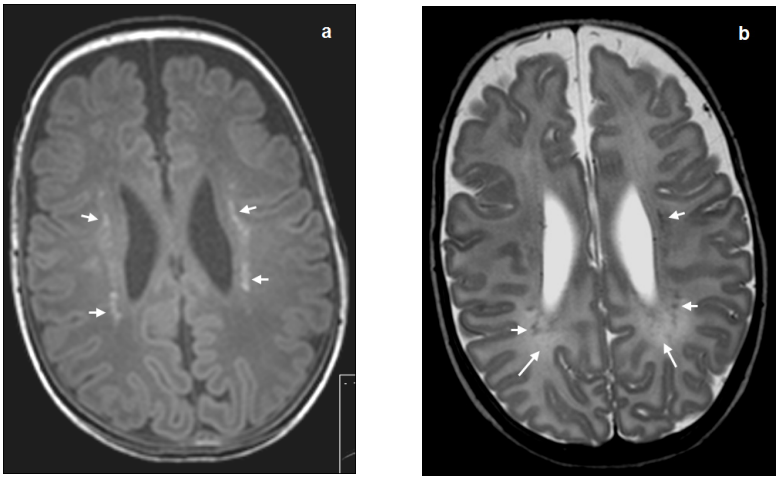


Figure 5. Transverse T_1- (a) and T_2- (b) weighted MR images at high ventricular level of a preterm infant (gestational age 26.9 weeks) at a postmenstrual age of 42.7 weeks showing bilateral, multiple punctate white matter lesions in the periventricular white matter (short arrows), being more obvious 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.

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Chapter 6

Brain imaging findings in very preterm infants throughout the neonatal period: Part II. Relation with perinatal clinical data

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Abstract

This study describes the relation between frequent and clinically relevant brain imaging findings in very preterm infants (gestational age < 32 weeks), assessed with sequential cranial ultrasonography throughout the neonatal period and magnetic resonance imaging (MRI) around term age, and several potential perinatal risk factors.

For ultrasound findings during admission the following independent risk factors were identified: male gender for periventricular echodensities and intraventricular haemorrhage, postnatal corticosteroid treatment for cystic white matter lesions, and lower gestational age for post-haemorrhagic ventricular dilatation. For MRI findings around term age, including punctate white matter lesions, ventricular dilatation, decreased cortical complexity, and diffuse and excessive high signal intensity, no independent risk factors were found.

In very preterm infants, the risk factors for frequently found changes on cranial ultrasound have largely remained unchanged over the last decades, while no risk factors could be identified for subtle and diffuse white matter injury as seen on MRI around term age.

Introduction

Very preterm infants have a high risk of brain injury, including intraventricular haemorrhage (IVH), periventricular haemorrhagic infarction (PVHI), cystic periventricular leukomalacia, and more diffuse white matter (WM) injury. These abnormalities are associated with suboptimal or abnormal neurodevelopmental outcome.

Identification of potential risk factors for frequently occurring brain abnormalities in preterm infants may contribute to early detection and intervention, and possibly to prevention of injury and consequently of neurological sequelae. However, recent studies on risk factors for brain abnormalities in very preterm infants are limited, and the relation between more diffuse and subtle forms of WM injury and clinical data is still largely unknown.

In the first part of this study we described the incidences and characteristics of brain imaging findings up to term equivalent age (TEA), as assessed with modern neuro-imaging techniques, being a combination of sequential cranial ultrasound (cUS) and a single magnetic resonance imaging (MRI) examination, in a large cohort of very preterm infants recently admitted to a tertiary neonatal referral centre (1). In the second part of this study, in order to identify potential risk factors, we assessed the relation between the most frequently encountered and clinically relevant brain imaging findings and several well-defined perinatal clinical parameters that have been associated with brain injury in preterm infants (2-19). In addition, we wanted to evaluate whether risk factors have changed over recent decades.

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 preferably around TEA (40-44 weeks' postmenstrual age

(PMA)). 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, other severe congenital anomalies, chromosomal disorders, metabolic disorders, and neonatal meningitis.

For 133 very preterm infants (80 male, 53 female) informed parental consent was obtained. Mean GA and birth weight of included infants were 28.9 (range 25.6-31.9) weeks and 1176 (range 520-1960) grams. In 113 infants (68 male, 45 female) contemporaneous cUS and MRI were performed, at a mean PMA of 44.7 (range 40.0-55.9) weeks. Details on informed consent, infants' characteristics, neuro-imaging techniques and protocols, and cUS and MRI assessment procedures are described in the first part of this study (1).

Clinical parameters

For all very preterm infants included in this study, the following perinatal clinical parameters were collected retrospectively by an investigator, blinded to the cUS and MRI findings:

- Antenatal corticosteroid treatment for prevention of respiratory distress syndrome (RDS)
- GA at birth (weeks)
- Birth weight (grams)
- Gender (male / female)
- Plurity (singleton / twin / triplet)
- RDS, defined as requirement of mechanical ventilation and at least one dose of intratracheal surfactant
- Bronchopulmonary dysplasia (BPD), defined as oxygen dependence at 36 weeks' PMA (20)
- Postnatal corticosteroid (i.e. dexamethasone) treatment for BPD
- Patent ductus arteriosus (PDA), defined as present if requiring medical and/or surgical treatment
- Hypotension, defined as present if requiring inotropic treatment
- Postnatal sepsis, defined as present if positive blood culture, and/or necrotizing enterocolitis (NEC), defined as present if grade ≥ 2a according to Bell et al. (21)

The above mentioned clinical parameters were selected based on previous studies describing these parameters as potential risk factors for brain injury in very preterm infants. This enabled comparison of risk factors found in our study with those reported previously.

Cranial ultrasound

cUS techniques and protocols, and assessment procedures are described in the first part of this study (1,22).

For the first part of this study, all sequential cUS scans were assessed for presence of brain imaging findings, including periventricular echodensities (PVE), cystic WM lesions, IVH, PVHI, post-haemorrhagic ventricular dilatation (PHVD), basal ganglia and/or thalamus abnormalities, and structural anomalies. Subsequently, the incidences and evolution of findings throughout the neonatal period were described. For details on classifications of PVE and IVH and definitions of various lesions, see part I (1).

For this second part of the study, only the brain imaging findings that were most frequently encountered on cUS during admission and/or have been suggested to be the most clinically relevant in very preterm infants, including PVE, cystic lesions in the WM, IVH, and PHVD, were assessed. As the number of infants with PVHI was small (n=7), this finding was not included in this part of the study. Details on the cUS findings are given in Table 1. As, in our opinion, homogeneous grade 1 PVE (the echogenicity of the periventricular WM being (almost) equal to that of the choroid plexus) may be a normal phenomenon in the preterm infant's brain, we decided to include only grade 2 PVE (the echogenicity of the periventricular WM exceeding that of the choroid plexus) and inhomogeneous grade 1 PVE for assessing the association between PVE and clinical parameters.

MRI

MRI techniques and protocols, and assessment procedures are described elsewhere in this issue (1,23).

For the first part of this study, all MRI examinations were assessed by at least two experienced investigators (LML, FTdB, GvWM, SJS) by consensus. The MR images were assessed for presence of punctate white matter lesions (PWML), diffuse and excessive

high signal intensity (DEHSI) (only on MRI scans performed between 40-44 weeks' PMA), other signal intensity changes in the WM, haemorrhage, PHVD, PVHI, basal ganglia and/or thalamus abnormalities, structural anomalies, and possible signs of atrophy (including ventricular dilatation (with the exception of PHVD), widened extracerebral spaces, and/or reduced complexity of gyration). Subsequently, the incidences of findings around TEA were calculated. For details see part I (1).

For this second part of the study, only the brain imaging findings that were most frequently encountered on MRI and/or have been suggested to be the most clinically relevant in very preterm infants around TEA, including PWML, ventricular dilatation, decreased complexity of gyration, and DEHSI, were assessed. Details on the MRI findings are given in Table 1. In order to make a clear distinction between mild abnormalities and more severe abnormalities with possible consequences for neurological development, we decided to include only multiple PWML (> 6) and severe ventricular dilatation, and not the milder spectrum of these abnormalities, for assessing associations with clinical parameters.

We regarded MRI as golden standard for the brain imaging findings around or shortly after TEA. The cUS findings obtained around TEA were therefore not used for this part of the study.

Table 1. Frequently encountered and clinically relevant neuro-imaging findings in very preterm infants during admission and around term equivalent age
(DEHSI, diffuse and excessive high signal intensity; IVH, intraventricular haemorrhage; n, number of infants; PHVD, post-haemorrhagic ventricular dilatation; PMA, postmenstrual age; PVE, periventricular echodensities; PWML, punctate white matter lesions; TEA, term equivalent age; WM, white matter)

Neuro-imaging findings	Number (%)
During admission (cUS; n=133)	
- PVE (excluding homogeneous grade 1 PVE)	87 (65.4)
- Cystic WM lesions	10 (7.5)
- IVH	37 (27.8)
- PHVD	21 (15.8)
Around TEA (MRI; n=113)	
- Multiple PWML (> 6)	19 (16.8)
- Severe ventricular dilatation (excluding PHVD)	12 (10.6)
- Decreased complexity of gyration	9 (8.0)
- DEHSI (of 70 infants with MRI between 40-44 weeks' PMA)	55 (78.6)

Data analysis

Statistical analyses were performed using SPSS software (version 14.0; SPSS inc., Chicago, Illinois, USA). The incidences of neuro-imaging findings during admission and around TEA were calculated for the first part of this study (1). For this part of the study, the incidences and means of clinical parameters were calculated.

The clinical data were compared between infants with and without the selected brain imaging findings, using a Fisher's Exact test for categorical variables and an unpaired t-test for continuous variables. Subsequently, the clinical variables in which the univariate analysis was demonstrated as $p < 0.1$ were entered into a stepwise logistic regression model to identify independent predictors of brain abnormalities. As several of the collected clinical parameters may be strongly related to GA at birth and, thus, GA may be a confounder, this parameter was always included in the model. The level of significance was $p \leq 0.05$.

Results

Clinical parameters

The characteristics of collected perinatal clinical parameters of all included infants are shown in Table 2.

Table 2. Characteristics of collected perinatal clinical parameters of all 133 very preterm infants included in the study
(BPD, bronchopulmonary dysplasia; GA, gestational age; n, number of infants; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome)

Clinical parameters	
Antenatal corticosteroids, *n* (%)	82 (61.7)
GA (weeks), *mean* (range)	28.9 (25.6-31.9)
Birth weight (grams), *mean* (range)	1176 (520-1960)
Male gender, *n* (%)	80 (60.2)
Plurity, *n* (%)	43 (32.3)
Sepsis / NEC, *n* (%)	54 (40.6)
RDS, *n* (%)	72 (54.1)
BPD, *n* (%)	60 (45.1)
Postnatal corticosteroid treatment, *n* (%)	16 (12.0)
Hypotension, *n* (%)	43 (32.3)
PDA, *n* (%)	38 (28.6)

Neuro-imaging findings

The incidences of selected neuro-imaging findings on cUS during admission and on MRI around term are summarized in Table 1.

Relation between neuro-imaging findings and clinical parameters

cUS during admission *(n=133)*

The relation between cUS findings during admission and perinatal clinical parameters is shown in Table 3.

A significant association was found between presence of PVE and male gender. When entered into a logistic regression analysis, male gender was found to be independently associated with PVE (odds ratio (OR)=2.67; 95% confidence interval (CI) 1.26-5.63).

Infants with cystic lesions in the WM were significantly younger at birth and required significantly more often postnatal corticosteroid treatment than infants without these lesions. Only postnatal corticosteroid treatment was identified as independent variable (OR=6.06; 95% CI 1.50-24.52).

Presence of IVH was significantly associated with male gender, more RDS and more postnatal corticosteroid treatment, and there was a tendency towards less antenatal corticosteroid treatment and shorter GA at birth in infants with IVH. Logistic regression analysis only identified male gender as an independent risk factor for IVH (OR=2.52; 95% CI 1.07-5.95).

In addition, PHVD was significantly associated with shorter GA and lower weight at birth and more RDS, BPD, and postnatal corticosteroid treatment. Of these associated parameters, only GA at birth was identified as an independent variable (OR=0.63; 95% CI 0.47-0.48).

Table 3. Relation between neuro-imaging findings in very preterm infants and perinatal clinical parameters
(*, independent variable; BPD, bronchopulmonary dysplasia; DEHSI, diffuse and excessive high signal intensity; GA, gestational age; IVH, intraventricular haemorrhage; n, number; NEC, necrotizing enterocolitis; NS, not significant; PDA, patent ductus arteriosus; PHVD, post-haemorrhagic ventricular dilatation; PVE, periventricular echodensities; PWML, punctate white matter lesions; RDS, respiratory distress syndrome; TEA, term equivalent age; VD, ventricular dilatation; WM, white matter)

Clinical parameters	Neuro-imaging findings, *p-value* (finding present versus absent)							
	During admission (cUS; n=133)				Around TEA (MRI; n=113)			
	PVE (n=87)	Cystic WM lesions (n=10)	IVH (n=37)	PHVD (n=21)	Multiple PWML (n=19)	Severe VD (excluding PHVD) (n=12)	Decreased complexity gyration (n=9)	DEHSI (n=55)
Antenatal corticosteroids (%)	NS	NS	0.062 (51 vs. 68)	NS	NS	0.081 (42 vs. 67)	NS	NS
GA (weeks)	NS	0.037 (27.7 vs. 29.0)	0.099 (28.5 vs. 29.1)	0.000* (27.6 vs. 29.2)	NS	NS	NS	NS
Birth weight (grams)	NS	NS	NS	0.022 (1007 vs. 1208)	0.061 (1357 vs. 1183)	0.080 (1035 vs. 1231)	NS	NS
Male gender (%)	0.013* (69 vs. 45)	NS	0.046* (76 vs. 55)	NS	NS	NS	NS	0.059 (67 vs. 50)
Plurity (%)	NS	NS	NS	NS	NS	NS	NS	NS
Sepsis / NEC (%)	NS	NS	NS	NS	NS	NS	NS	NS
RDS (%)	NS	NS	0.040 (69 vs. 49)	0.033 (76 vs. 52)	NS	NS	0.062 (88 vs. 53)	NS
BPD (%)	NS	NS	NS	0.034 (67 vs. 42)	NS	NS	NS	NS
Postnatal corticosteroids (%)	NS	0.020* (40 vs. 10)	0.043 (22 vs. 9)	0.005 (33 vs. 8)	NS	NS	NS	NS
Hypotension (%)	NS	NS	NS	NS	NS	NS	NS	NS
PDA (%)	NS	NS	NS	NS	NS	NS	NS	NS

MRI around TEA *(n=113)*

The relation between MRI findings around TEA and perinatal clinical parameters is shown in Table 3.

No significant associations were found between any of the findings on MRI and collected clinical parameters. In infants with multiple PWML there was a tendency towards a higher birth weight, and in infants with DEHSI towards more boys. In addition, there were strong but non-significant associations between severe ventricular dilatation and less antenatal corticosteroid treatment and lower birth weight, and between decreased complexity of gyration and more RDS.

Discussion

We assessed the relation between frequently occurring and/or severe brain imaging findings and several potential perinatal risk factors in a cohort of very preterm infants. Several risk factors were found for the selected brain imaging findings, detected on cUS during admission, which are partly consistent with those found in previous studies (2-12,14,17).

Male gender was identified as an independent risk factor for PVE during the early neonatal period. Cystic lesions in the WM, mostly detected after the first few postnatal weeks, were significantly associated with lower GA and postnatal corticosteroid treatment. Even when corrected for GA at birth, postnatal corticosteroid treatment was associated with a significantly higher risk of cystic WM lesions. None of the other clinical parameters were identified as risk factors for these WM findings. This is largely in agreement with previous studies, and supports the results of other authors demonstrating the negative effects of postnatal corticosteroid treatment on the developing WM in preterm infants (2,4-6,10-11,14,24).

IVH, the second most frequently encountered finding on cUS during the early neonatal period, was significantly associated with male gender, RDS and postnatal corticosteroid treatment. In addition, infants with IVH tended to be younger at birth, and, although not significant, antenatal corticosteroid therapy seemed to have a preventive effect on IVH development. When variables were entered into a logistic regression model,

including correction for GA, only male gender was identified as an independent risk factor for IVH. Again, our results are largely in agreement with those reported by others, who identified infection, lower GA and weight at birth, hypotension, PDA, and a more complicated respiratory course as potential risk factors and antenatal corticosteroid treatment as a potential protective factor for the development of IVH in preterm infants (3,6,8,10,12,14,17).

In contrast with several other studies (4-6,10,14), we did not find a significant association between presence of IVH and lower GA and weight at birth, which may be related to the fact that we only included preterm infants of < 32 weeks' gestation. In a study by Kadri et al. (17), no significant difference in incidence of IVH was found between infants of < 30 weeks' gestation and those between 30 and 34 weeks. However, they did find a significant difference in IVH incidence with older GA groups.

Our finding that male gender is associated with IVH has, to our knowledge, not been reported before. As regression analysis showed an independent association, influence of lower GA and/or more severe respiratory disease, as reported in boys, could thus be excluded. We therefore feel that male gender is an independent risk factor for brain injury in preterm infants.

IVH was complicated by PHVD in just over half of the cases. We found PHVD to be significantly more common in the younger and smaller infants, infants with RDS and/or BPD, and infants requiring postnatal corticosteroid treatment. Only GA at birth was identified as an independent variable, indicating that the other variables were related to the lower GA in infants with PHVD. This is partly in consistence with previous studies proposing hypotension and respiratory problems as risk factors and higher GA and weight at birth as protective factors for PHVD (6,9-10).

Severe lateral ventricular dilatation and decreased complexity of gyration, reported to be associated with WM injury and/or to represent loss of brain volume, were frequent MRI findings around or shortly after TEA (13,15). Although there was a tendency towards less antenatal corticosteroid treatment and lower birth weight in infants with severe ventricular dilatation, and towards more RDS in infants with decreased complexity of cortical folding, no significant associations were found between clinical parameters, and thus potential risk factors, and these findings. In a study by Ment et al. (7), dilatation of the lateral ventricles on cUS performed around TEA was associated with BPD, but

not with any other clinical parameter. However, they also included infants with mild-moderate lateral ventricular dilatation and in all their cases IVH was detected on cUS during the early neonatal period, while we only included infants with severe ventricular dilatation present around TEA and regarded PHVD as a separate finding.

Impaired growth of the cortical gray matter in preterm infants on term equivalent MRI has been reported to be associated with postnatal corticosteroid (i.e. dexamethasone) treatment (24). Our results could not confirm this. However, in those studies cortical growth was quantified using volumetric MRI techniques, while we visually assessed complexity of cortical folding. In another study, no associations were found between cortical gray matter development and perinatal clinical data (13). Finally, in a study by Horsch et al. in preterm infants (16), signs of atrophy on cUS at discharge were significantly associated with lower GA and weight at birth, and more respiratory problems and postnatal corticosteroid treatment.

Finally, subtle changes in the WM, including PWML, in particular multiple (> 6), and DEHSI, were frequent findings on MRI around term; no cUS-correlate was found for these MRI phenomena (1). Although there was a tendency towards a higher birth weight in infants with multiple PWML and more boys in the group of infants with DEHSI, no significant associations were found between clinical parameters and these MR imaging findings. Our results are largely in agreement with those of scarce previous studies, which did not find associations between either PWML or DEHSI and any of the clinical parameters assessed by us (15,18-19).

Although the risk factors for changes in the preterm infant's brain, particularly those detected on cUS during the early neonatal period, found in this study are largely consistent with those reported in other studies, our results do not confirm all the previously proposed risk factors. There are several possible explanations for this inconsistency. Firstly, the associations between brain imaging findings and clinical parameters depend on the homogeneity of the population studied. We only included very preterm infants with a GA of < 32 weeks, being a relatively homogeneous group with respect to severity of illness and occurrence of cerebral abnormalities. In addition, the definitions of brain imaging findings and the criteria for including findings, and the definitions of clinical parameters and the inclusion criteria may have been different between our and some previous studies (2-7,10-12,14). Finally, in our study, in order

to identify independent risk factors for brain findings, correction for GA at birth and logistic regression analysis were applied, resulting in loss of statistical significance of associations in the univariate analysis. This was true for associations between IVH and PHVD and RDS, BPD and postnatal corticosteroid treatment. However, not in all studies these additional analyses were applied (2,10,17).

We appreciate several limitations of our study. Firstly, as was expected when studying very preterm infants, our number of preterm infants without any abnormal brain imaging finding was small. Secondly, we did not take co-occurring findings into account when assessing associations between brain imaging findings and clinical parameters. In consistence with previous studies (12-13,15), IVH and changes in the periventricular WM often co-existed in our infants, and therefore IVH may have confounded the associations with clinical parameters found for WM changes, and vice versa. However, as these two brain findings may have common or overlapping aetiologies in preterm infants, and can therefore be expected to be associated with common or overlapping clinical parameters, and our results are largely consistent with those of previous studies, we feel that this will not have influenced our results considerably. Some of the brain imaging findings, including decreased complexity of gyration and cystic lesions in the WM, were only detected in a small number of infants. This may partly have caused the lack and/or the inconsistency with previous studies in significant associations with clinical parameters. In addition, we regarded MRI as golden standard for the brain imaging findings around TEA. This may have contributed to our lack in association between decreased complexity of gyration and clinical parameters, especially as this finding was more often scored on contemporaneous cUS. However, we feel that we rather overestimated this finding on cUS than underestimated it on MRI (1). We did not match our infants for GA and weight at birth. However, as we corrected for GA and applied multivariate logistic regression analysis, this will not have influenced our results considerably. Finally, we only collected the most frequently proposed, well-defined perinatal risk factors for brain injury in preterm infants. Therefore, we may have missed some relevant associations, and thus risk factors, for the imaging findings.

In conclusion, this study has shown that male gender is an independent risk factor for the development of IVH and PVE, while a lower GA is independently associated with PHVD. Finally, postnatal treatment with corticosteroids for BPD is significantly associated

with cystic WM lesions. Despite advances in neonatal intensive care and changes in the distribution of WM injury in preterm infants, the risk factors for frequently occurring and clinically relevant findings in the preterm infant's brain are still largely the same as those reported in the past, while no risk factors could be identified for subtle and diffuse WM injury as seen on MRI around term age.

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Part IV

White matter

Chapter 7

Frequently encountered cranial ultrasound features in the white matter of preterm infants: correlation with MRI

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Abstract

Background and Aim:

Bilateral symmetrical echogenic and echolucent areas in the white matter are frequently seen on the cranial ultrasound scans of apparently well preterm infants without overt pathology. Our aim was to determine whether these features reflect maturational processes as seen on magnetic resonance imaging (MRI).

Patients and Methods:

Preterm and term-born infants without overt pathology on contemporaneous brain ultrasound and MRI were studied. Ultrasound scans were compared with T_2-weighted MRI to identify MR-correlates for the bilateral and symmetrical echogenic and echolucent phenomena in the white matter seen on ultrasound.

Results:

Forty-four sets of scans (26 preterm, eight term-born infants) were assessed. Echogenic features were better and more frequently seen on early ultrasound as compared to nearer term age. Echogenic blushes in the white matter correlated well with high signal intensity areas and echogenic lines with low signal intensity lines on MRI. Echolucent areas correlated with the site of the internal capsule and the myelinated posterior pons. The subplate was not reliably identified.

Conclusions:

Many echogenic and echolucent features in the white matter of well preterm and some term-born infants correlated well with areas of differing signal intensity on MRI. They most likely reflect normal maturational processes but the echogenic hemispheric features may represent delayed or abnormal maturation.

Introduction

In newborn infants, especially those born prematurely, many maturational processes take place in the brain after birth (1-3). Preterm infants are at high risk of hypoxic, haemorrhagic and inflammatory brain lesions (4-6) and disturbed cerebral development (7-10). They are also at risk of abnormal neurological development (11-13), even when no overt cerebral lesions are detected (14-15).

Cranial ultrasound (cUS) reliably demonstrates many forms of cerebral injury (11,15-18) and shows anatomical features and their changes with gestation. However, magnetic resonance imaging (MRI) shows maturational processes in greater detail (1-3,16-21) and it enables quantification of brain growth and maturation (7-10).

There are several MRI and pathological studies on normal and abnormal cerebral white matter (WM) development in newborn infants (2,5,16,21-27), but few equivalent cUS studies (12,16,28) or studies comparing cUS to MRI (16-17). As cUS is the most readily available and usually the initial technique used for imaging the newborn brain (4,11), it is desirable that its capability for assessing maturational features is understood. To do this, it is important to define appearances representing normal developmental processes as visualized on neonatal scans.

Bilateral symmetrical areas of increased echogenicity are frequently encountered on the cUS scans of apparently well preterm infants. These areas are mainly located periventricularly in the frontal WM and at the margins of the lateral ventricles (LV) and do not evolve into lesions. They tend to be linear or smoothly rounded. Some of these areas have correlated anatomically with areas of glial cell migration in the preterm brain before term equivalent age (TEA) (16). Areas of altered signal intensity (SI) in the periventricular WM may represent features of developing WM on MRI (16,22-25,27). Echolucent areas are seen in more peripheral regions of the hemispheres and more centrally where defined WM tracts run; these areas have not been compared to MRI but might represent the subplate, the internal capsule and the posterior myelinated pons. We hypothesize that bilateral symmetrical echogenic or echolucent areas on cUS, seen in apparently normal (preterm) newborn infants and not evolving into lesions, reflect maturational rather than pathological processes in the newborn infant brain. Our aim was to determine whether such features reflect maturational processes as seen on contemporaneous brain MR imaging.

Materials and Methods

Patients

During the study-period (February 2005-February 2006), all preterm and term-born infants admitted to the neonatal unit of the Hammersmith and Queen Charlotte's Hospital, London, with a cUS and MRI examination performed on the same day were included. All infants were examined prior to scanning and their growth characteristics were recorded. Ethical approval for brain MR imaging studies was given by the Hammersmith Hospitals Research Ethics Committee and parental consent was always obtained. All cUS scans were done as part of routine assessment. Some MRI examinations were part of ongoing research cohort studies of apparently well newborn infants. Other infants were scanned for different clinical indications, including neonatal encephalopathy and suspected but unconfirmed metabolic and neuromuscular disorders. No infant with overt pathology on their cUS was included.

Exclusion criteria were major congenital anomalies or acquired injurious brain abnormalities, brain abnormalities on cUS scans, chromosomal disorders, metabolic disorders or neonatal meningitis.

Neuro-imaging

Ultrasonography

All cUS scans were performed by the same observer (LML), using a Siemens Antares ultrasound scanner with a multifrequency transducer (Siemens, Bracknell, UK). Scanning was done through the anterior fontanel in at least six coronal and five sagittal planes. The transducer frequency was set at 7.3 MHz. To evaluate the peripheral regions of the hemispheres where the cortical subplate and the subcortical WM can be identified on T_2-weighted MR images of very preterm infants, higher frequencies were applied. cUS scans were evaluated during and immediately after the procedure by the examiner and all scans were digitally stored and later analyzed by LML and FMC by consensus, using the software program Escape Medical Viewer (Escape Medical Imaging, Thessaloniki, Greece).

All scans were assessed for presence, location and appearance of the following echogenic features in the WM. These comprised:

- Frontal echogenic blush
- Echogenic lines around/below the LV
- Echogenicity running supero-laterally from the LV
- Echogenic lines running parallel to the LV
- Temporo-occipital echogenic blush

Scans were also assessed for areas of persistent echolucency in the WM that might represent:

- The cortical subplate
- The internal capsule
- WM tracts in the pons

MRI

MRI was performed according to a standard protocol for newborn infants, using a 3 Tesla Philips MR system (Philips Medical Systems, Best, the Netherlands). If needed, infants were sedated using oral chloral hydrate (30-50 mg/kg), a regimen we have found safe and effective. They were placed supine and snugly swaddled. Ear protection was used (5) and the head immobilized using a polystyrene bead-filled pillow from which the air was evacuated. The infant's temperature, heart rate and oxygen saturation were monitored throughout the procedure by an experienced neonatologist.

The MR sequence parameters were as follows:

T_1-weighted magnetization prepared rapid-acquisition gradient echo volumes: repetition time, 17 ms; echo time, 4.6 ms; flip angle, 30°; field of view, 210 mm; matrix, 256 x 256; number of acquisitions, 1; and voxel size, 0.8 x 0.8 x 1.6 mm;

T_2-weighted fast-spin echo pseudo volumes: repetition time, 12,000 ms; echo time, 160 ms; flip angle, 90°; field of view, 220 mm; matrix, 224 x 224; voxel size 0.86 x 0.86 x 2.0 mm.

T_1-weighted volume images were acquired in the sagittal plane and reformatted into transverse and coronal planes. T_2-weighted images were acquired in the transverse plane.

All MRI examinations were evaluated by two experienced observers (LS and MAR) to exclude focal pathology. The MR images were then assessed using the software program ViewForum (Philips Medical Systems, Best, the Netherlands). With this program different planes, including coronal and sagittal planes, comparable to those obtained with cUS scanning, could be reconstructed, enabling the best possible comparison between cUS and MRI examinations. For this study, T_2-weighted MR images were used as they have been shown to be a more sensitive indicator for assessing brain development (29), particularly before TEA.

The T_2-weighted MR examinations were assessed for presence of features possibly correlating with the echogenic features in the WM detected on cUS, as well as evaluated for presence of the cortical subplate, visibility of the internal capsule and WM tracts in the pons. For comparing the cUS and MRI examinations, the MR image most closely resembling the cUS plane in which the cUS feature was detected was evaluated.

Data analysis

All contemporaneous cUS and MRI examinations were first assessed separately and later assessed simultaneously to obtain the most accurate comparison of both examinations. Statistical analyses were performed using StatsDirect statistical software (StatsDirect Ltd, Cheshire, UK). The predictive values, including sensitivity, specificity, positive predictive value and negative predictive value, of the cUS features for the presence of correlating features on MRI were calculated. The level of significance was taken at 0.05.

Results

Patients

Twenty-six preterm (13 male) and eight term-born infants (all male) without overt pathology on their cUS and MRI examinations were studied. Mean gestational age (GA) and birth weight were, respectively, 29.5 (range 24.4-32.7) weeks and 1230 (586-1848) grams for preterm infants and 39.4 (38.0-40.6) weeks and 3218 (2986-3400) grams for term-born infants. In nine of 26 preterm and one of eight term-born infants two sets

of cUS and MRI examinations were performed on different days; mean time-interval between the sets of scans was 7.4 (3.7-14.9) weeks. In total 44 sets of examinations were analyzed. Mean postmenstrual age (PMA) and weight at scanning were, respectively, 37.5 (27.1-57.0) weeks and 2296 (870-4210) grams for preterm infants and 42.9 (38.9-49.0) weeks and 4007 (3127-5450) grams for term-born infants. Nineteen of the 35 sets of examinations of preterm infants were performed around TEA (36.0-44.0 weeks' PMA).

Ultrasound imaging and comparative cUS-MRI data

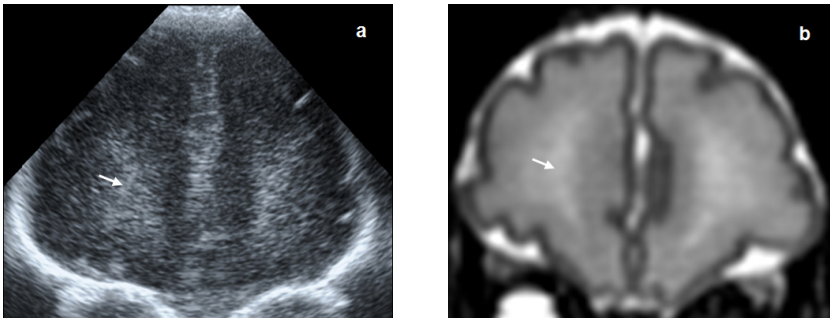
Areas of increased echogenicity

Frontal echogenic blush

An echogenic blush in the frontal WM was seen in 32 of 35 (91%) preterm infant cUS scans and five of nine (56%) term-born infant scans (Figure 1). This feature was always bilateral and homogeneous in appearance. No significant differences in mean GA, birth weight and PMA and weight at day of scanning for preterm infants with and without this feature were found; nor were these parameters different between term-born infants with and without this feature except that weight at scanning was significantly lower for infants in whom the blush was seen (p=0.006).

In all preterm and four term-born infants with frontal blushes on cUS, bilateral areas of marked high SI were detected in the same location on the T_2-weighted MR images (Figure 1). In two preterm infants and the four term-born infants without these blushes, areas of high SI were also seen in the frontal WM on MRI. The predictive values of the frontal echogenic blushes for correlating features on MRI are shown in Table 1.

Figure 1. Bilateral frontal echogenic blushes on an anterior coronal cUS (a, arrow) of a preterm infant (gestational age 26.0 weeks) with a postmenstrual age at day of scanning of 33.6 weeks correlating with high signal intensity areas on contemporaneous reconstructed coronal T_2-weighted MR image (b, arrow).

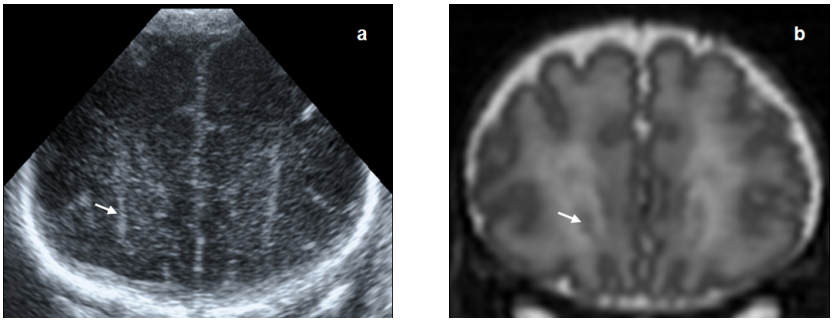


Echogenic lines around/below the LV

Echogenic lines around/below the anterior horns of the LV were seen in 29 of 35 (83%, 26 bilateral, three unilateral) preterm infant scans and four of nine (44%, all bilateral) term-born infant scans (Figure 2). GA, birth weight and PMA and weight at day of scanning were not significantly different between the preterm and term-born infants with and without these lines.

In all preterm infants and in all but one term-born infant with and without these echogenic lines, low SI lines were seen in the same location on MRI (Figure 2). The predictive values of the echogenic lines for correlating features on MRI are shown in Table 1.

Figure 2. Bilateral echogenic lines around/below the lateral ventricles on an anterior coronal cUS (a, arrow) of a preterm infant (gestational age 27.7 weeks) with a postmenstrual age at day of scanning of 38.3 weeks correlating with low signal intensity lines on contemporaneous reconstructed coronal T_2-weighted MR image (b, arrow).



Echogenic areas running supero-laterally from the LV

Echogenic areas running supero-laterally from the LV were seen in 29 of 35 (83%, bilateral in all but one) preterm scans and in seven of nine (78%, always bilateral) term-born infant scans (Figures 3 and 4). GA, birth weight and PMA and weight at day of scanning were not significantly different between preterm and term-born infants with and without these areas.

In 27 preterm and three term-born infants with supero-lateral echogenic areas, high SI areas were seen in the same location on the MR images (Figures 3 and 4 and also well illustrated on the parasagittal view in Figure 5). In three of six preterm infants without the echogenic areas, high SI areas were detected supero-laterally from the LV on MRI. No term-born infants without echogenic areas had high SI areas on MRI. The predictive values of these echogenic areas for correlating features on MRI are shown in Table 1.

Figure 3. Bilateral echogenic lines parallel to the lateral ventricles on a coronal cUS (a, short arrow) of a preterm infant (gestational age 27.7 weeks) with a postmenstrual age at day of scanning of 33.0 weeks correlating with low signal intensity lines on contemporaneous reconstructed coronal T_2-weighted MR image (b, short arrow). The cUS scan also illustrates bilateral echogenic areas supero-laterally from the lateral ventricles (a, long arrow) correlating with high signal intensity areas on the T_2-weighted MR image (b, long arrow).

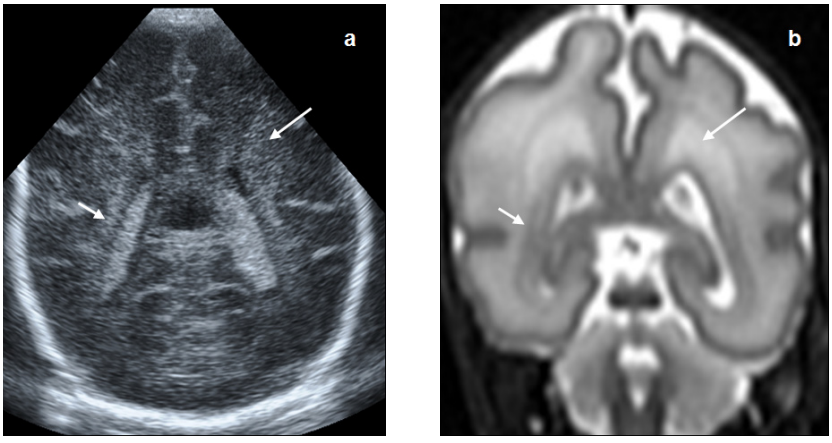


Table 1. Prevalence of echogenic cUS features and predictive values of cUS features for correlating features on contemporaneous T_2-weighted MRI
(LV, lateral ventricles; n, number of infants; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value)

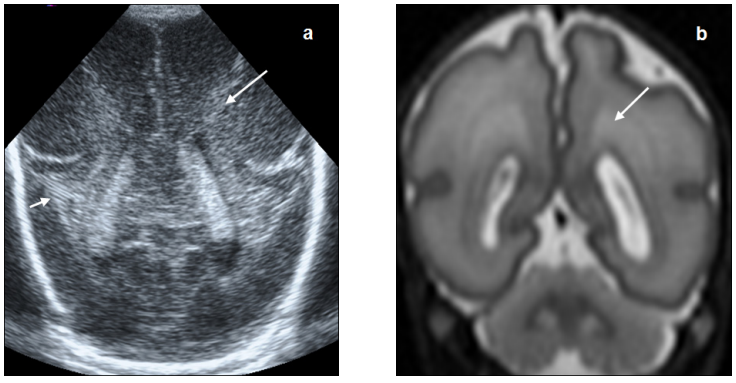
cUS features	Group of infants	Prevalence on cUS (%) (n seen)	Predictive values of correlation cUS – MRI (%)			
			Sensitivity	Specificity	PPV	NPV
Frontal echogenic blush	Preterm (n=35)	91 (32)	100	33	94	100
	Term (n=9)	56 (5)	80	NA	50	NA
Echogenic lines around/ below LV	Preterm (n=35)	83 (29)	100	NA	83	NA
	Term (n=9)	44 (4)	100	20	50	100
Echogenicity supero-laterally of LV	Preterm (n=35)	83 (29)	93	50	90	60
	Term (n=9)	78 (7)	43	100	100	33
Echogenic lines parallel to LV	Preterm (n=35)	51 (18)	89	53	67	82
	Term (n=9)	11 (1)	100	50	20	100
Temporo-occipital echogenic blush	Preterm (n=35)	26 (9)	NA	100	NA	74
	Term (n=9)	0 (0)	NA	100	NA	100

Echogenic lines running parallel to the LV

Echogenic lines running parallel to the posterior horns of the LV were seen in 18 of 35 (51%, 14 bilateral, four unilateral) preterm infant scans and in one of nine (11%, all bilateral) term-born infant scans (Figure 3). For the preterm infants mean PMA and weight at scanning were significantly lower for the infants with the lines than for those without (p=0.004 for both).

In 16 preterms and the one term-born infant with echogenic lines parallel to the LV, low SI lines were seen in the same location on MRI (Figure 3). In eight of 17 preterm infants and four of eight term-born infants without these echogenic lines, low SI lines were seen on MRI. The predictive values of these echogenic lines for correlating features on MRI are shown in Table 1.

Figure 4. Bilateral temporo-occipital echogenic blushes on a coronal cUS (a, short arrow) of a preterm infant (gestational age 26.6 weeks) with a postmenstrual age at day of scanning of 27.1 weeks and contemporaneous reconstructed coronal T_2-weighted MR image without correlating feature (b). The cUS scan also illustrates bilateral echogenic areas supero-laterally from the lateral ventricles (a, long arrow) correlating with high signal intensity areas on the T_2-weighted MR image (b, long arrow).



Temporo-occipital echogenic blush

A temporo-occipital echogenic blush was detected in nine (26%, bilateral in all) of the preterm cUS scans and in none of term-born infant scans (Figure 4). Mean PMA and weight at scanning were significantly lower for the preterm infants with the blushes than for those without (p=0.0004 and p=0.002, respectively).

No correlating feature for the temporo-occipital echogenic blushes was seen on the T_2-weighted MRI for either preterm or term-born infants (Figure 4). The predictive values of the echogenic blushes for correlating features on MRI are shown in Table 1.

Areas of echolucency

Cortical subplate

In the more peripheral regions of the hemispheres echogenicity was generally low and lower than in the more central areas of the hemispheric WM but was, even when higher frequencies up to 10 MHz were applied, not specifically lower in the regions identified as representing subplate on the MRI scans (Figures 5 and 6). On the T_2-weighted MR images, regions corresponding to the cortical subplate were seen in 29 preterm infants and one term-born infant.

Figure 5. The cortical subplate visible as a high signal intensity layer on a sagittal T_2-weighted MR image (b, asterisks) of a preterm infant (gestational age 26.6 weeks) with a postmenstrual age at day of scanning of 27.1 weeks. On the contemporaneous parasagittal cUS scan of the same infant the cortical subplate cannot be identified (a). The cUS scan illustrates an echogenic area supero-laterally from the lateral ventricles (a, arrow) correlating with a high signal intensity area on the T_2-weighted MR image (b, arrow), as shown in Figures 3 and 4.

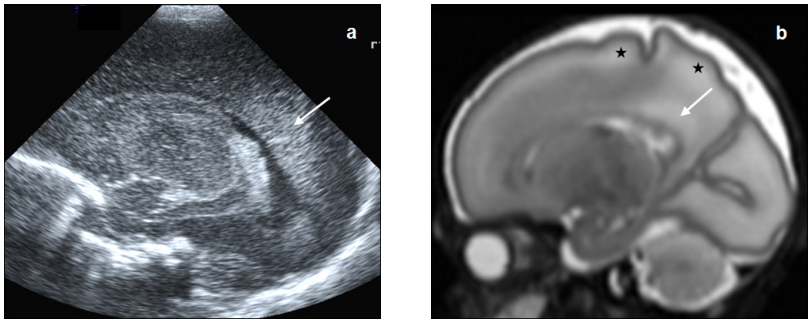
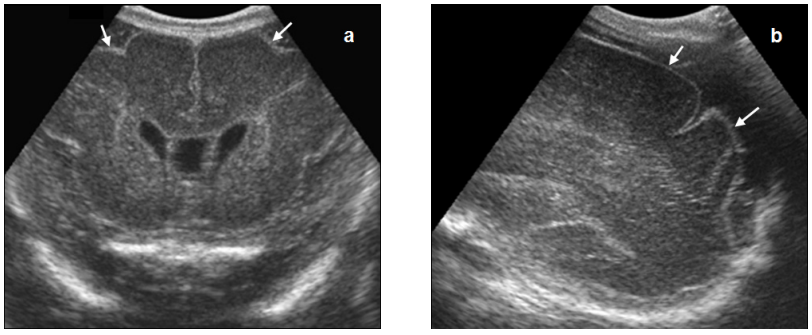


Figure 6. Coronal (a) and parasagittal (b) cUS of a preterm infant (gestational age 26.9 weeks) with a postmenstrual age at day of scanning of 26.9 weeks, performed with a transducer frequency set at 10 MHz and focusing on the cortical area. The cortical layer (arrows) can be nicely distinguished, being of higher echogenicity as compared to the white matter, but the cortical subplate and the subcortical white matter cannot be distinguished separately.

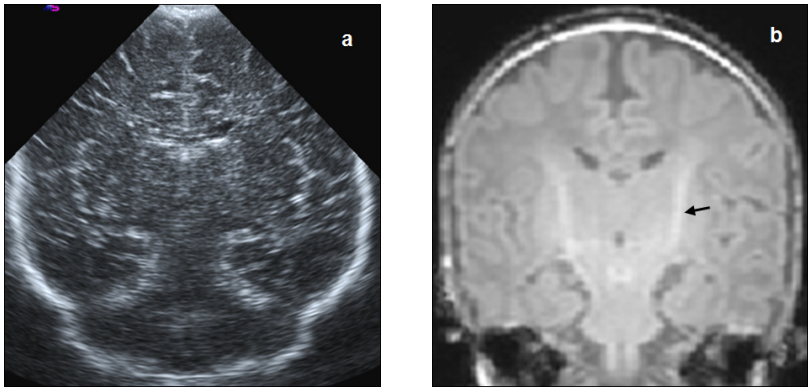


Internal capsule

In five preterm and four term-born cUS scans bilateral echolucent bands were seen running vertically through the basal ganglia between the lentiform and thalamic nuclei at a range of PMAs both before and after TEA. The site of these echolucent bands correlated with the site of the posterior limb of the internal capsule (PLIC) on contemporaneous MRI. On all MR images from both the preterm and term-born infants

the site of the PLIC was distinguished (Figure 7), whether or not the PLIC was myelinated on MRI. On the MR images myelin was detected in the PLIC in 20 preterm infants, who were all > 36 weeks' PMA at time of scanning, and all term-born infants (Figure 7). No significant differences in GA, birth weight and PMA and weight at scanning were found between infants with and without this echolucent band.

Figure 7. Myelination of the posterior limb of the internal capsule visible as high signal intensity at the site of the posterior limb of the internal capsule on a reconstructed coronal T_1-weighted MR image (b, arrow) of a preterm infant (gestational age 31.6 weeks) with a postmenstrual age at day of scanning of 44.0 weeks. On a contemporaneous coronal cUS scan of the same infant myelination of the posterior limb of the internal capsule cannot be identified (a).



Pons

The posterior pons, which myelinates early and before the age at which all scans in this study were obtained, was always very echolucent compared to the anterior pons which was of intermediate echogenicity (Figure 8). The posterior pons was of short T_2 on all the MR images obtained in this study, consistent with myelination. Myelinated tracts were not identified in the anterior pons on the T_2-weighted images as expected at this gestation.

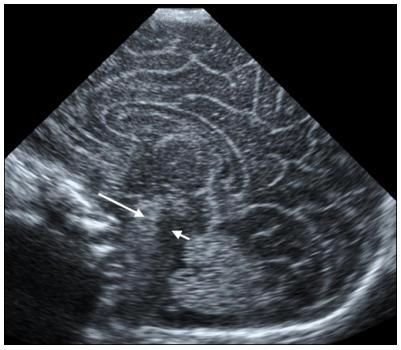


Figure 8. cUS scan in the mid-sagittal plane of a preterm infant (gestational age 31.7 weeks) with a postmenstrual age at day of scanning of 34.3 weeks showing that the posterior part of the pons (short arrow) is relatively echolucent compared the anterior part of the pons (long arrow).

Discussion

Our study has shown that except for the temporo-occipital echogenic blush, bilateral symmetrical areas of increased echogenicity, located in the frontal and periventricular WM, correlate well with areas of altered SI in WM, described as maturational features, on MRI (2,16,21-25,27). Occasionally the site of the PLIC could be distinguished as an echolucent line running vertically between the basal ganglia and the thalami, and the myelinated WM tracts in the posterior pons were always very echolucent compared to the anterior pons. The region of the cortical subplate, which is usually considered as subcortical WM on cUS, could not be reliably identified though this region tended to be of low echogenicity on scans of all gestation.

No significant differences in GA and birth weight were found between preterm and term-born infants with and without the echogenic cUS features. Although the bilateral features were present in preterm and term-born infants, they were better seen in the preterm infants. Their symmetry, prevalence, persistence and gradual diminution with increasing GA in a population of apparently well preterm infants without overt cerebral abnormalities would suggest a non-pathological origin. This is in agreement with van Wezel-Meijler's study describing localized echogenic areas in the frontal periventricular WM, probably comparable to our frontal echogenic blushes and echogenic lines around/below and parallel to the LV in preterm infants scanned before TEA. These echodensities faded or disappeared around TEA, correlated well with areas of altered SI on MRI and were considered a normal phenomenon. They were hypothesized to be remnants of the germinal matrix (16).

Boxma et al. have recently described an echogenic area running parallel to the postero-lateral ventricular margin in 84% of preterm infants < 32 weeks' gestation. They also argued that its location, prevalence, symmetry and unchanged character between 26 and 31 weeks' GA suggests that it represents an anatomical structure, probably part of the optic radiation, and is a normal feature of developing WM (28).

The frontal echogenic blushes and the echogenic areas supero-laterally from the LV correlated well with high SI areas on T_2-weighted MR images, recently called crossroad areas, considered to reflect areas of dense WM fibres (27). The echogenic lines around/below and parallel to the LV correlated well with low SI lines on T_2-weighted images, considered to reflect areas of accumulating microglial cells (27). These altered SI areas are thought to represent features of developing WM (22-25,27).

The reason for the variability in signal on T_2-weighted MR images, i.e. some echogenic features correlated with high SI areas, others with low SI areas, is interesting. On T_2-weighted images, high SI generally represents a higher water content and unmyelinated fibre-rich areas and low SI a lower water content and cell-dense areas, though this may not always be the case with the cortical subplate. Echogenic areas on cUS can represent various normal and abnormal processes and different structures and tissue compositions, making the distinction between cell-dense and fibre-rich areas difficult. To explore the signal inconsistency further precise histological correlates are needed.

The reason that we did not find a MRI-correlate for the temporo-occipital echogenic blush is not clear. Boxma et al. did not see the echogenic area they described via the posterior fontanel (28). They argued that this was related to the direction of insonation of fibres. As different angles are used for obtaining cUS and MR images and, consequently, cerebral structures and tissues are approached differently, this might be an explanation. However, contrary to Boxma et al. we also detected the temporo-occipital blushes via the posterior fontanel (data not given). In addition, for all other cUS features a MRI-correlate was found. Another contributory explanation might be that cUS and MRI are different imaging techniques; ultrasound imaging is based on differences in speed of sound waves between and within tissues, whereas MR imaging exploits differences in tissue proton density and relaxation times. The tissue composition at the site of the temporo-occipital blush may, compared to surrounding tissue, induce a change in speed of sound waves but might not be different with respect to proton density.

Although it is most likely that the bilateral echogenic WM features on cUS represent maturational processes, they may not be entirely normal. A fetal cUS study has shown that echogenic areas in the frontal periventricular WM occurred at a later GA in high-risk than low-risk fetuses (30). Different layers in the WM (i.e. inner periventricular, intermediate and outer subcortical layer), anterior caps and posterior arrowheads, seen as areas of altered SI, are present on almost all early preterm brain MR images and usually become less obvious with increasing GA. Early loss of these features or delay in fading with increasing GA has been associated with cerebral abnormalities (16,22-25). The WM in preterm infants at TEA appears less mature than in term-born infants (9,26). Layers of altered SI on MRI can be distinguished in fetal WM becoming less obvious around 28 weeks' GA, corresponding with the completion of neuronal migration from the ventricular zone to the cortical plate (27,31). Judas et al. have recently described that after 28 weeks' gestation, the periventricular crossroad areas in post-mortem brains of preterm infants retain their MR features only on T_1-weighted images (27). In our study, using T_2-weighted MR images, the cUS and correlating MRI features were seen in all infants scanned at a PMA of > 28 weeks. These findings support the hypothesis that some of the MRI features described as maturational processes of the preterm brain may, in part, be a sign of delayed or abnormal rather than normal maturation. Thus the correlating cUS features we describe may also represent delayed maturation or even mild WM injury and be an imaging correlate for the neurodevelopmental problems in preterm infants without evidence of focal brain injury.

The cortical subplate is a cell- and water-rich layer, visible on T_2-weighted images as a high SI layer (27,32-33). Even when using higher frequencies, we were not able to identify positively the cortical subplate, apparent on our T_2-weighted images, on cUS though the corresponding area was usually of low echogenicity (Figures 5 and 6). An explanation for this may be that although it has a higher cellular content than the adjacent (subcortical) WM and might therefore be expected to be more echogenic, the high water content opposes this, rendering the cortical subplate equally echogenic as the (subcortical) WM.

In a few infants the site of the PLIC was distinguished as an echolucent band running between the normally appearing basal ganglia and thalami. Myelin in the PLIC can probably not be distinguished on cUS, especially as there was no consistency between the PLIC being visible on cUS and myelin being present on MRI and we saw this low

signal line on cUS scans done both before and after TEA. It is interesting to note, however, that on all scans the posterior pons was always very echolucent compared to the anterior part. The posterior pons myelinates early and signs of myelination are seen on T_1-weighted MR images from 23 weeks´ GA, whereas the anterior pons shows myelination only after term age (3). The difference in echogenicity might be explained by a difference in myelination or rather a difference in water content related to myelination and be especially obvious when insonated parallel to fibre orientation. The visibility of the site of the PLIC on some scans may also reflect early tract development of fibres in a similar plane but not been so easily seen as in the pons as the PLIC is small and fibres do not run exactly parallel to the plane of insonation (34). To our knowledge, this has not been described before and needs further investigation. However, the difference in echogenicity in the pons may also be explained by the difference in orientation of fibres between the anterior and posterior pons. Of interest, in an abnormal context, the visibility of the site of the internal capsule has been reported in severe perinatal asphyxia (35) but this may be dependent on the adjacent abnormal echogenicity in the central grey matter structures which is not the explanation in this study.

We accept limitations to our study; it was sometimes difficult to view cUS and MR images in exactly the same planes. No direct histological correlates were obtained and, therefore, the correlation between cUS and histology is presumptive. However, we believe that by matching the cUS scans with contemporaneous MRI and histological data in the literature, the associations described in this study are valid. Serial cUS and MRI data were not obtained and, therefore, it was not possible to explore whether the cUS features fade consistently with increasing GA and, if so, when. We did not include infants with overt cerebral pathology. It would be important to explore whether there are differences in presence and appearance of the cUS features between infants with and without cerebral pathology. This would help to determine whether the features in the WM reflect normal maturational processes or rather abnormal maturation or injury. Finally, assessment of echogenicity by visual analysis is subjective. So far, no easily applicable and reliable technique for quantifying echogenicity is available.

In conclusion, this study has shown that bilateral symmetrical echogenic areas in the frontal and periventricular WM are frequently seen on early preterm cUS scans and, except for the temporo-occipital echogenic blush, correlate well with areas of altered SI in WM on MRI. We could not reliably identity the cortical subplate or the PLIC.

However, the site of the PLIC was sometimes visible and the posterior myelinated pons was always echolucent. The imaging features, both on MRI and cUS, described in this study most likely reflect normal but may in some cases reflect delayed or even abnormal maturational processes in the hemispheres. Approaches to understand their significance include follow-up studies of infants in whom the time-course of these features has been carefully documented from cUS and MRI, histological studies where cUS and MR imaging have been obtained shortly prior to death and studies comparing these features seen in infants born preterm with sequential optimized fetal neuro-imaging studies.

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Chapter 8

Comparing brain white matter on sequential cranial ultrasound and MRI in very preterm infants

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Abstract

Background and Aim:

Periventricular white matter (WM) echodensities, frequently seen in preterm infants, can be associated with suboptimal neurodevelopment. Major WM injury is well detected on cranial ultrasound (cUS). cUS seems less sensitive for diffuse or more subtle WM injury. Our aim was to assess the value of cUS and magnetic resonance imaging (MRI) for evaluating WM changes and the predictive value of cUS and/or MRI findings for neurodevelopmental outcome in very preterm infants with normal to severely abnormal WM on sequential high-quality cUS.

Patients and Methods:

Very preterm infants (< 32 weeks) who had sequential cUS and one MRI within the first 3 postnatal months were included. Periventricular WM on cUS and MRI was compared and correlated with neurodevelopmental outcome at 2 years corrected age.

Results:

Forty preterm infants were studied; outcome data were available in 32. WM changes on sequential cUS were predictive of WM changes on MRI. Severely abnormal WM on cUS/MRI was predictive of adverse outcome, and normal/mildly abnormal WM of favourable outcome. Moderately abnormal WM on cUS/MRI was associated with variable outcome. Additional MRI slightly increased the predictive value of cUS in severe WM changes.

Conclusions:

Sequential cUS in preterm infants is reliable for detecting WM changes and predicting favourable and severely abnormal outcome. Conventional and diffusion-weighted MRI sequences before term equivalent age in very preterm infants, suggested on cUS to have mild to moderately abnormal WM, do not seem to be warranted.

Introduction

Cranial ultrasound (cUS) is the preferred and most readily available tool to assess the neonatal brain (1). It is a safe and reliable technique for demonstrating the most frequently occurring forms of cerebral injury in preterm infants, assessing the evolution of lesions, and following brain development (1-7). Magnetic resonance imaging (MRI) demonstrates site and extent of cerebral lesions more precisely and shows maturational processes in detail (3-4,8-10).

In preterm infants, increased echogenicity in the periventricular white matter (WM), so-called periventricular flaring, may represent ischaemic and/or inflammatory damage. Flares are transient, persisting for a variable period of time, and can subsequently resolve or evolve into cystic lesions (2). When persisting for over one week and when the echogenicity exceeds that of the choroid plexus, flares are considered the first stage of periventricular leukomalacia (PVL) (2). Cystic forms of PVL are associated with neurological impairment and are well demonstrated by cUS (6,11-12). Milder flares, not evolving into cysts, are more frequently encountered in preterm infants and, if long-lasting, may also be associated with suboptimal or deviant neurological development, especially if there is change in ventricular size or shape (2,4-6,13-16). However, they may also represent normal maturational phenomena in the immature brain (9,17). Therefore, it is important to recognize pathological flares, especially those associated with neurological sequelae.

Diffuse WM injury has been described in MRI and pathology studies in newborn infants (4-5,10,12,18-24). Several studies have found a poor predictive value of cUS for detecting diffuse or more subtle WM injury (4-5,7,11-12,18,21,23). It has been suggested that MRI should be performed in all very preterm infants, particularly in those with only mild (non-cystic) or no WM changes on cUS (5,11-12,23). However, as MRI is more burdening to the newborn infant and more time-consuming and expensive than cUS, it is not a good tool for serial imaging of the neonatal brain, and it is important to know when MRI is warranted in sick, vulnerable preterm infants. In addition, if MRI is performed, it should be optimally timed in order to detect clinically significant lesions, assess brain maturation, and accurately predict outcome.

The aims of our study were to evaluate the predictive value of WM changes on sequential, high-quality cUS for those seen on MRI, to explore the additional value of MRI within the first 3 postnatal months for detecting WM changes, and to assess the predictive value of cUS and/or MRI findings for neurodevelopmental outcome in very preterm infants. This was done by comparing findings on sequential cUS examinations with MRI findings and by relating cUS and MRI findings to neurodevelopmental outcome at 2 years corrected age.

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 2001 and April 2004 and underwent at least one MRI examination during the neonatal period, were included in the study. Exclusion criteria were neonatal meningitis, metabolic disorders, chromosomal disorders, congenital cardiac abnormalities and specific syndromes. In unstable infants with septicaemia, the MRI procedure was postponed until the infant was in a stable clinical condition. Medical records, neuro-imaging findings and follow-up data were reviewed.

After exclusion, data of 40 very preterm infants (31 male) were studied. Mean GA of the infants was 28.6 (range 25.1-31.9) weeks and mean birth weight 1203 (689-2062) grams. The mean number of cUS scans performed in each infant during admission was seven (3-16). MRI examinations were performed for various indications including very preterm birth, ventricular dilatation, (suspicion of) parenchymal injury and/or grade 2 echodensities on cUS.

Mean postnatal age and corrected GA at MRI were, respectively, 34.4 (4-111) days and 33.2 (27.3-45.1) weeks. Eight out of 40 infants were scanned at a very young postnatal age of less than 10 days and 32 out of 40 infants thereafter. In five infants, MRI was performed around term equivalent age (TEA) at a mean corrected GA of 39.4 (38.9-40.9) weeks.

Cranial ultrasound

Sequential cUS scans were performed routinely in all very preterm infants, from the day of birth until discharge or transfer to another hospital, and around TEA, according to a standard protocol. The transducer frequency was set at 7.5 MHz. For detection of cortical and/or subcortical abnormalities, higher frequencies up to 10.0 MHz were used, whereas deeper structures were assessed with lower frequencies down to 5.0 MHz. All images were saved on magneto-optical disks.

Of all included infants, the first cUS scan, the cUS scan performed closest to the day of the MRI examination and the last cUS scan before discharge were evaluated retrospectively by at least two experienced investigators (LML, research physician, IPdB, neonatologist, and GvWM, neonatologist) by consensus. The names of the infants were masked on the cUS scans, so the investigators were unaware of the MRI findings and outcome of the infants. Special attention was paid to the presence of echogenicity changes in the brain WM. For each area in the brain (frontal, parietal, occipital, and temporal) the presence and appearance of periventricular echodensities was recorded. The degree of echogenicity of the WM was scored according to the classification by van Wezel-Meijler et al. (9), which gives information on the intensity of periventricular echogenicity. A comment on homogeneity or inhomogeneity of the WM was added (10):

- Grade 0: Normal echogenicity of the periventricular WM (< choroid plexus)
- Grade 1: Moderately increased echogenicity of the periventricular WM, the affected region (or smaller areas within the affected region) being almost as bright or as bright as the choroid plexus. Separate notation: homogeneous, inhomogeneous
- Grade 2: Severely increased echogenicity, the affected region (or smaller areas within the affected region) being obviously brighter than the choroid plexus. Separate notation: homogeneous, inhomogeneous

PVL was scored according to the classification by de Vries et al. (2):

- Grade 1: Transient periventricular echodensities, persisting ≥ 7 days
- Grade 2: Transient periventricular echodensities, evolving into small, localized fronto-parietal cysts
- Grade 3: Transient periventricular echodensities, evolving into extensive periventricular cystic lesions
- Grade 4: Echodensities extending into the deep WM, evolving into extensive cystic lesions

Peri- and intraventricular haemorrhages were classified according to Volpe (25). The presence of other abnormalities was recorded.

The cUS scans of each infant were scored based on WM changes, i.e. grade of echogenicity and/or PVL. Subsequently, the cUS scans were classified according to the most severe changes in the WM during admission. This was done to enable comparison of the cUS and MRI findings. Sequential cUS scans without echodensities or with homogeneous grade 1 echogenicity were classified as normal (9). cUS scans with inhomogeneous grade 1 echogenicity were classified as mildly abnormal, regardless of the total duration (9-10). Scans with grade 2 echogenicity, regardless of the total duration, and/or localized, small cystic lesions (PVL grade 2) were classified as moderately abnormal, and those with multicystic PVL (PVL grades 3 and 4) and/or focal echodensities within the WM as severely abnormal (2,9-10).

MRI

MR images were obtained in 40 preterm infants according to a standard MR imaging protocol for newborn infants, using a 1.5 Tesla Philips MR system (Philips Medical Systems, Best, the Netherlands). This protocol comprised T_1-, T_2-, and diffusion-weighted images in the axial plane (slice thickness 4-5 mm, field of view 18-20 cm^2), and T_1-weighted images in the sagittal plane.

The infants were laid supine and snugly swaddled-up during the scanning procedure. Ear protection consisted of neonatal earmuffs (Natus MiniMuffs; Natus Medical Inc, San Carlos, CA, USA). The infant's head was immobilized with moulded foam, placed around the head. Temperature was maintained and heart rate and oxygen saturation were monitored throughout the procedure. A paediatrician experienced in resuscitation and MR procedures was present during the scanning.

All MRI examinations were assessed by consensus by two experienced investigators (GvWM, neonatologist, and LL, paediatric neuroradiologist). The names of the infants were masked on the MR images, so the investigators were unaware of the cUS findings and outcome of the infants. Special attention was paid to the signal intensity (SI) of brain WM. WM injury was scored according to Sie et al. (10). This scoring system was used to rate increasingly severe changes in the periventricular WM. Whenever characteristics of more than one MRI score were present, the highest score was used. MRI scores were

subdivided into different groups to enable comparison of MRI with cUS and to relate MRI to outcome. MRI examinations without WM changes (grade 1) were classified as normal, those with grade 2 and 3 changes (i.e. periventricular zone of changed SI, or ≤ 6 punctate WM lesions) as mildly abnormal, those with grade 4 changes (i.e. > 6 punctate WM lesions and/or small periventricular cysts and/or a few larger focal haemorrhages) as moderately abnormal, and those with grade 5 (i.e. extensive SI changes with haemorrhagic or (pre)cystic lesions in the periventricular WM, with, at most, focal subcortical extension) and grade 6 changes (i.e. diffuse SI changes with haemorrhagic or (pre)cystic lesions involving both the periventricular and subcortical WM) as severely abnormal. Presence of abnormalities other than WM changes was recorded. For MRI examinations performed around TEA (38-42 weeks' gestation), the presence of areas of diffuse and excessive high SI, diffusely distributed within the periventricular or subcortical WM (DEHSI) (19), was recorded on T_2-weighted MR images as a separate entity.

Neurodevelopmental outcome

Preterm infants born at a GA of < 32 weeks and admitted to the neonatal unit of the LUMC participated in a standardized follow-up program until the corrected age of 5 years. In a total of 32 out of 40 preterm infants (80%) with sequential cUS examinations and one or more MRI examinations outcome data were available. From eight out of 40 infants (20%), no outcome data at the corrected age of 24 months were available; two infants (5%) died during the neonatal period, one because of respiratory complications, and the other because of circulatory problems, and six infants were lost to follow-up. The infants were assessed by neonatologists with advanced training. For the purpose of this study, neurodevelopmental outcome data of the examination closest to the corrected age of 24 months were recorded. Mean corrected age at the follow-up examination was 23.2 (22.5-26.0) months. For most infants (n=24), Bayley Scales of Infant Development II scores for motor and mental development were available (26). A Mental or Psychomotor Developmental Index (MDI, PDI) of ≥ 85 was considered normal, a MDI or PDI between 70 and 84 as mildly abnormal, a MDI or PDI between 55 and 69 as moderately abnormal, and a MDI or PDI of < 55 as severely abnormal. Infants of whom Bayley II scores were not available, were assigned to one of the four outcome groups based on the available data from the outpatient clinic.

For this study, normal and mildly abnormal outcome were considered as favourable outcome and moderately and severely abnormal outcome as adverse outcome.

Data analysis

Statistical analyses were performed using SPSS software (version 12.0; SPSS inc., Chicago, Illinois, USA). cUS and MRI findings were compared. Predictive values of cUS findings for MRI findings and cUS and/or MRI findings for neurodevelopmental outcome were calculated. For the purpose of this study, normal and mildly abnormal neuro-imaging findings and normal and mildly abnormal outcome findings were considered together as one group.

Results

Cranial ultrasound (n=40)

In 37 out of 40 infants (93%), periventricular echodensities were seen on sequential cUS. The echodensities persisted for over 7 days and evolved into cystic lesions in 35%. In 22 out of 37 infants, the echodensities had an inhomogeneous appearance in one or more areas of the periventricular WM, while in the other infants, echodensities were consistently homogeneous. In three infants (8%), no echodensities were seen. Twenty-three infants (58%) had grade 1 (14 homogeneous, nine inhomogeneous) and one (3%) grade 2 (homogeneous) echogenicity, and seven infants (18%) had grade 2 and six (15%) grade 3 PVL. In 26 infants (65%), the WM was scored as normal to mildly abnormal, in eight (20%) as moderately abnormal, and in six (15%) as severely abnormal.

MRI (n=40)

In eight out of 40 infants (20%), no WM abnormalities were detected on MRI (grade 1). Eleven infants (28%) showed high SI areas in the periventricular WM (grade 2). In 16 infants (40%) punctate lesions were seen in the WM on both T_1- and T_2-weighted images; in seven infants (18%) six or less (grade 3) and in nine (23%) more than six (grade 4). Four infants (10%) had extensive SI changes in the periventricular WM with haemorrhagic and/or cystic lesions (grade 5) and one infant (3%) had diffuse SI changes

in the periventricular and subcortical WM with haemorrhagic and cystic lesions (grade 6).

In 26 infants (65%), the WM was scored as normal to mildly abnormal, in nine (23%) as moderately abnormal, and in five (13%) as severely abnormal on MRI. In all five infants who underwent MRI around TEA, DEHSI was seen in the frontal and occipital WM on T_2-weighted images.

Relation between cUS and MRI (n=35)

Twenty-four out of 35 infants had normal to mildly abnormal, six moderately abnormal, and five severely abnormal WM on both cUS and MRI. The relation between WM changes on cUS and those on MRI are depicted in Table 1. The predictive values of normal to mildly abnormal WM on cUS for normal to mildly abnormal WM on MRI were: sensitivity 0.92, specificity 0.86, positive predictive value (PPV) 0.92, and negative predictive value (NPV) 0.86; those of moderately abnormal WM on cUS for moderately abnormal WM on MRI, respectively, 0.75, 0.91, 0.67, and 0.94; and those of severely abnormal WM on cUS for severely abnormal WM on MRI, respectively, 0.83, 1.00, 1.00, and 0.97. So, sequential cUS predicted WM changes on neonatal MRI.

In 14 out of 23 infants with grade 1 echodensities on cUS, the echodensities had a homogeneous appearance, while in nine out of 23, they appeared inhomogeneous. In the 14 infants with homogeneous echodensities, MRI showed normal WM in four, a periventricular zone of changed SI in eight and punctate lesions in two. In the nine infants with inhomogeneous echodensities, MRI showed normal WM in one, a periventricular zone of changed SI in two, and punctate lesions in six. In the infant with homogeneous grade 2 echodensities, MRI showed punctate WM lesions.

In six out of seven infants with punctate WM lesions on MRI, cUS showed inhomogeneous echodensities in the periventricular WM. These were grade 1 echodensities in five infants and grade 2 echodensities in one infant.

In none of the infants, additional lesions were seen on sequential cUS after the MRI was performed, and the longest time-interval between the MRI and the last cUS examination that was scored was 10 days.

Examples of WM changes on cUS and MRI examinations of studied infants are presented in Figures 1-5.

Table 1. Relation between white matter changes on sequential cUS and on neonatal MRI within the first 3 postnatal months
(n, number of infants)

cUS findings (n=40)	MRI findings		
	Normal/mildly abnormal (n=26)	Moderately abnormal (n=9)	Severely abnormal (n=5)
Normal/mildly abnormal (n=26)	24	2	
Moderately abnormal (n=8)	2	6	
Severely abnormal (n=6)		1	5

Figure 1. Coronal (a) and parasagittal (b) cUS scan of a preterm infant (gestational age 25.1 weeks) at a corrected gestational age of 32.0 weeks (postnatal age 48 days) showing normal appearing brain white matter (classified as normal white matter). Note the symmetrical, subtle echodensities in the frontal white matter that are considered a normal finding in this age group (arrow; reference 9), and the symmetrical echodensities in the area of the basal ganglia (asterisks; reference 36). Transverse T_1- (c) and T_2- (d) weighted MR image at the level of the basal ganglia of the same infant, performed on the same day as the cUS scans, also showing normal appearing brain white matter (classified as normal white matter). Note the normal maturational phenomena of the white matter, especially prominent on the T_2-weighted MR image, showing bands of alternating signal intensity within the white matter (arrows; reference 19). This infant had a normal outcome at 2 years corrected age.

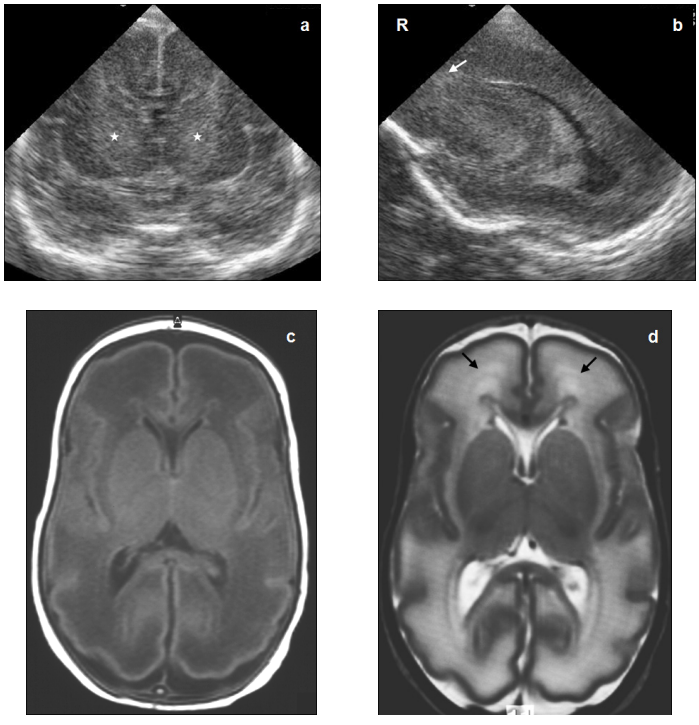


Figure 2. Parasagittal cUS scans (a and b) of a preterm infant (gestational age 28.0 weeks) at a corrected gestational age of 32.4 weeks (postnatal age 31 days) showing mildly increased echogenicity (less than the echogenicity of the choroid plexus) in the parietal white matter (arrows; classified as normal white matter). cUS also demonstrated a right-sided intraventricular haemorrhage grade 2 (not shown here). Transverse T_1- (c) and T_2- (d) weighted MR image at high ventricular level of the same infant, performed 3 days after the cUS scans (postnatal age 34 days), showing punctate haemorrhages (< 6) in the periventricular white matter on the right (arrows; classified as mildly abnormal white matter), an intraventricular haemorrhage on the right, and a very small germinal matrix haemorrhage on the left. This infant had a mildly abnormal outcome at 2 years corrected age.

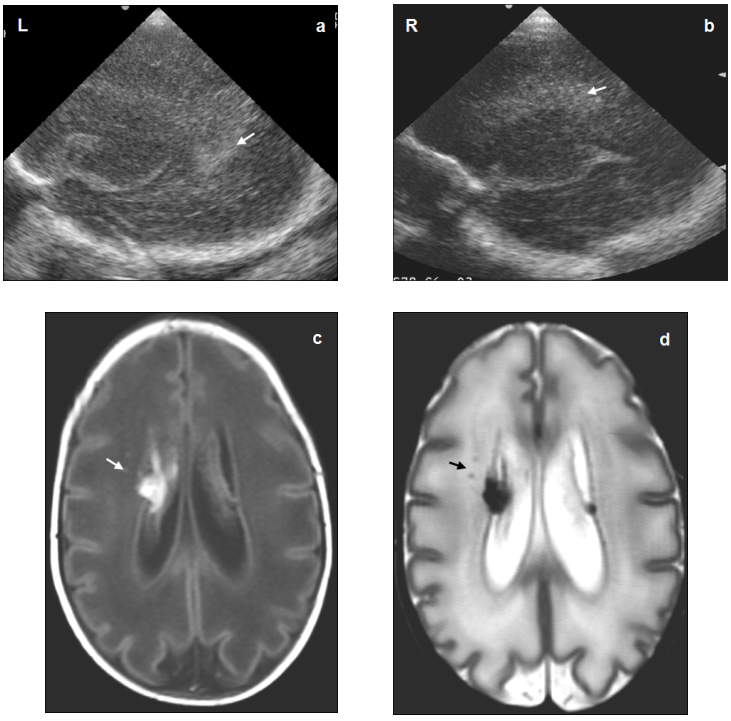


Figure 3. Coronal (a) and parasagittal (b and c) cUS scans of a preterm infant (gestational age 28.1 weeks) at a corrected gestational age of 31.0 weeks (postnatal age 20 days) showing an intraventricular haemorrhage (long arrow) with periventricular intraparenchymal echodensity on the left (medium arrow), rather localized inhomogeneously increased echogenicity in the parietal white matter on the left (short arrow; classified as severely abnormal white matter), and mildly increased echogenicity in the parietal white matter on the right (short arrow; classified as normal white matter). Transverse T_1- (d) and T_2- (e) weighted MR image at the level of the centrum semiovale of the same infant, performed 1 day before the cUS scans (postnatal age 19 days), showing bilateral signal intensity changes in the parieto-occipital white matter on the T_2-weighted MR image (e, long arrows), possibly a normal finding at this age, and several small cystic lesions and punctate haemorrhagic lesions (> 6) in the parietal white matter on the left on the T_1- (d) and T_2- (e) weighted MR image (short arrows; classified as severely abnormal white matter). These abnormalities were also seen at a lower level and extended into the ipsilateral basal ganglia and internal capsule. This infant had a severely abnormal outcome at 2 years corrected age.

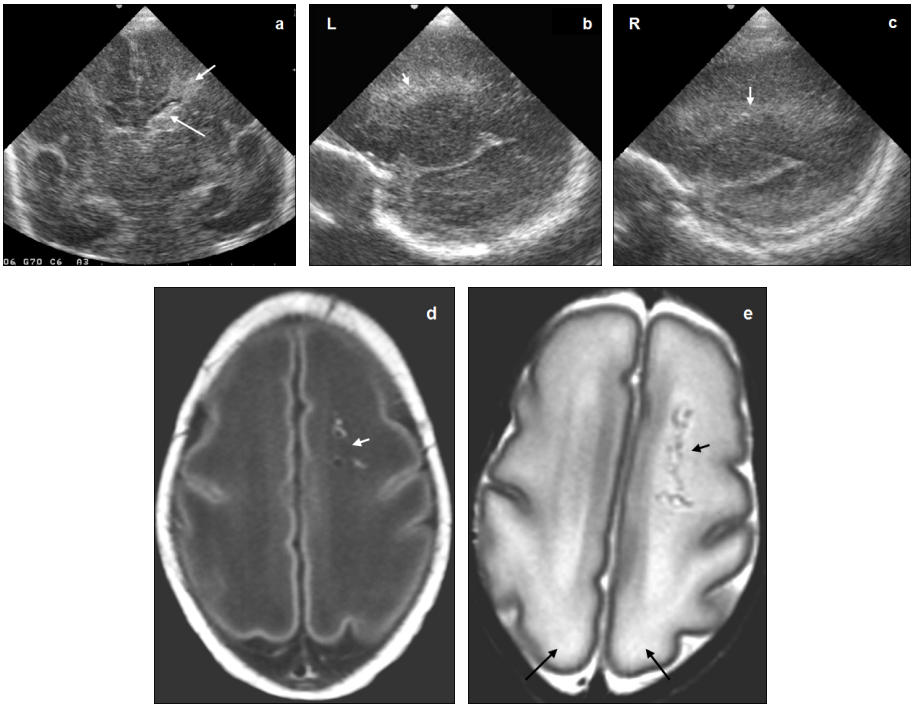


Figure 4. Coronal (a) and parasagittal (b and c) cUS scans of a preterm infant (gestational age 29.1 weeks) at a corrected gestational age of 33.0 weeks (postnatal age 27 days) showing inhomogeneously increased echogenicity in the parietal white matter on both sides (arrows; classified as moderately abnormal white matter). Note the symmetrical echodensities in the area of the basal ganglia (reference 36). Parasagittal T_1-weighted MR image (d) through the right lateral ventricle and basal ganglia region and transverse T_2-weighted MR image (e) at the level of the centrum semiovale of the same infant, performed 2 days after the cUS scans (postnatal age 29 days), showing multiple haemorrhagic lesions (> 6) in the white matter, being punctate on the right (short arrows) and also more extensive on the left (long arrow; classified as moderately abnormal white matter). This infant had a moderately abnormal outcome at 2 years corrected age.

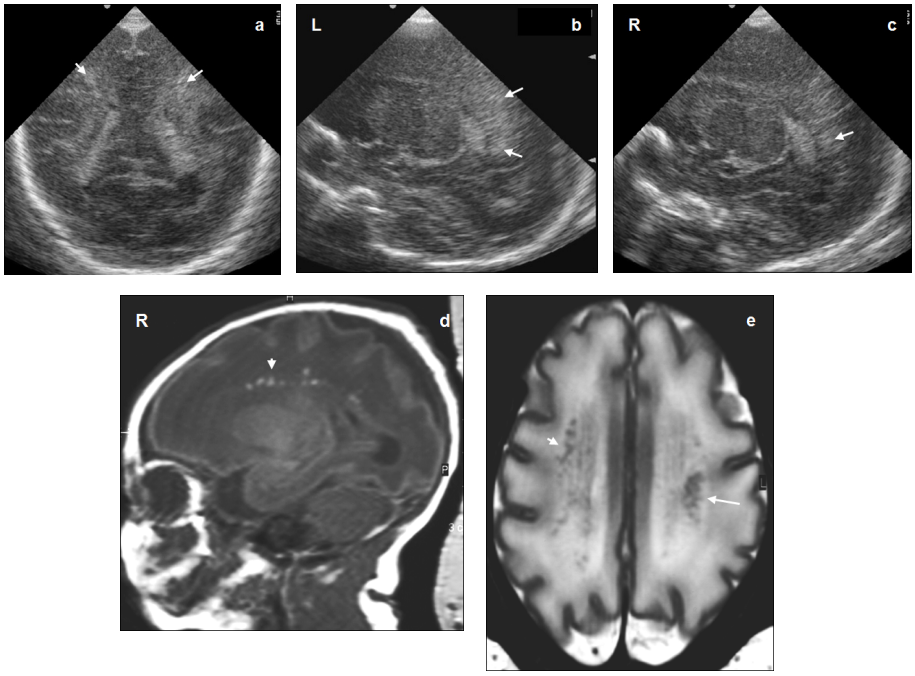
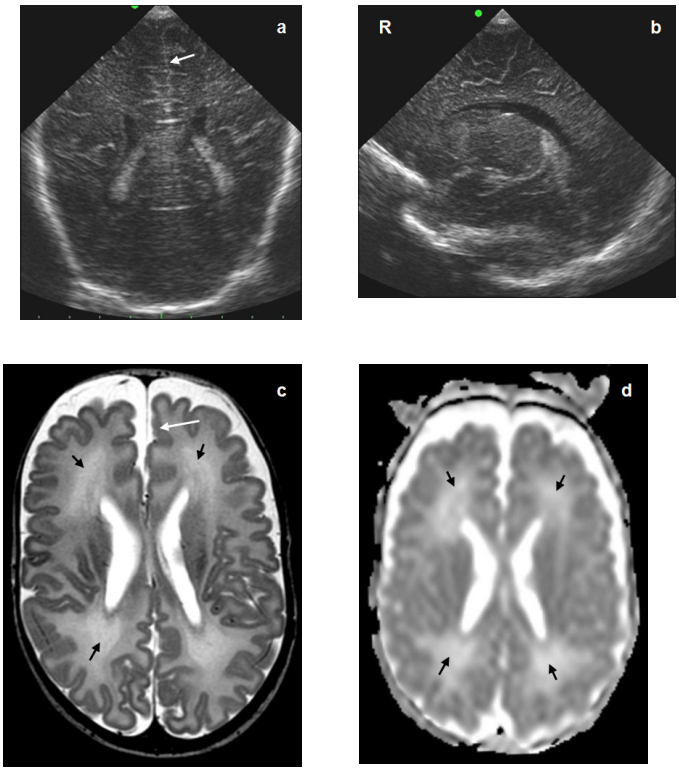


Figure 5. Coronal (a) and parasagittal (b) cUS scan of a preterm infant (gestational age 26.3 weeks) around term equivalent age (corrected gestational age 42.0 weeks, postnatal age 105 days) showing a widened interhemispheric fissure (arrow) and normal appearing brain white matter (classified as normal white matter). Transverse T_2- (c) and diffusion-weighted (d) MR image at high ventricular level of the same infant, performed on the same day as the cUS scans, showing a widened interhemispheric fissure in the frontal region (long arrow). Also showing diffuse and excessive high signal intensity in the frontal and parieto-occipital white matter on the T_2-weighted image (c, short arrows), and high signal in the frontal and parieto-occipital white matter on the diffusion-weighted image (d, short arrows). This infant had a mildly abnormal outcome at 2 years corrected age.



Neurodevelopmental outcome (n=32)

Twenty out of 32 infants (63%) were classified as normal to mildly abnormal, five (16%) as moderately abnormal, and seven (22%) as severely abnormal.

Relation between cUS and outcome (n=32)

The relation between cUS findings and neurodevelopmental outcome is shown in Table 2. The predictive values of normal to mildly abnormal and severely abnormal cUS findings for, respectively, normal to mildly abnormal (favourable) and severely abnormal outcome are shown in Table 3. Moderately abnormal cUS findings were associated with variable outcome. So, normal to mildly abnormal WM on cUS was predictive of normal to mildly abnormal outcome and severely abnormal WM on cUS of severely abnormal outcome, while moderately abnormal WM on cUS had low predictive values for moderately abnormal outcome.

Table 2. Relation between cUS findings and neurodevelopmental outcome at 2 years corrected age
(n, number of infants)

cUS findings (n=32)	Outcome		
	Normal/mildly abnormal (n=20)	Moderately abnormal (n=5)	Severely abnormal (n=7)
Normal/mildly abnormal (n=21)	17	2	2
Moderately abnormal (n=7)	3	2	2
Severely abnormal (n=4)		1	3

Table 3. Predictive values of normal to mildly abnormal and severely abnormal cUS and/or MRI findings for, respectively, normal to mildly abnormal and severely abnormal neurodevelopmental outcome at 2 years corrected age
(n, number of infants; NPV, negative predictive value; PPV, positive predictive value)

Neuro-imaging findings		Predictive values for outcome			
		Sensitivity	Specificity	PPV	NPV
cUS findings (n=32)	Normal/mildly abnormal	0.81	0.73	0.85	0.67
	Severely abnormal	0.75	0.86	0.43	0.96
MRI findings (n=32)	Normal/mildly abnormal	0.80	0.67	0.80	0.67
	Severely abnormal	1.00	0.86	0.43	1.00
cUS and MRI findings (n=28)	Normal/mildly abnormal	0.79	0.78	0.88	0.64
	Severely abnormal	1.00	0.84	0.43	1.00

Relation between MRI and outcome (n=32)

The relation between MRI findings and neurodevelopmental outcome is shown in Table 4. Like for the cUS findings, the predictive values of MRI findings for outcome are shown in Table 3. Comparable predictive values for outcome were found for the MRI findings as for the cUS findings, although severely abnormal WM on MRI was highly predictive of severely abnormal outcome.

In six out of 32 infants, MRI was performed before the postnatal age of 10 days and in 26 out of 32 after 10 days. No differences were found in predictive values of MRI findings for outcome between the two subgroups.

There was no tendency for more severe WM changes (grades 4-6) occurring more often on MRI scans performed after 10 days than before 10 days.

None of the infants developed adverse events after the MRI examination that could be of importance for outcome.

Table 4. Relation between MRI findings and neurodevelopmental outcome at 2 years corrected age
(n, number of infants)

MRI findings (n=32)	Outcome		
	Normal/mildly abnormal (n=20)	Moderately abnormal (n=5)	Severely abnormal (n=7)
Normal/mildly abnormal (n=20)	16	2	2
Moderately abnormal (n=9)	4	3	2
Severely abnormal (n=3)			3

Relation between cUS combined with MRI and outcome (n=28)

From 19 infants with normal to mildly abnormal, all six infants with moderately abnormal and three infants with severely abnormal WM on both cUS and MRI, outcome data were available. The relation between cUS and MRI findings and neurodevelopmental outcome is shown in Table 5. Like for the cUS and MRI findings separately, the predictive values of the combined cUS and MRI findings for outcome are shown in Table 3. Comparable predictive values for outcome were found for the combined cUS and MRI findings as for the cUS findings alone, although severely abnormal WM on cUS and MRI was highly predictive of severely abnormal outcome. Thus, MRI performed within

the first 3 postnatal months slightly increased the predictive value of cUS for severely abnormal outcome.

Table 5. Relation between cUS and MRI findings and neurodevelopmental outcome at 2 years corrected age
(n, number of infants)

cUS and MRI findings (n=28)	Outcome		
	Normal/mildly abnormal (n=17)	Moderately abnormal (n=4)	Severely abnormal (n=7)
Normal/mildly abnormal (n=19)	15	2	2
Moderately abnormal (n=6)	2	2	2
Severely abnormal (n=3)			3

Relation between DEHSI and cUS and outcome findings (n=5)

In all five infants in whom MRI was performed around TEA, DEHSI was present in the frontal and occipital WM. DEHSI on MRI was associated with variable other neuroimaging findings; one infant had normal WM on cUS and MRI, one mildly abnormal WM and two moderately abnormal WM, and one mildly abnormal WM on cUS and normal WM on MRI. Four of the five infants (80.0%) with DEHSI did not have a normal outcome at 2 years corrected age.

Discussion

This study retrospectively assessed cUS and brain MRI findings within the first 3 postnatal months in very preterm infants, focusing on the periventricular WM. cUS and MRI findings were compared and related to neurodevelopmental outcome. Sequential cUS was predictive of WM changes on neonatal MRI. Our findings are partially consistent with several cUS, pathology, and MRI correlation studies in preterm infants, showing that cUS is a reliable tool for demonstrating major forms of WM lesions, including cystic PVL and parenchymal infarction (2-5,7,10-12,21), but a poorer predictor of diffuse and more subtle WM lesions, such as punctate WM lesions (4-5,7,10-12,18,21,23). In nearly all infants with punctate WM lesions on MRI, cUS showed inhomogeneous grade

1 echodensities in the periventricular WM. We therefore hypothesize that inhomogeneous grade 1 echodensities are the cUS correlate of punctate WM lesions. This is different from previous studies showing that in preterm infants with punctate WM lesions on MRI, no corresponding lesions are detected on cUS (10-11,21) and can be explained by our performance of frequent cUS examinations throughout the neonatal period until TEA. For this study, we did not only assess the cUS performed close to the MRI examination, but assessed three cUS examinations and used the cUS with the most severe WM changes for comparison with MRI.

In the 14 infants with homogeneous grade 1 echodensities, MRI showed normal WM or a periventricular zone of changed SI in all but two infants, while in the nine infants with inhomogeneous grade 1 echodensities, MRI showed punctate lesions in six. In the infant with homogeneous grade 2 echodensities, MRI showed punctate WM lesions. These findings suggest that inhomogeneous echodensities are associated with more severe WM changes on MRI than homogeneous echodensities, which is consistent with a previous study (10).

In all five infants with MRI around TEA, DEHSI was present in the WM. DEHSI is found in up to 80% of preterm infants around TEA and may persist for several weeks (4,19,27). It is associated with cerebral atrophy, WM lesions and significantly increased diffusivity, suggesting that it represents diffuse WM injury (19,22,24,27). Infants with DEHSI have a less optimal neurodevelopment than those with normal appearing WM around TEA (27-28), indicating that DEHSI can be of clinical importance and may be related to the high incidence of neurodevelopmental impairment in preterm infants (29). So far, no cUS correlate has been established for DEHSI. In our infants with DEHSI, WM changes on cUS were variable. Neurodevelopmental outcome of these infants tended to be suboptimal, which may not only be attributable to DEHSI but also to other (WM) abnormalities. From this small group of infants, no conclusions can be drawn about the relation between DEHSI and certain WM changes on cUS and neurodevelopmental outcome.

We found severely abnormal WM on cUS to be predictive of adverse neurodevelopmental outcome at 2 years corrected age, while normal or only mildly abnormal WM was predictive of favourable outcome. If the WM was moderately abnormal on cUS, outcome was variable. These results are partially consistent with those from previous

studies, indicating that severely abnormal WM on cUS generally predicts adverse outcome (3,6-7,30). However, in infants with normal WM, cUS has been suggested to be a poor predictor of neurodevelopmental outcome, attributed to the lower sensitivity of cUS for detecting diffuse and more subtle WM injury (4-5,11-12,18,21,23). Differences between those and our studies include the cUS classification of WM changes; we did not consider the total duration of periventricular echodensities but focused on their degree and homogeneity, comparing the echogenicity of the WM to that of the choroid plexus, and relating outcome to the most severe WM changes during admission. Only homogeneous grade 1 echodensities were considered a normal finding. Grade 2 echodensities were classified as moderately abnormal. Also the frequency and continuation of, and the interval between cUS examinations may differ between studies. We continued cUS throughout the neonatal period until TEA, while others performed cUS less frequently and/or only during the early neonatal period (23).

Several studies have suggested that milder echodensities, if long-lasting, may be associated with suboptimal or deviant neurological development (2,4-6,13-16). Although inhomogeneous echodensities seem to be associated with more severe WM changes on MRI (10), these studies did not make a distinction in appearance of echodensities. Of the 11 infants with homogeneous grade 1 echodensities for whom outcome data were available, 10 were normal or mildly abnormal (seven normal, three mildly abnormal) and only one was severely abnormal at 2 years. This latter infant showed bilateral intraventricular haemorhages grade 3 with post-haemorrhagic ventricular dilatation on neonatal cUS and MRI, which probably explains his severely abnormal outcome. We therefore hypothesize that homogeneous grade 1 echodensities represent normal maturational phenomena in the immature brain, especially if occurring in the frontal or parietal WM (9,17).

Like cUS, severely abnormal WM on MRI within the first 3 postnatal months was highly predictive of adverse outcome, while normal or only mildly abnormal WM predicted a favourable outcome in almost all cases. Moderately abnormal WM on MRI was associated with variable outcome. Previous studies have shown a good correlation between WM changes as detected on MRI and outcome (3,30-31). In our study, moderately abnormal WM on MRI was associated with more variable outcome than in other studies. This may be related to the timing and the variance in timing of the MRI examinations. During

the study-period, MRI in preterm infants was still done before discharge or transfer to another hospital, so mostly before TEA. Nowadays, it is preferably performed around TEA. DEHSI, possibly associated with less favourable outcome, is mostly not seen before TEA (27). MR imaging performed before TEA is probably less predictive of neurodevelopmental outcome than MRI performed around TEA. Normal or only mildly abnormal WM on cUS and/or MRI was not conclusive of a favourable outcome; two infants were moderately and two severely abnormal at 2 years. This is consistent with previous studies (3,6-7,30) and may partially be related to the fact that we did not take other abnormalities into account when assessing the predictive value of cUS and MRI for outcome, and/or to the fact that brain growth and/or maturation may be globally delayed in very preterm infants, even without overt WM lesions (32-34). Both infants with normal or mildly abnormal cUS/MRI but moderately abnormal outcome had an intraventricular haemorrhage grade 2 on one side, in one infant combined with echogenicity increase in the basal ganglia; of the two infants with severely abnormal outcome, one had bilateral intraventricular haemorrhages grade 3 with severe post-haemorrhagic ventricular dilatation, while the other did not have other cerebral lesions on cUS or MRI.

Because MRI is more burdening than cUS and cannot be easily repeated, it is important to know when MRI has additional value for detecting cerebral lesions and predicting outcome. MRI did not detect mild WM lesions better than cUS. In infants with severely abnormal WM, MRI performed within the first 3 postnatal months predicted outcome more accurately. However, MRI within the first 3 postnatal months, alone or in combination with sequential cUS, had no additional value for predicting outcome in infants with moderately abnormal WM, a group in which outcome is variable and therefore difficult to predict. In addition, in all infants in whom other cerebral lesions that might have prognostic importance, such as severe intraventricular haemorrhage, were detected on MRI, these were also detected on cUS. Based on our study, we think that routine MRI within the first 3 months is not warranted in very preterm infants, suggested to have mild or moderately abnormal WM on cUS.

We appreciate several limitations of our study. Firstly, we only scored the degree of WM changes on cUS and not the timing (4,14) and total duration of echodensities (15). Because in all our cases, echodensities persisted for at least seven days, and no significant differences were observed in the duration of echodensities between the different groups of WM changes, we feel that this will not have influenced our findings considerably. Secondly, we evaluated the most severe cUS findings and the MRI findings obtained at different ages, and not cUS and MRI findings obtained on the same day. This may limit the reliability of the MRI and its predictive value for neurodevelopmental outcome. Thirdly, we only obtained neuro-imaging data around TEA in a few infants and were therefore not able to assess brain growth and maturation properly. In only five infants, MRI was performed around TEA, which is probably the most optimal time for MR imaging in preterm infants (3-4,19,27,30-31). There was a substantial variability in postnatal age at MRI scanning. This may have influenced our results; it is possible that some abnormalities (such as SI changes) are best seen on early diffusion-weighted scans, while others (such as cystic lesions) need time to develop and are therefore better or only recognized on scans performed at older age. However, no differences in predictive values of MRI findings for outcome were found between the infants scanned at a very young postnatal age (< 10 days) and those scanned later (≥ 10 days). And there was no tendency of severe lesions occurring more often in the infants scanned at older age (≥ 10 days) than in the infants scanned at very young age (< 10 days). Another possible limitation is that our study was retrospective and performed in a relatively small number of infants. Because of the small number of infants, we did not assess a possible relation between the site and shape of the WM changes and outcome (15,35). However, comparable data have been obtained in a prospective study in preterm infants (12). Finally, not in all infants Bayley II scores or neurodevelopmental outcome data at 2 years were available and outcome was assessed at a relatively young age, so, developmental problems may still occur in these infants. A larger, prospective study with longer-term follow-up is needed to analyze the relation between neuro-imaging findings and neurodevelopmental outcome in more detail.

In conclusion, this study shows that in very preterm infants, sequential, high-quality cUS throughout the neonatal period is a reliable tool for detecting WM changes. Homogeneous grade 1 echodensities on cUS probably represent normal (maturational)

phenomena in the preterm brain and inhomogeneous grade 1 echodensities possibly reflect punctate WM lesions. cUS is predictive of favourable and severely abnormal outcome at 2 years corrected age. MRI within the first 3 postnatal months is only of clinical importance for outcome prediction in infants with severe WM changes on cUS. So, conventional and diffusion-weighted MRI sequences before TEA in very preterm infants, suggested on cUS to have mild to moderately abnormal WM, do not seem to be warranted and a combination of sequential cUS and a MRI around TEA probably provides more valuable information and is more predictive of neurodevelopmental outcome.

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Chapter 9

Does sequential cranial ultrasound predict white matter injury on MRI in very preterm infants?

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Abstract

Background and Aim:

Cranial ultrasound (cUS) seems not a good tool to detect diffuse white matter (WM) injury. Our aim was to prospectively assess the reliability of a classification system for detecting WM injury in very preterm infants on frequent, sequential high-quality cUS throughout the neonatal period, using a magnetic resonance imaging (MRI) classification system as reference standard.

Patients and Methods:

In 110 very preterm infants (gestational age < 32 weeks), sequential cUS during admission (median 8, range 4-22), and cUS and MRI around term equivalent age (TEA) were performed. cUS during admission were assessed for WM changes, and contemporaneous cUS and MRI around TEA additionally for abnormality of lateral ventricles. Sequential cUS up to TEA and MRI were classified as normal/mildly abnormal, moderately abnormal or severely abnormal, based on a combination of findings of the WM and lateral ventricles. Predictive values of the cUS classification for the MRI classification were calculated.

Results:

cUS were classified as normal/mildly abnormal, moderately abnormal and severely abnormal in respectively 14%, 73% and 13%, and MRI in respectively 25%, 57% and 18% of infants. The positive predictive value of the cUS classification for the MRI classification was high for severely abnormal cUS (0.79) but lower for normal/mildly abnormal (0.50) and moderately abnormal (0.65) cUS.

Conclusions:

When using the classification system, sequential neonatal cUS up to TEA detects severely abnormal WM in very preterm infants, but is less reliable for detecting mildly and moderately abnormal WM. MRI around TEA is needed to reliably detect WM injury in very preterm infants with normal to moderately abnormal WM.

Introduction

Diffuse white matter (WM) injury is frequently encountered in very preterm infants (1-15). On magnetic resonance imaging (MRI) it is reflected by signal changes in the WM (2-11,13). Concerns have been raised that cranial ultrasound (cUS) is not a good tool to detect diffuse WM injury as the abnormalities may be subtle (2-10). Preterm infants with diffuse WM injury are at risk for motor and mental impairment (3-5,11,13). Several authors have therefore suggested a standard MRI examination in all infants born very prematurely (gestational age (GA) < 32 weeks) (6-9).

In preterm infants, WM injury has been associated with reduced WM and deep (i.e. basal ganglia and thalami) and cortical grey matter volumes and increased cerebrospinal fluid volumes around term equivalent age (TEA) (16-18). However, previous cUS studies on WM injury in very preterm infants have only assessed changes within the WM, but did not assess associated changes such as ventricular dilatation (3-4,6-8). Most studies assessed either cUS or MRI, but none included frequent, sequential cUS throughout the neonatal period.

In this prospective study we assess the reliability of a classification system for WM injury in very preterm infants, based on a combination of findings of the WM and lateral ventricles on frequent, sequential high-quality cUS throughout the neonatal period, using a MRI classification system as reference standard.

Materials and Methods

Patients

Very preterm infants (GA < 32 weeks), admitted to the tertiary neonatal intensive care unit of the Leiden University Medical Center between May 2006 and October 2007, were eligible for a prospective neuro-imaging study, assessing WM injury by cUS and MRI. The study was approved by the Medical Ethics Committee and informed consent was obtained from the parents. Exclusion criteria were congenital anomalies of the central nervous system, severe other congenital anomalies, chromosomal and metabolic disorders, and neonatal meningitis.

Cranial ultrasound

Image acquisition

Sequential cUS scans were performed by a team of experienced examiners (LML, SJS, GvWM), using an Aloka α10 scanner (Biomedic Nederland B.V., Almere, the Netherlands) and according to our standard protocol: scanning with a transducer frequency of 7.5 MHz within 24 hours of birth, at least weekly from the day of birth or admission until discharge or transfer to another hospital, and again on the day of the MRI examination around TEA (19-20).

Visual assessment

WM. On the sequential cUS scans performed during admission (i.e. adm-cUS), special attention was paid to the WM. Periventricular echodensities (PVE) were defined and classified according to van Wezel-Meijler et al. (21), relating the echogenicity of the WM to that of the choroid plexus, and their appearance (homogenous or inhomogeneous) was noted (Figures 1, 2 and 3) (2). Subtle, symmetrical echogenic areas in the frontal WM or adjacent and parallel to the atrium of the lateral ventricles were considered normal phenomena and not scored as PVE (21-22).

Figure 1. Coronal (a) and sagittal (b) cUS of preterm infant (gestational age 27.9 weeks), scanned at postmenstrual age 31.1 weeks, showing normal echogenicity of periventricular white matter (Adm-cUS white matter score: normal/mildly abnormal). Also showing grade 1 intraventricular haemorrhage.

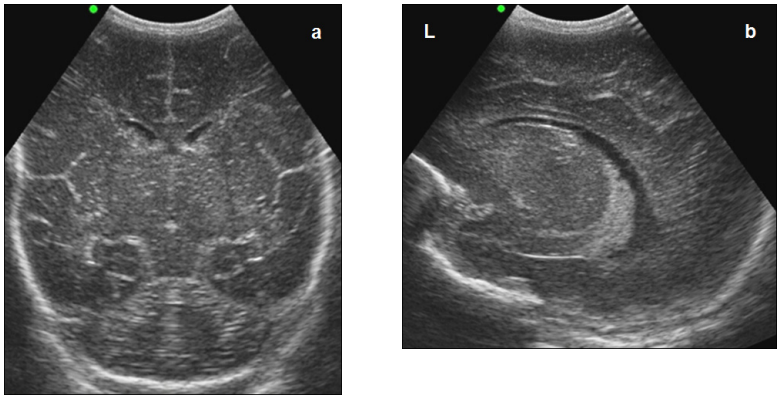


Figure 2. Coronal (a) and sagittal (b) cUS of preterm infant (gestational age 28.0 weeks), scanned at postmenstrual age 28.1 weeks, showing homogeneous grade 1 periventricular echodensities in parieto-occipital white matter (arrows) (Adm-cUS white matter score: normal/mildly abnormal).

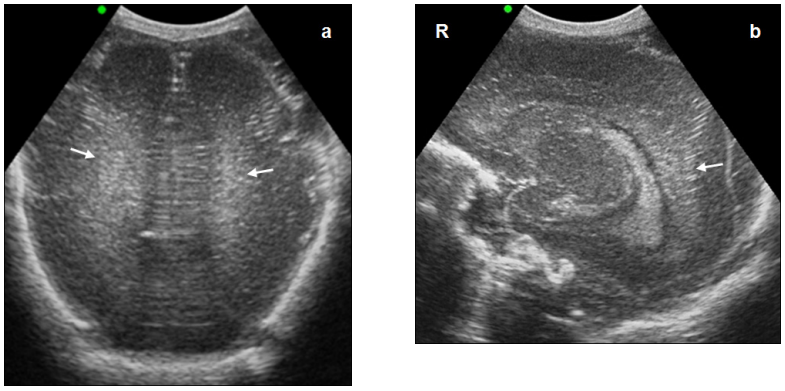
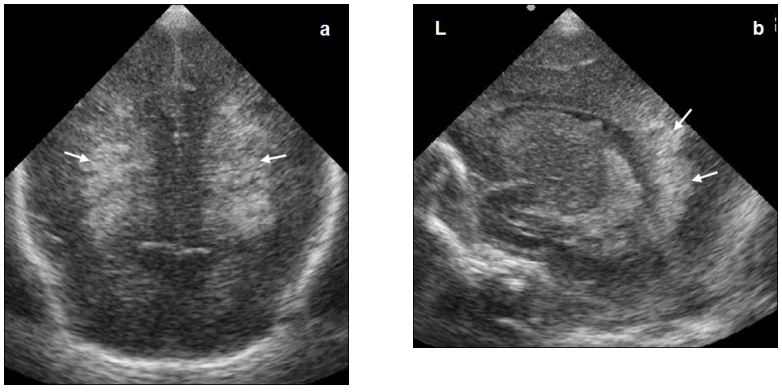


Figure 3. Coronal (a) and sagittal (b) cUS of preterm infant (gestational age 29.3 weeks), scanned at postmenstrual age 29.7 weeks, showing inhomogeneous grade 2 periventricular echodensities in parieto-occipital white matter (arrows) (Adm-cUS white matter score: moderately abnormal).



Unilateral or asymmetrical, more localized areas of high echogenicity within the WM were scored as focal WM echodensities. If co-existing with an intraventricular haemorrhage on the ipsilateral side, these mostly represent periventricular haemorrhagic infarction (PVHI; Figure 4) (23). When in doubt whether an echodensity in the WM represented PVE or a focal echodensity, it was scored as inconclusive. Porencephalic cyst was defined as a large cystic lesion, communicating with the lateral ventricle (Figure 5) (23).

Figure 4. Coronal (a) and sagittal (b) cUS of preterm infant (gestational age 25.6 weeks), scanned at postmenstrual age 25.7 weeks, showing left-sided periventricular haemorrhagic infarction in the parietal white matter (arrows), complicating an intraventricular haemorrhage (not shown) (Adm-cUS white matter score: severely abnormal).

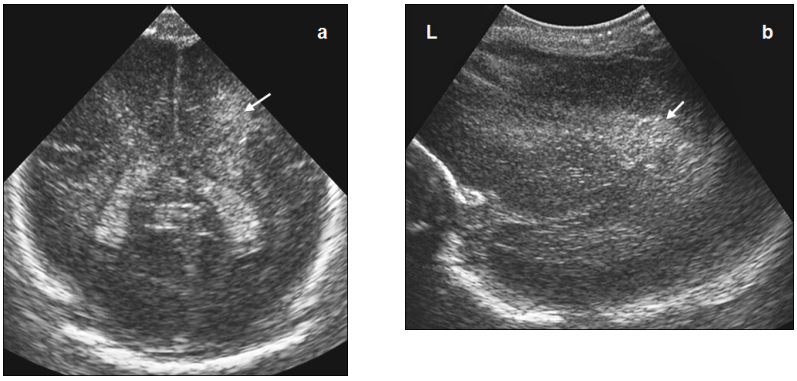
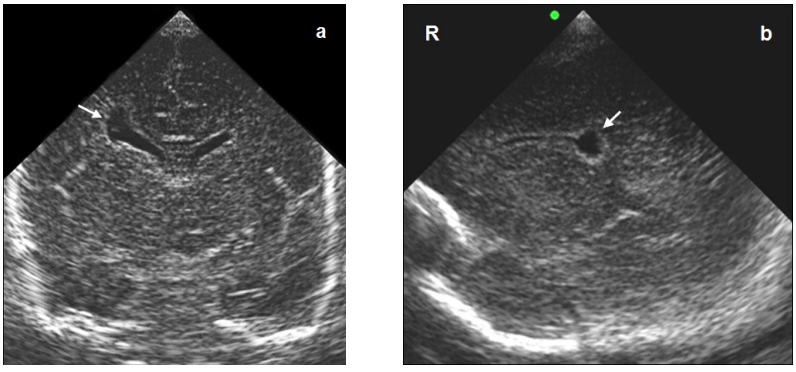


Figure 5. Coronal (a) and parasagittal (b) cUS of preterm infant (gestational age 27.0 weeks), scanned around term equivalent age (postmenstrual age 44.7 weeks), showing a porencephalic cyst in parietal white matter (arrows) (MRI-cUS white matter score: severely abnormal).



Ventricles. The size and shape of the lateral ventricles were visually assessed on the cUS performed within several hours of the MRI (i.e. MRI-cUS) by two separate investigators (LML and GvWM or SJS), and graded as normal/mildly abnormal (i.e. normal or mildly dilated and/or abnormal shape) (Figures 6 and 7), moderately abnormal (i.e. moderately dilated and/or abnormal shape, including irregular, plump or square-shaped ventricles) or severely abnormal (i.e. severely dilated and/or abnormal shape) (Figure 7). In case of discordance consensus was reached.

Figure 6. Coronal (a) and sagittal (b) cUS of preterm infant (gestational age 26.0 weeks), scanned at postmenstrual age 42.7 weeks, showing normal white matter and size and shape of lateral ventricles (MRI-cUS white matter score: normal/mildly abnormal). Also note lenticulostriate vasculopathy.

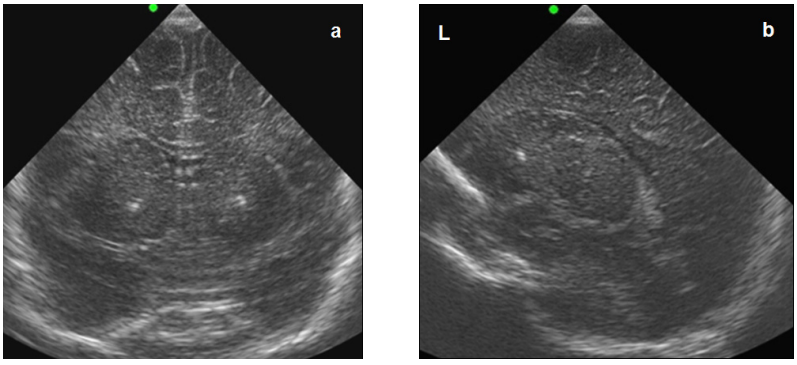
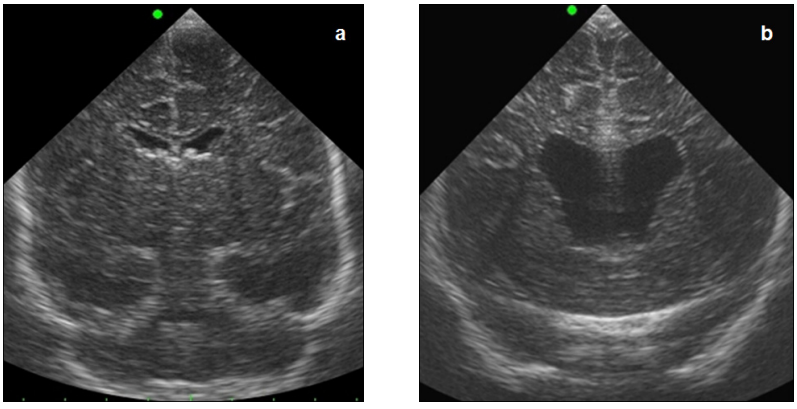


Figure 7. Coronal cUS (a) of preterm infant (gestational age 25.0 weeks), scanned at postmenstrual age 42.0 weeks, showing mild dilatation of lateral ventricles (MRI-cUS white matter score: normal/mildly abnormal), and coronal cUS (b) of another infant (gestational age 30.3 weeks), scanned at postmenstrual age 41.9 weeks, showing severe lateral ventricular dilatation (MRI-cUS white matter score: severely abnormal).



WM classification

WM classification for adm-cUS:

- Normal/mildly abnormal: no PVE or homogeneous grade 1 PVE (21)
- Moderately abnormal: inhomogeneous grade 1 PVE (regardless of duration), grade 2 PVE (regardless of appearance and duration), and/or small, localized cystic lesions (periventricular leukomalacia (PVL) grade 2) (21,24)

- Severely abnormal: multicystic lesions (PVL grades 3 and 4), focal WM echodensity, and/or porencephalic cyst (24)

The WM score of the adm-cUS was based on the most severe changes over time.

WM classification for MRI-cUS:

- Normal/mildly abnormal: homogeneous WM and normal/mildly abnormal lateral ventricles
- Moderately abnormal: inhomogeneous WM and/or moderately abnormal lateral ventricles
- Severely abnormal: multicystic PVL, focal WM echodensity, porencephalic cyst, and/or severely abnormal lateral ventricles

The WM score of the MRI-cUS was based on the most severe changes.

WM classification for adm-cUS combined with MRI-cUS:

The WM score for the sequential cUS during admission combined with the cUS around TEA (adm-cUS combined with MRI-cUS) was based on the most severe changes over time.

MRI

Image acquisition

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) as recently described (25). The MRIs were preferably performed around or just after TEA (40-44 weeks' postmenstrual age (PMA)). For infants who were still unstable and/or ventilator dependent around that age, MRI was postponed. The T_1- and T_2-weighted sequences were analyzed by at least two experienced investigators (FTdB, LML, SJS, GvWM).

Visual assessment

WM. The signal intensity (SI) of the brain WM was graded according to Sie et al. (2), indicating increasingly severe WM changes (Figures 8, 9, 10 and 11).

Figure 8. Transverse T_1- (a) and T_2-weighted (b) MRI at mid-ventricular level of preterm infant (gestational age 27.1 weeks), scanned at postmenstrual age 42.1 weeks, showing normal signal in periventricular white matter. Also showing normal size and shape of lateral ventricles (MRI white matter score: normal/mildly abnormal).

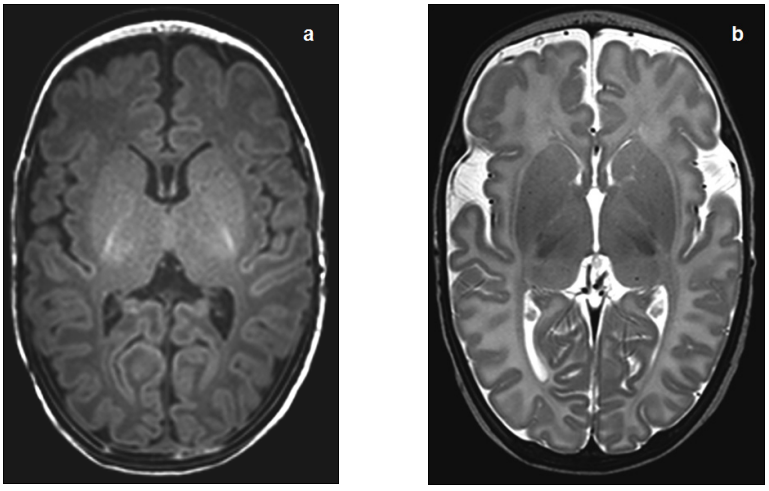


Figure 9. Transverse T_1- (a) and T_2-weighted (b) MRI at mid-ventricular level of preterm infant (gestational age 27.9 weeks), scanned after term equivalent age (postmenstrual age 48.7 weeks), showing a single punctate white matter lesion adjacent to the optic radiation (short arrows). Also showing mildly dilated, square-shaped occipital horns of lateral ventricles (long arrows) (MRI white matter score: normal/mildly abnormal).

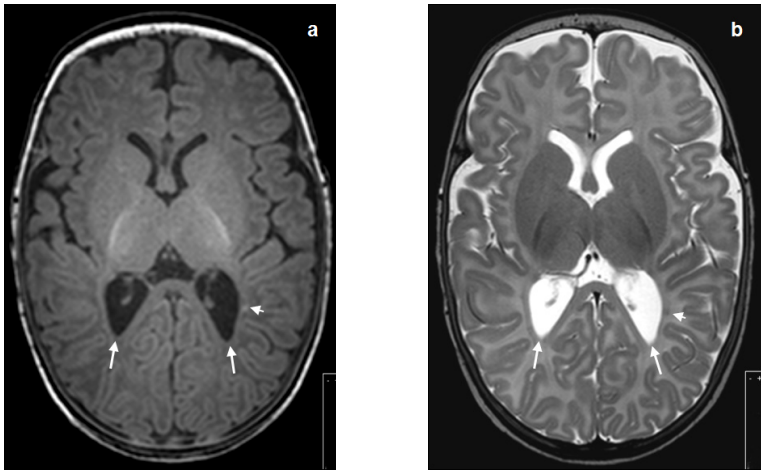


Figure 10. Transverse T_1- (a) and T_2-weighted (b) MRI of preterm infant (gestational age 26.9 weeks), scanned at postmenstrual age 42.7 weeks, showing bilateral, multiple punctate white matter lesions (short arrows). Also showing dilated, irregularly shaped lateral ventricles and widening of extracerebral spaces. T_2 additionally shows diffuse and excessive high signal intensity in occipital white matter (long arrows) (MRI white matter score: moderately abnormal).

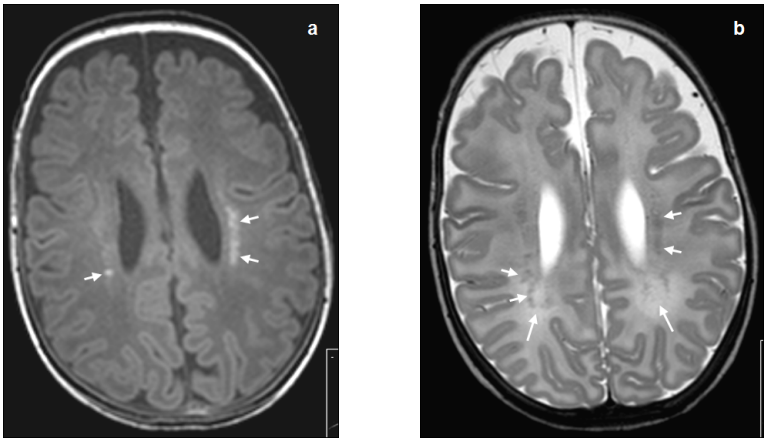
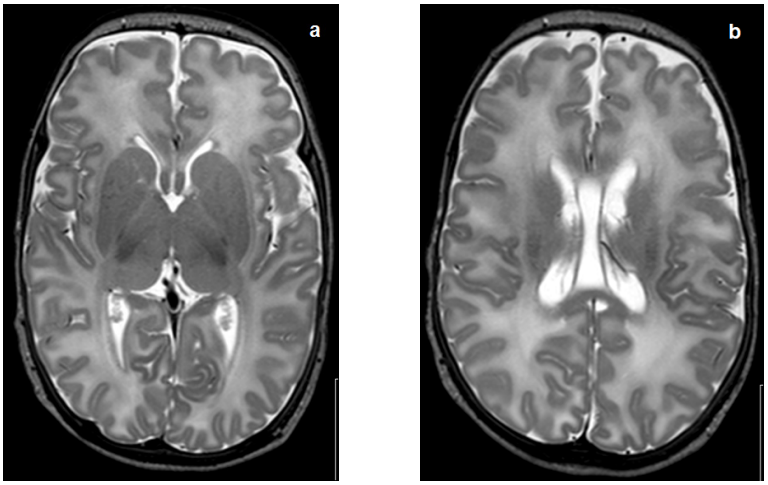
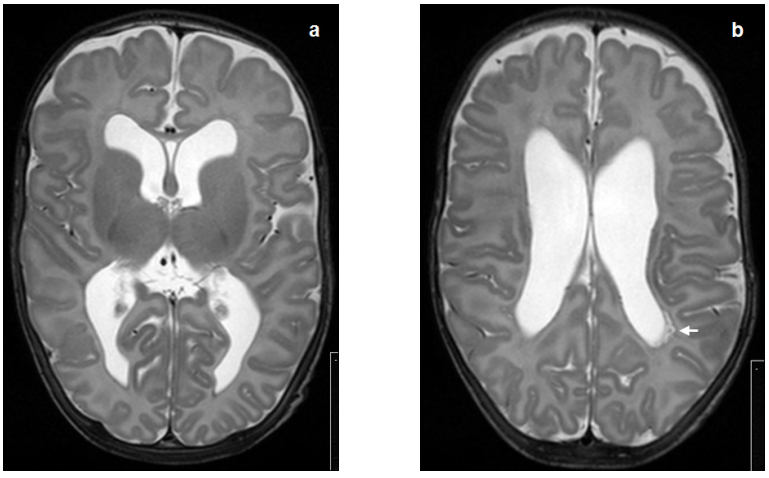


Figure 11. Transverse T_2-weighted MRI at mid- (a) and high-ventricular (b) level of preterm infant (gestational age 30.6 weeks), scanned at postmenstrual age 41.9 weeks, showing inhomogeneous, diffuse SI changes in periventricular and subcortical white matter (MRI white matter score: severely abnormal). Also showing normal lateral ventricles and cavum septum pellucidum and vergae.



Ventricles. The size and shape of the lateral ventricles were assessed visually by two separate investigators (LML and FTdB), and graded as normal/mildly abnormal (Figures 8, 9 and 11), moderately abnormal or severely abnormal (Figure 12) as described for MRI-cUS. In case of discordance consensus was reached.

Figure 12. Transverse T_2-weighted MRI at mid- (a) and high-ventricular (b) level of preterm infant (gestational age 31.6 weeks), scanned at postmenstrual age 43.4 weeks), showing severely dilated and abnormally shaped lateral ventricles (MRI white matter score: severely abnormal). Also showing cystic degeneration along the occipital horn of left lateral ventricle (arrow).



WM classification

WM classification for MRI:

- Normal/mildly abnormal: WM grade 1, 2 or 3, and normal/mildly abnormal lateral ventricles (2)
- Moderately abnormal: WM grade 4 and/or moderately abnormal lateral ventricles (2)
- Severely abnormal: WM grade 5 or 6 and/or severely abnormal lateral ventricles (2)

The WM score was based on the most severe changes.

Data analysis

Statistical analyses were performed using SPSS software (version 14.0; SPSS inc., Chicago, Illinois, USA). Predictive values of the WM classifications of adm-cUS, MRI-cUS and adm-cUS combined with MRI-cUS for the WM classification of MRI were calculated.

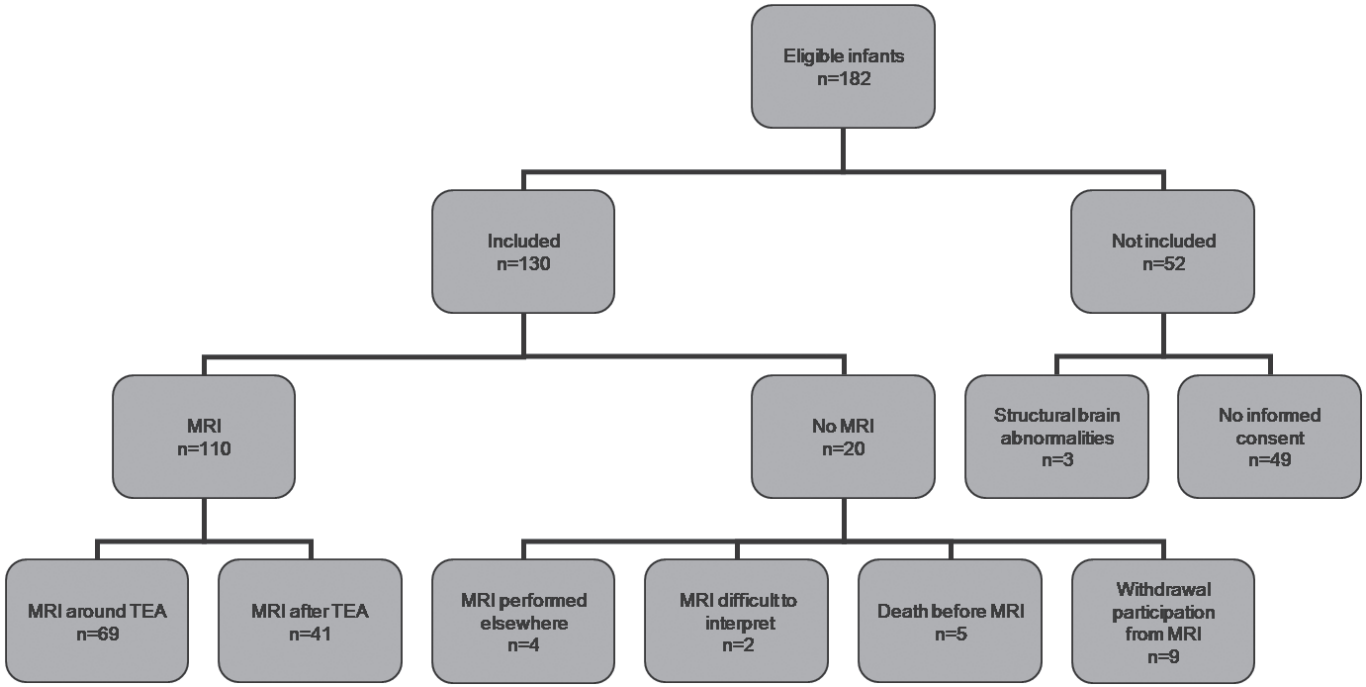
Results

Patients

During the study-period, 182 very preterm infants were eligible for the study, of which 130 infants (80 male) were included. Fifty-two infants were excluded from the study; three because of structural brain abnormalities and 49 because informed parental consent was not obtained (Figure 13). Reasons for not obtaining consent included transfer to another hospital or death within a very short period of birth, rejection of participation, and practical problems such as language barrier and travel distance to hospital. Median GA and birth weight of included infants were 29.0 (range 25.6-31.9) weeks and 1141 (520-1960) grams. There were no significant differences in GA and birth weight between infants with and without informed consent.

In all 130 infants, sequential adm-cUS scans (median 8, range 4-22) were performed. In 20 infants no or inadequate MRI-cUS and MRI were obtained (Figure 13). So, in 110 infants (68 male) contemporaneous cUS and MRI were obtained at a median PMA of 43.4 (40.1-55.9) weeks. In 69 infants this was around TEA, and in 41 infants between 44.0 and 55.9 weeks' PMA.

Figure 13. Flow diagram showing the number of infants eligible for the study, the number of infants included and not included in the study, and the final number of infants with sequential cUS and MRI around term equivalent age
(n, number of infants)



Cranial ultrasound

Adm-cUS

In 27 infants (24.5%) the WM classification was scored as normal/mildly abnormal, in 75 (68.2%) as moderately abnormal, and in eight (7.3%) as severely abnormal.

MRI-cUS

In 50 infants (45.5%) the WM classification was scored as normal/mildly abnormal, in 46 (41.8%) as moderately abnormal, and in 14 (12.7%) as severely abnormal.

Adm-cUS combined with MRI-cUS

In 16 infants (14.5%) the WM classification for sequential cUS throughout the neonatal period was scored as normal/mildly abnormal, in 80 (72.7%) as moderately abnormal, and in 14 (12.7%) as severely abnormal.

MRI

In 27 infants (24.5%) the WM classification was scored as normal/mildly abnormal, in 63 (57.3%) as moderately abnormal, and in 20 (18.2%) as severely abnormal.

Relation between cUS and MRI

Details on the relation between the WM classifications of cUS and MRI are given in Tables 1, 2 and 3. Predictive values of the WM classifications of adm-cUS, MRI-cUS and adm-cUS combined with MRI-cUS for the WM classification of MRI are presented in Table 4.

Table 1. Relation between white matter classifications of adm-cUS and MRI (n, number of infants; WM, white matter)

WM classifications		MRI, *n*		
		Normal/mild (n=27)	Moderate (n=63)	Severe (n=20)
Adm-cUS, *n*	Normal/mild (n=27)	9	14	4
	Moderate (n=75)	18	48	9
	Severe (n=8)	0	1	7

Table 2. Relation between white matter classifications of MRI-cUS and contemporaneous MRI
(n, number of infants; WM, white matter)

WM classifications		MRI, *n*		
		Normal/mild (n=27)	Moderate (n=63)	Severe (n=20)
MRI-cUS, *n*	Normal/mild (n=50)	25	25	0
	Moderate (n=46)	2	35	9
	Severe (n=14)	0	3	11

Table 3. Relation between white matter classifications of adm-cUS combined with MRI-cUS and term equivalent MRI
(n, number of infants; WM, white matter)

WM classifications		MRI, *n*		
		Normal/mild (n=27)	Moderate (n=63)	Severe (n=20)
Adm-cUS and MRI-cUS, *n*	Normal/mild (n=16)	8	8	0
	Moderate (n=80)	19	52	9
	Severe (n=14)	0	3	11

Table 4. Predictive values of the white matter classifications of adm-cUS, MRI-cUS and adm-cUS combined with MRI-cUS for the white matter classification of MRI
(NPV, negative predictive value; PPV, positive predictive value; WM, white matter)

cUS WM classification		Predictive values for MRI WM classification			
		Sensitivity	Specificity	PPV	NPV
Adm-cUS	Normal/mild	0.33	0.78	0.33	0.78
	Moderate	0.76	0.43	0.64	0.57
	Severe	0.35	0.99	0.88	0.87
MRI-cUS	Normal/mild	0.93	0.70	0.50	0.97
	Moderate	0.56	0.77	0.76	0.56
	Severe	0.55	0.97	0.79	0.91
Adm-cUS and MRI-cUS	Normal/mild	0.30	0.90	0.50	0.80
	Moderate	0.83	0.40	0.65	0.63
	Severe	0.55	0.97	0.79	0.93

Discussion

To our knowledge, this is the first prospective study comparing WM injury on cUS and MRI in very preterm infants based on newly designed classification systems, not only including changes within the WM but also scoring other changes in the brain thought to be related to WM injury. We considered MRI as reference standard for WM injury.

The appearance of the lateral ventricles was incorporated in the classification, as WM injury in preterm infants is associated with reduced WM and grey matter volumes and increased cerebrospinal fluid volumes (16-18). In addition, cystic PVL and PVHI may lead to prominent changes in ventricular size and shape (24,26-27). Finally, around TEA echogenicity changes within the WM are only rarely encountered on cUS, while widening of the ventricular system is a frequent finding (20,26-27).

The positive predictive value of the cUS WM classification for the MRI WM classification was high for severely abnormal WM; (nearly) all infants classified as severely abnormal for cUS were also classified as severely abnormal for MRI. However, cUS was less predictive for the moderately abnormal and normal/mildly abnormal groups. So, even when our classification system, based on frequent, sequential cUS and evaluating not only WM changes but also other changes indicative of WM injury, is used, cUS may underestimate WM injury.

There are several possible explanations for these results. MRI was performed with a 3 Tesla MR system, providing a high resolution that cannot be obtained with ultrasonography. Using this high field strength and a special neonatal imaging protocol, small lesions, including very small punctate WM lesions (PWML), are depicted (20,25). In addition, in accordance with Sie et al. (2), we used six as cut-off number for 'few' (mildly abnormal WM) or 'multiple' (moderately abnormal WM) PWML on MRI, which is rather arbitrary. In 12 of the 14 infants whose MRI classification was based on 'multiple' PWML, just over six lesions were detected, mostly isolated in organization and located in the periventricular WM at the level of the centrum semiovale and/or adjacent to the optic radiation. Only in two infants, the number of PWML was considerably higher and lesions were more widely distributed in the WM and organized linearly and/or in clusters. We therefore feel that, by using this cut-off, we may have overrated the severity of WM changes on MRI in several infants. Another explanation may be the discrepancy

between contemporaneous cUS and MRI for detecting ventricular dilation. In our recent study in very preterm infants, describing incidences of brain imaging findings and comparing cUS and MRI for these findings, ventricular dilatation was more often scored on MRI than on cUS (20). So, visual scoring of ventricular size may not be reliable (enough) and if quantitative measurements of ventricular size had been included in the classification systems, this might have improved the agreement between cUS and MRI and the reliability of cUS for detecting WM injury.

cUS not only underestimated, but also overestimated WM injury in some cases. This was especially true for adm-cUS and can be explained by the fact that the WM score of adm-cUS was based on the most severe changes over time and by the transient nature of some WM changes (20).

Combining the WM classification of adm-cUS with that of MRI-cUS slightly improved the predictive value of sequential cUS for MRI in case of normal/mildly abnormal WM, but did not improve its predictive value for moderately abnormal WM and even decreased it for severely abnormal WM. So, if MRI is performed around TEA in addition to sequential cUS throughout the neonatal period, contemporaneous cUS does not contribute to detecting WM injury.

The results of this study may arouse the erroneous suggestion that frequent, sequential cUS performed until discharge does not contribute to detection of WM injury in very preterm infants. However, our classification systems are used to grade the severity of WM injury and do not provide information on separate imaging findings or the evolution of lesions. By substantially limiting the number of cUS examinations during admission, details on (transient) WM changes will be lost, the evolution of lesions cannot be followed, and distinction between several forms of WM injury (i.e. focal or more diffuse) may not be possible as only the end stages of WM injury are visualized. By restricting cUS to the early neonatal period and TEA, as suggested by some authors (28), no information will be available on the evolution of lesions, lesions may remain undetected, and their severity underestimated (6,24,26,29).

Our results are in agreement with those of others comparing WM findings on cUS and MRI, showing that MRI is more sensitive for detecting (particularly subtle) WM changes than cUS (2-10,24,29). In agreement with our previous, retrospective study (14), in most cases with WM injury detected by cUS, MRI demonstrated the exact site and extent of

lesions more precisely. However, in that study, sequential cUS during admission was reliable for detecting WM changes, including mildly and moderately abnormal changes, on MRI (14). Our current results partially contradict these findings. An explanation may be that in the retrospective study, MRI was obtained within 3 months of birth, well before TEA. This may not be the optimal time in very preterm infants, as MRI before TEA only has additional value for assessing the extent of cystic lesions, PWML and PVHI, but not for other WM changes (4,8,11,29).

We appreciate some limitations of our study. Firstly, the most stable infants with (nearly) normal cUS findings were discharged sooner than those being less stable and/or having more severe findings. We may therefore have missed progression towards more severe changes in some infants with minor changes, or changes developing after discharge. This may have biased our results and negatively influenced the reliability of cUS as cUS was the least reliable in infants with normal/mildly abnormal WM. Secondly, we only performed a single MRI examination around TEA. Therefore, while cUS also reflected early and/or transient WM changes and the evolution of changes, MRI reflected only the later stages of WM injury. Following our standard cUS protocol, we did not investigate the minimum number of cUS scans needed for reliable classification of WM injury. Finally, we are not yet informed on the clinical significance of our WM classifications, and the implications of the milder and subtle WM changes, including PVE without cystic evolution on cUS and PWML and more diffuse SI changes on MRI, for neurological outcome. Follow-up data are currently obtained.

In conclusion, our classification systems enable systematical grading of WM injury and comparison of cUS and MRI. We have further demonstrated that cUS is reliable for the severe spectrum of WM injury, but may underestimate WM injury in cases classified as normal/mildly or moderately abnormal. Routine MRI around TEA is needed in very preterm infants as it may detect (more serious) WM injury in infants with normal to, at the most, moderately abnormal WM on cUS, while in infants with severely abnormal WM on cUS, MRI assesses the site and extent of lesions more precisely. When MRI is performed around TEA, contemporaneous cUS is of no additional value for detecting WM injury. As MRI is a burdening procedure and repetitive MRI examinations are undesirable, sequential cUS throughout the neonatal period is necessary to assess the timing, origin and evolution of lesions and depict transient changes in these vulnerable

patients. Future studies on WM injury in preterm infants should focus on the optimal number of and interval between sequential cUS, on improving the WM classifications, including quantitative measurements of the ventricular system, and on the clinical significance of the WM classifications and the separate changes, both on cUS and MRI, indicative of WM injury.

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Part V

Deep grey matter

Chapter 10

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

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Neuropediatrics 2004; 35(5): 283-289

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

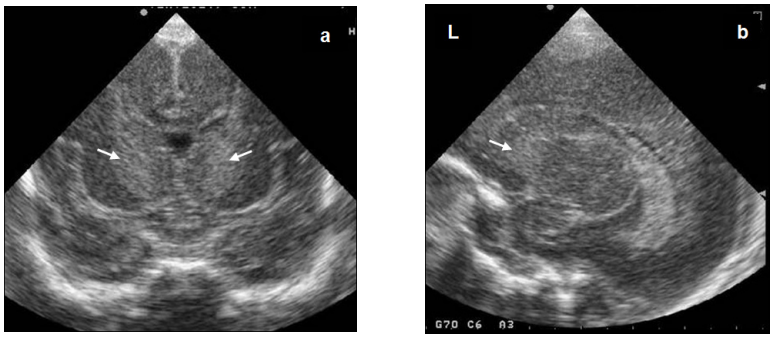
Serial bedside cUS were done in all infants from birth until discharge or transfer to another hospital by an experienced neonatologist according to standard scanning protocols. cUS scans were performed within 24 hours of birth, on the third day after birth, and at least weekly until discharge or transfer 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.



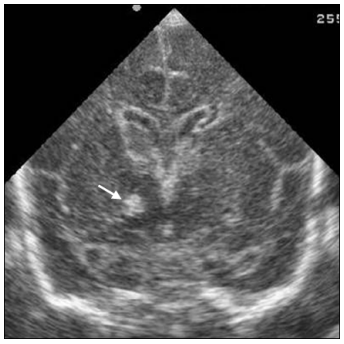


Figure 2. Coronal cUS scan in a preterm infant, postconceptional age 33.4 weeks, showing a localized area of increased echogenicity in the right thalamic region (arrow) and intraventricular haemorrhages.

MRI

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 T_1-, T_2-, and diffusion-weighted images in the axial plane (slice thickness 4-5 mm, field of view 18-20 cm^2); T_1-weighted images were also obtained in the sagittal plane. MRI scans were evaluated immediately after the scanning procedure by the attending neuroradiologist. The T_1-, T_2-, 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

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 χ^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.

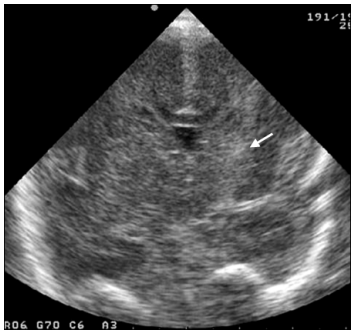


Figure 3. Coronal cUS scan in a preterm infant, postconceptional age 26.1 weeks, showing diffuse hyperechogenicity BGT with an inhomogeneous appearance (arrow).

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.

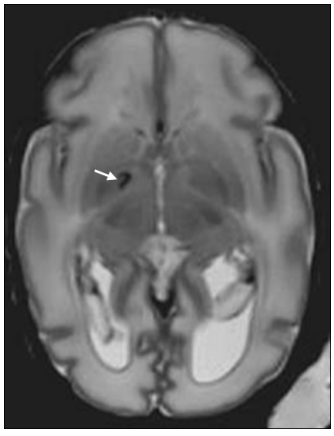


Figure 4. Transverse T_2-weighted MRI scan showing intraventricular haemorrhages and inhomogeneous signal intensity in the right lentiform nucleus compatible with haemorrhage (arrow).

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)

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

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)

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

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

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

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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Chapter 11

Imaging of the basal ganglia and thalami in very preterm infants

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Submitted for publication

Abstract

Background and Aims:

Imaging data on the basal ganglia and thalami (BGT) in preterm infants are limited. Our aims were to systematically describe imaging findings (cranial ultrasonography (cUS) and magnetic resonance imaging (MRI)) of BGT in very preterm infants, and to assess the relation between cUS and MRI findings and quantitative measurements, indicative of growth and development, of BGT and between quantitative measurement and age and white matter (WM) injury.

Patients and Methods:

Sequential, neonatal cUS of 130 very preterm infants (gestational age < 32 weeks) were evaluated for echogenicity of BGT, and term equivalent MRI (n=110) for changes in myelination and signal in BGT and for WM injury. Diffusivity values of BGT were obtained from diffusion-tensor images and BGT volumes were measured by manual segmentation. BGT changes on cUS and MRI were compared and related to quantitative measurement (diffusivity values and volumes) of BGT. Quantitative measurements were related to age at birth and MRI and to WM injury.

Results:

Bilateral, diffuse and subtle echogenicity of BGT was seen in nearly all very preterm infants (92%), predominantly in the youngest and smallest infants. It gradually faded with age and was no longer seen after 1 month post-term. No association was found with changes in signal, myelination, diffusivity values or volumes of BGT on MRI. None of the infants had focal BGT lesions on cUS, while only one infant had BGT changes on MRI. Quantitative measurements correlated with age at MRI, but not with age at birth. WM injury correlated negatively with BGT volumes, but not with diffusivity values.

Conclusions:

In very preterm infants, diffuse, subtle echogenicity of BGT is a frequent and probably normal prematurity-related finding, while focal BGT lesions are rare and should be regarded as non-physiological. WM injury negatively influences BGT growth. Growth and development of BGT are ongoing around term age.

Introduction

In preterm infants, injury to and deviant growth and development of the basal ganglia and thalami (BGT) are associated with neurodevelopmental and visual impairments (1-3). White matter (WM) injury, including diffuse WM injury, cystic WM lesions and periventricular haemorrhagic infarction, has a negative effect on BGT growth (1-9). However, neuro-imaging studies on growth and development of the deep grey matter (GM) and their relation with WM injury in very preterm infants are limited (1,3,8).

Echogenicity of the BGT region (EG-BGT) is frequently encountered on cranial ultrasound (cUS) scans of very preterm infants and fetuses (10-13). EG-BGT is mostly bilateral, subtle and diffuse. Its origin and clinical significance remain largely unclear (10-13). In our retrospective study, very preterm infants with diffuse, subtle EG-BGT were younger and smaller at birth than those without this finding; neurological outcome at 1 year corrected age was similar (10). Diffuse, subtle EG-BGT in very preterm infants, like symmetrical homogeneous echodensities in the periventricular WM (14-16), may represent a normal maturational phenomenon in the immature preterm brain. However, like often more distinct, demarcated and inhomogeneous echodensities in BGT in (near) full-term neonates (17-19), EG-BGT may also reflect ischaemic and/or inflammatory damage. Subtle EG-BGT should be distinguished from more localized echodensities in the BGT of preterm infants, mostly reflecting infarction of the lenticulostriate branches of the middle cerebral artery or haemorrhage, which have been associated with suboptimal neurodevelopmental outcome (20-24).

The principal aim of this prospective study was to systematically describe imaging findings of the BGT in a large cohort of very preterm infants, as shown by sequential cUS throughout the neonatal period and a MRI around term equivalent age (TEA). In addition, we wanted to explore whether there is a MRI-equivalent for EG-BGT and the relation between EG-BGT and quantitative measurements, indicative of growth and development, of the BGT. Finally, we wanted to assess the relation between quantitative measurements of the BGT and age and WM injury.

Patients and Methods

Patients

Very preterm infants (gestational age (GA) < 32 weeks), 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, assessing the deep GM (i.e. BGT). The study was approved by the Medical Ethics Committee and informed consent was obtained from the parents. Exclusion criteria were congenital anomalies of the central nervous system, severe other congenital anomalies, chromosomal and metabolic disorders, and neonatal meningitis.

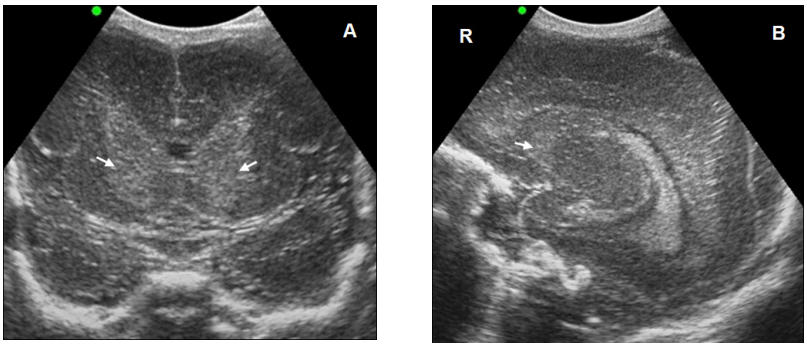
Cranial ultrasound

As part of the routine care, sequential cUS scans were performed by the attending (fellow) neonatologists, using an Aloka α10 scanner with multifrequency transducer (Biomedic Nederland B.V., Almere, the Netherlands). cUS scans were performed according to our standard protocol, and assesses by at least two experienced (LML, SJS, GvWM) as recently described (25-26).

Presence of echogenicity changes in the BGT was recorded. EG-BGT was considered present if, on at least one cUS examination, the echogenicity of the BGT (or of areas within BGT) was increased as compared to that of surrounding brain tissue, on both coronal and sagittal views. Echogenicity changes were described as diffuse or local and unilateral or bilateral (Figure 1). Lenticulostriate vasculopathy, shown as a punctate or linear echogenic structure in the distribution of the thalamo-striatal vessels, was not considered EG-BGT (26). Postnatal and postmenstrual age (PMA) at first and last detection of EG-BGT and its evolution and duration (up to the day of the term equivalent cUS) were recorded.

Other changes, including echodensities in the frontal and periventricular WM, cystic WM lesions, periventricular haemorrhagic infarction, intraventricular haemorrhage, and post-haemorrhagic ventricular dilatation, were recorded (14,26).

Figure 1. Coronal (A) and sagittal (B) cUS scans of a preterm infant (gestational age 27.1 weeks), scanned at postmenstrual age 27.3 weeks, showing bilateral, diffuse and subtle EG-BGT (arrows).



MRI

Image acquisition and visual assessment

MRI examinations were performed in all very preterm infants, preferably around or just after TEA (40-44 weeks' PMA), according to a standard protocol, using a 3 Tesla MR system (Philips Medical Systems, Best, the Netherlands) as recently described (27). For infants who were unstable and/or ventilator dependent around that age, MRI was postponed.

MRI examinations included T_2-weighted turbo spin echo sequences (repetition time 6269 ms, echo time 120 ms), T_1-weighted turbo field echo 3D volume sequences (repetition time 9.7 ms, echo time 4.6 ms), and diffusion-tensor imaging (DTI) sequences (repetition time 10383 ms, echo time 56 ms). All sequences were performed in transverse planes with field of view of 180x230 mm. Slice thickness was 1 mm for T_1-, and 2 mm for T_2- and DTI-weighted images, all without interslice gap. For this study, the T_1-, T_2-, and DTI-weighted sequences were analyzed.

All MRIs were assessed as recently described by at least two experienced investigators (FTdB, LML, SJS, GvWM), who were blinded to the cUS findings (26). Signal intensity (SI) changes in the BGT were recorded, and described as diffuse or local and unilateral or bilateral. Myelination in the BGT was compared to reference images (28-31).

White matter injury classification

To score WM injury, the SI of the WM was graded according to Sie et al. (32), indicating increasingly severe WM changes. The size and shape of the lateral ventricles were assessed visually and graded as normal/mildly abnormal (normal or mildly dilated and/or abnormal shape), moderately abnormal (moderately dilated and/or abnormal shape), or severely abnormal (severely dilated and/or abnormal shape). Subsequently, WM injury was classified into three groups, based on the most severe changes:

- Normal/mildly abnormal: WM grade 1, 2 or 3, and normal/mildly abnormal lateral ventricles (32)
- Moderately abnormal: WM grade 4, and/or moderately abnormal lateral ventricles (32)
- Severely abnormal: WM grade 5 or 6, and/or severely abnormal lateral ventricles (32)

Quantitative assessment of basal ganglia and thalami

Diffusivity values

Apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values were measured in the caudate and lentiform nuclei and thalamus, separately for the left and right hemisphere. DTI analysis was performed off-line on an independent workstation. ADC and FA values were obtained from DTI-derived ADC and FA maps and calculated from circular regions of interest (ROI). ROIs were positioned bilaterally in the different structures on the slice showing the structure largest. The *b*0 maps of the DTI were used for ROI localization. Subsequently, ROIs were directly registered to the corresponding FA maps. For consistency, all ROIs were positioned by a single investigator (LML). The intra-observer variability for the ADC and FA values, determined by repeating the measurements in 15 infants, was < 2%.

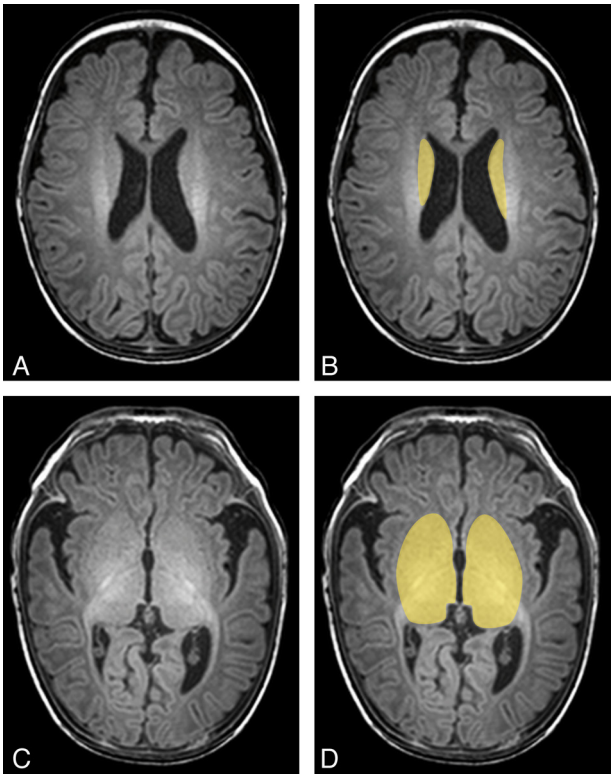
Volume measurements

All BGT volumes were measured separately by two observers (of whom one being a neuroradiologist, FTdB), and mean volumes of both observers were used for further analysis. Measurements were done on both T_1- and T_2-weighted images, and consistency between the two images was checked using simple linear regression. Image processing

and manual segmentation was performed using a MR analytical software system research package (MASS V2008-EXP, Leiden University Medical Center, Leiden, the Netherlands) (33). We decided to use manual instead of automated segmentation for measuring BGT volumes as, so far, no automated segmentation programme has proven reliable for segmenting the BGT in newborn infants. On each slice containing BGT, assessed with the aid of a reference brain atlas (34), these were segmented as one continuous structure and the area of segmentation was calculated, separately for the left and right hemisphere. BGT volume was calculated by multiplying all area calculations with the slice thickness. Total BGT volume was calculated by the sum of the left and right volumes.

To maintain the best consistency between measurements, the borders of the BGT region were defined prior to analysis. The lateral border was formed by the external capsule, and the medial border by the 3rd ventricle. The superior border was defined as the level where the BGT could not be distinguished from the surrounding periventricular WM anymore (Figure 2), and the inferior border as the level of the 3rd ventricle and posterior commissure (Figure 2). We separated the posterior limb of the internal capsule from the BGT only on the upper three slices, as it was impossible to reliably separate these structures on lower slices. An example of manual segmentation is shown in Figure 3. The intra-observer variability for the measurements, determined by repeating the measurements in 25 infants, was <2%.

Figure 2. T_1-weighted MR images of a very preterm infant, scanned around term equivalent age, showing the superior (A and B) and inferior (C and D) border of the basal ganglia and thalami as defined prior to segmentation. The superior border was defined as the level where the basal ganglia and thalami (light grey in part B) could still be distinguished from the surrounding periventricular white matter (A and B) but was not distinguishable anymore on subsequent, higher slice. The inferior border was defined as the level of the 3rd ventricle and posterior commissure (C and D); the basal ganglia and thalami are shown in light grey in part D.



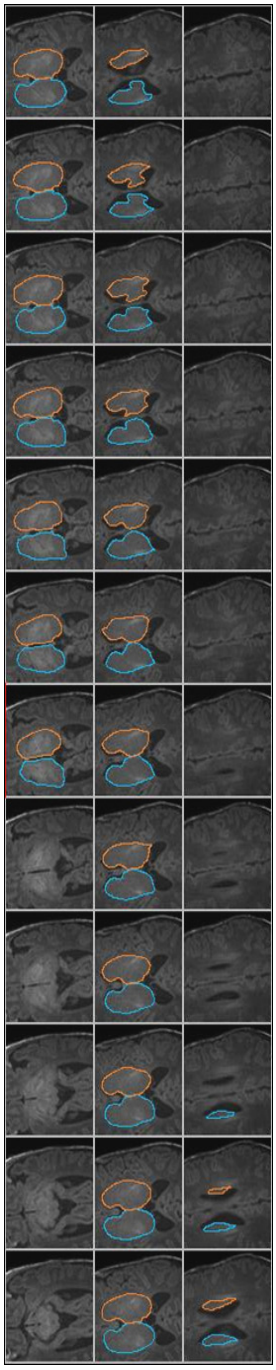


Figure 3. Example of manual segmentation of the basal ganglia and thalami on consecutive slices of a T_1-weighted MRI examination of a very preterm infant scanned around term equivalent age.

Data analysis

Statistical analyses were performed using SPSS software (version 14.0; SPSS inc., Chicago, Illinois, USA). The incidence of EG-BGT and other changes on cUS and of changes in BGT on MRI was calculated. The association between EG-BGT and other changes on cUS or BGT changes on MRI was assessed using a Pearson χ^2 test.

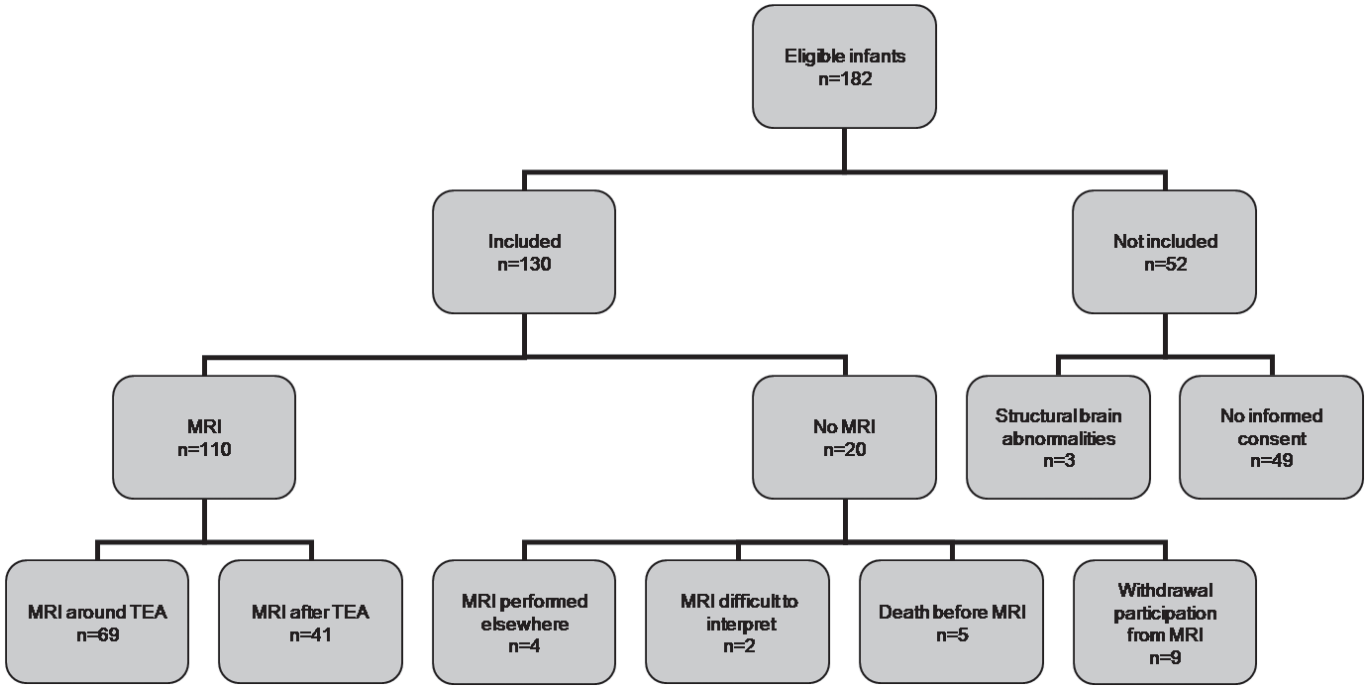
Quantitative measurements (diffusivity values and volumes) of BGT were tested for normality using a Shapiro-Wilk test prior to each analysis. Correlations between quantitative measurements and GA at birth and PMA at MRI scanning were assessed using a simple linear regression analysis. Univariate analysis of covariance (ANCOVA) with correction for PMA at MRI was applied to assess the correlation between EG-BGT and quantitative measurements. Correlations between quantitative measurements and WM classification were calculated using an univariate analysis of covariance (ANCOVA) with correction for PMA at MRI. Level of significance was $p \leq 0.05$.

Results

Patients

During the study-period, 182 very preterm infants were eligible for the BGT study, of whom 130 infants (80 male, 50 female) were included (Figure 4). Reasons for not obtaining informed parental consent (n=49) included transfer to another hospital or death within a very short period of birth, rejection of participation by the parents, and practical problems (language barrier and travel distance). Median GA and birth weight were 29.0 (range 25.6-31.9) weeks and 1141 (520-1960) grams. There were no significant differences in GA and birth weight between infants with and without informed consent. In all 130 infants, sequential cUS (median 8, range 4-22) were performed during admission, but in 20 infants no or inadequate cUS and MRI around TEA were obtained (Figure 4). So, in 110 infants (68 male, 42 female) contemporaneous cUS and MRI were obtained at a median PMA of 43.4 (40.1-55.9) weeks. In 69 infants MRI was performed around TEA, in the other 41 infants between 44.0 and 55.9 weeks' PMA.

Figure 4. Flow diagram showing the number of infants eligible for the study, the number of infants included and not included in the study, and the final number of infants with sequential cUS and MRI around term equivalent age
(n, number of infants)



Cranial ultrasound

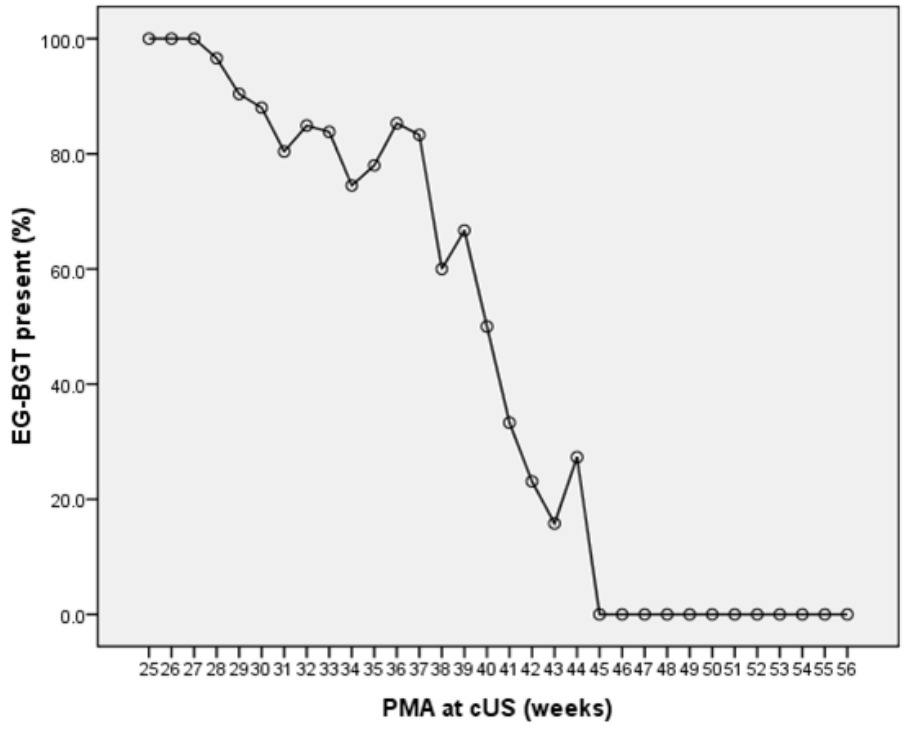
EG-BGT

In 120 of the 130 (92%) included infants, EG-BGT was seen on sequential cUS scan during admission. Details are shown in Table 1. Median GA and birth weight were respectively 28.8 (25.6-31.9) weeks and 1100 (520-1960) grams and 31.2 (29.9-31.9) weeks and 1488 (585-1880) grams for infants with and without EG-BGT; GA being significantly different between both groups. EG-BGT gradually faded with age. The distribution of EG-BGT over PMA at cUS scanning is presented in Figure 5, showing a gradual decline in incidence with increasing PMA. In 19 of the 100 (19%) infants with EG-BGT and contemporaneous cUS and MRI around TEA, EG-BGT was still seen at that time.

Table 1. Incidence and characteristics of EG-BGT as seen on sequential cUS during admission and around term equivalent age
(n, number of infants; PMA, postmenstrual age; pn, postnatal; TEA, term equivalent age)

EG-BGT			
During admission (n=130)	Total, *n* (%)		120 (92.3)
	Appearance, *n* (%)	Diffuse	120 (100)
		Focal	0 (0)
	Side, *n* (%)	Unilateral	0 (0)
		Bilateral	120 (100)
	Seen on first postnatal cUS, *n* (%)		98 (81.7)
	First seen, *median* (range)	Pn age (days)	1 (0-12)
		PMA (weeks)	29.0 (25.6-32.6)
	Last seen, *median* (range)	Pn age (days)	41 (0-110)
		PMA (weeks)	33.6 (27.0-44.1)
	Duration (days), *median* (range)		40 (1-110)
Around TEA (n=110)	Total, *n* (%)		19 (17.3)

Figure 5. Relation between incidence of EG-BGT and postmenstrual age at cUS scanning in the 130 very preterm infants (PMA, postmenstrual age).



Association with other changes

In most infants, both with and without EG-BGT, other changes were seen on cUS (26). Infants with EG-BGT during admission significantly more often had frontal echodensities during admission than those without EG-BGT. Infants with EG-BGT still present around TEA significantly more often had periventricular echodensities during admission and frontal echodensities still present around TEA. For none of the other cUS changes associations were found with EG-BGT.

MRI

Visual assessment *(n=110)*

In one (1%) infant, SI change was detected in the BGT, consisting of a punctate lesion in the left lentiform nucleus. Myelination in the BGT region was normal in all infants as compared to reference images.

White matter classification

In 27 (25%) infants the WM was scored as normal/mildly abnormal, in 63 (57%) as moderately abnormal, and in 20 (18%) as severely abnormal.

Quantitative assessment

Diffusivity values (n=109)

For one infant no DTI images were available, so, in 109 infants ADC and FA values were obtained. Mean ADC and FA values for the BGT structures are shown in Table 2, representing the mean values of the pooled structures of the left and right hemisphere. A significant negative correlation was found between ADC and PMA at scanning for the caudate nucleus, lentiform nucleus and thalamus (p=0.000 for all). A significant positive correlation was found between FA and PMA for the lentiform nucleus (p=0.008). For none of the BGT structures, a correlation was found between ADC or FA and GA at birth. No differences in left and right ADC or FA were found for any of the BGT structures.

Table 2. Apparent diffusion coefficient and fractional anisotropy values (x 10^{-3} mm^2/s) for the different structures within the basal ganglia and thalami region, and relation with white matter classification; correction for postmenstrual age at day of MRI was applied
(ADC, apparent diffusion coefficient; FA, fractional anisotropy; n, number of infants; nc, nucleus; NS, not significant; SD, standard deviation)

Diffusivity values, *mean* (±SD)		Total group of infants (n=109)	WM classification			p-value
			Normal/mildly abnormal (n=27)	Moderately abnormal (n=62)	Severely abnormal (n=20)	
ADC	Caudate nc	1.065 (0.08)	1.067 (0.08)	1.067 (0.08)	1.056 (0.10)	NS
	Lentiform nc	0.999 (0.08)	0.992 (0.07)	1.003 (0.08)	0.995 (0.09)	NS
	Thalamus	0.975 (0.07)	0.968 (0.07)	0.981 (0.06)	0.968 (0.09)	NS
FA	Caudate nc	0.130 (0.05)	0.132 (0.05)	0.124 (0.02)	0.146 (0.08)	NS
	Lentiform nc	0.148 (0.03)	0.159 (0.04)	0.145 (0.03)	0.142 (0.02)	NS
	Thalamus	0.167 (0.04)	0.186 (0.05)	0.157 (0.03)	0.170 (0.02)	NS

Volume measurements (n=105)

In 105 infants, BGT volumes were measured on T_1-weighted MRI; in the other infants image quality was suboptimal due to movement artefacts. Mean total BGT volumes are shown in Table 3, representing the pooled volumes of the left and right hemisphere. A significant positive correlation was found between BGT volumes and PMA at scanning

(p=0.000). No correlation was found between volumes and GA at birth. There were no differences in left and right BGT volumes.

Table 3. Total basal ganglia and thalami volumes (ml), and relation with white matter classification; correction for postmenstrual age at day of MRI was applied
(n, number of infants; SD, standard deviation; WM, white matter)

Infants with volume measurements		Total BGT volumes, mean (±SD)	p-value
Total group of infants (n=105)		20.44 (2.92)	
WM classification	Normal/mildly abnormal (n=24)	21.40 (1.80)	0.000
	Moderately abnormal (n=61)	20.56 (2.90)	
	Severely abnormal (n=20)	18.90 (3.54)	

Relation between EG-BGT and MRI findings

There was no association between EG-BGT, either during admission or around TEA, and changes in signal or myelination in BGT on MRI.

After correction for PMA at scanning, no differences in mean ADC or FA for the different BGT structures or mean BGT volumes were found between infants with and without EG-BGT, either during admission or around TEA.

Relation between quantitative measurements and white matter classification

Diffusivity values *(n=109)*

No correlations were found between mean ADC or FA for the different BGT structures and the WM classification (Table 2).

Volume measurements *(n=105)*

A significant negative correlation was found between mean BGT volumes and the WM classification (p=0.000) (Table 3).

Discussion

To our knowledge, this is the first prospective study on imaging findings (sequential cUS throughout the neonatal period and MRI) of the deep GM in a large cohort of very preterm infants. Quantitative measurements of the BGT were related to EG-BGT, age and WM injury.

We found EG-BGT in 92% of very preterm infants, present on the first postnatal cUS in most, bilateral and diffuse in all, and mainly located and most prominent in the basal ganglia. This incidence is considerably higher than previously reported by us and others (10-11,13), possibly explained by assessment of sequential cUS over a longer period (up to TEA), advances in ultrasound equipment and techniques, and inclusion of preterm infants < 32 weeks' GA only. EG-BGT gradually faded with age and its incidence decreased with increasing PMA; in only 19% of infants it was still present around TEA and in none after 44 weeks' PMA. Our current findings on the evolution of EG-BGT are consistent with previous findings by us and others (10-11). EG-BGT was related to lower GA and birth weight, being consistent with previous studies (10-11,13). An association was found with frontal echodensities, also frequently seen in very preterm infants, gradually fading with increasing PMA, and no longer seen after 1 month post-term. They reflect a maturational phenomenon in the immature WM, probably representing remnants of the germinal matrix (14,16). No equivalent was found for EG-BGT on MRI. Although the origin of EG-BGT remains unclear, these results indicate that EG-BGT is a prematurity-related, normal maturational phenomenon. It can be hypothesized that the echogenic appearance of the BGT results from a relative difference in echogenicity between the immature deep GM and WM related to differences in water content and/or myelination. The immature WM is not yet myelinating during the early preterm period and has a very high water content, while myelination in the BGT starts at the beginning of the third trimester of pregnancy (28-31). The echogenic appearance may also be related to differences in cell content and/or density of fibres between the immature deep GM and WM. Presence of EG-BGT around TEA was associated with echodensities in the periventricular WM during admission and persistence of frontal echodensities, suggesting that persistence of EG-BGT beyond TEA reflects abnormal or delayed maturation, comparable to persisting frontal echodensities in high-risk fetuses (35).

In none of our infants localized EG-BGT was detected, while MRI showed abnormal SI in the BGT in only one (1%) infant. Our incidence of localized BGT abnormality is lower than reported previously. In preterm infants, incidences of focal BGT lesions of up to 5% have been reported for cUS and up to 8% for MRI (3,6,10-11,22,24,36-37). These lesions appear to resolve before TEA (6,36). So, focal BGT lesions are rare in very preterm infants, and, if present, generally seem to resolve before TEA. As we used a strict ultrasound protocol with frequent high-quality cUS (25), performed MRI around term on a 3 Tesla system using small slice thickness without interslice gaps (27), and studied a large cohort of very preterm infants prospectively, our low incidence is probably representative for other preterm populations.

Myelination in the BGT appeared appropriate for PMA in all infants. However, using a 3 Tesla field strength, myelination is depicted at an earlier stage than with lower field strengths. Therefore, by comparing our images with those obtained with lower field strengths, we may have missed subtle delay (28-31).

Although no correlations were found with GA at birth, we, consistent with others (38-40), found negative correlations between ADC and positive correlations between FA and PMA at scanning. ADC is a measure for random diffusion of water molecules in cerebral tissue, while FA is a measure for restriction of diffusion of water molecules in one direction relative to all other directions. ADC decreases and FA increases with ongoing maturation (41). Our findings suggest that low GA at birth is not related to abnormal BGT development and that in very preterm infants this process is ongoing around TEA. No differences in mean ADC and FA were found between infants with or without EG-BGT, confirming that EG-BGT is a normal finding in very preterm infants.

We did not find a correlation between BGT volumes and GA at birth. So, in a relatively homogeneous cohort of very preterm infants, with GA ranging from 25 to 32 weeks, GA did not influence BGT volumes measured around TEA. Others, using different volumetric techniques and studying different populations including (more) extremely preterm infants, reported smaller BGT volumes in preterm infants around TEA than in full-term neonates, being more marked with decreasing GA at birth (1,5,8). We found a positive correlation between BGT volumes and PMA at scanning, indicating ongoing growth of these structures around TEA. No differences in volumes were found between infants with or without EG-BGT, again confirming that EG-BGT is a normal finding in very preterm infants.

Previous studies reported associations between WM injury and quantitative or visual reductions in BGT volumes (1-6,8). We confirmed this finding in this larger group of very preterm infants. No correlations were found between the WM classification and diffusivity values. These results indicate reduction of BGT volumes in infants with WM injury, while WM injury does not seem to influence developmental processes in remaining BGT tissue, at least up to TEA. Injury to the developing WM may induce axonal and neuronal damage and, consequently, disturbances in the thalamo-cortical connectivity. This may lead to direct injury and/or secondary developmental disturbances, and thereby volume reductions, of the BGT, particularly of the thalamus (1,4,7-9).

There are some limitations to our study. In several infants early transfer limited the number of cUS. It was therefore not always possible to assess the exact duration of EG-BGT and we may have missed (focal) BGT lesions developing after discharge. However, as MRI around TEA showed BGT changes in only one infant, this seems unlikely. Secondly, PMA at MRI varied between 42 and 55 weeks. As the SI of the WM changes with age, this may have influenced our WM classification. However, we feel that the SI changes included in the WM classification are very well recognizable, also after TEA. So far, we are not informed on the clinical significance of deviant growth of the BGT. Follow-up studies, including standardized neurological examinations, visual assessments and developmental tests, are currently ongoing in our study-population.

In conclusion, bilateral, diffuse and subtle EG-BGT is a prematurity-related ultrasound finding in very preterm infants before TEA, probably representing maturation of the BGT. Focal changes in the BGT, mostly resolving before TEA, are rare in very preterm infants and should be regarded as non-physiological. In very preterm infants growth and development of the BGT seem to be ongoing around TEA, while WM injury negatively influences BGT growth. To study these processes after TEA, long-term imaging studies are necessary. Neurological follow-up is needed to assess the clinical significance of deviant growth and development of the deep GM and of focal BGT lesions.

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Chapter 12

Lenticulostriate vasculopathy in very preterm infants

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Abstract

Background and Aim:
Lenticulostriate vasculopathy (LSV) can be seen on neonatal cranial ultrasound (cUS) scans and has been associated with various clinical conditions. Studies in preterm infants are limited. Our aim was to assess for LSV on cUS of very preterm infants: incidence and aetiology, evolution during neonatal period, association with clinical parameters, and magnetic resonance imaging (MRI-)equivalent.

Patients and Methods:
Very preterm infants (< 32 weeks), admitted to our tertiary neonatal referral centre, underwent sequential cUS throughout the neonatal period and MRI around term age. cUS were evaluated for LSV and other changes, and MRI for changes in signal and myelination in deep grey matter. LSV was divided in early-onset (≤ 7 postnatal days) and late-onset (> 7 postnatal days). Perinatal clinical parameters were collected for all infants and compared between groups.

Results:
In 22 out of 111 (20%) infants LSV was detected: early-onset in five and late-onset in 17. LSV mostly presented some weeks after birth and persisted for several months. There were no associations between LSV and other changes on cUS or deep grey matter changes on MRI. Infants with late-onset LSV were younger and smaller at birth than infants with early-onset LSV. Postmenstrual age at first detection was comparable for both LSV groups. There were no associations between LSV and perinatal clinical parameters, but infants with LSV had less episodes of hypotension than infants without LSV.

Conclusions:
LSV is a frequent finding on cUS in very preterm infants, but does not show on MRI. The postmenstrual age, rather than gestational and postnatal age, seems important in LSV development. LSV is not associated with clinical parameters. When encountered in otherwise healthy preterm infants, LSV is probably a benign temporary phenomenon.

Introduction

Lenticulostriate vasculopathy (LSV), presenting as hyperechogenic vessels in the basal ganglia and/or thalamus (BGT) region, can be detected on cranial ultrasound (cUS) scans of neonates (1). The incidence of LSV in neonates varies between 0.3-32% (2-16). LSV can be unilateral or bilateral, and punctate, linear or branching (4-5,9-10,17). Histological studies show intramural and perivascular depositions of amorphous basophilic material in the lenticulostriate vessels, probably causing the hyperechogenic appearance on cUS. The vessels are usually medium sized, having thickened and hypercellular walls without fibrosis or hyalinisation (2,5,9,13).

LSV has been associated with several clinical conditions, including infections, both congenital (e.g. Toxoplasmosis, Other, Rubella, Cytomegalovirus, Herpes (including Parvo B19) (TORCH) infections) and acquired, chromosomal abnormalities, congenital heart disease, other congenital malformations, hypoxic-ischaemic events, fetal alcohol and drug exposure, twin-to-twin transfusion syndrome, neonatal lupus erythematosus, hydrops fetalis, metabolic disorders and diabetic fetopathy (2-10,12-13,15,17-28). It occurs more often in infants of multiple than of singleton pregnancies and in full-term than in preterm neonates (12-13,25-26). However, the aetiology and clinical significance of LSV are largely unclear (8,13,15).

Prospective studies on the incidence and aetiology of LSV and associated clinical parameters in preterm infants are limited (4-5,10,12,14-15). The aims of our prospective study were to assess the incidence, aetiology and evolution of LSV in a large cohort of very preterm infants. Additional aims were to assess its association with various perinatal clinical parameters, previously associated with brain injury in preterm infants, presence of an equivalent on magnetic resonance imaging (MRI), and presence of changes in maturation of the BGT in infants with as compared to without LSV.

Patients and Methods

Patients

Very preterm infants (gestational age (GA) < 32 weeks), admitted to the tertiary neonatal unit of the Leiden University Medical Center between May 2006 and October 2007, were eligible for a neuro-imaging study, assessing and comparing brain imaging findings on cUS and MRI. For this part of the study, emphasis was placed on LSV. 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 and metabolic disorders, and neonatal meningitis.

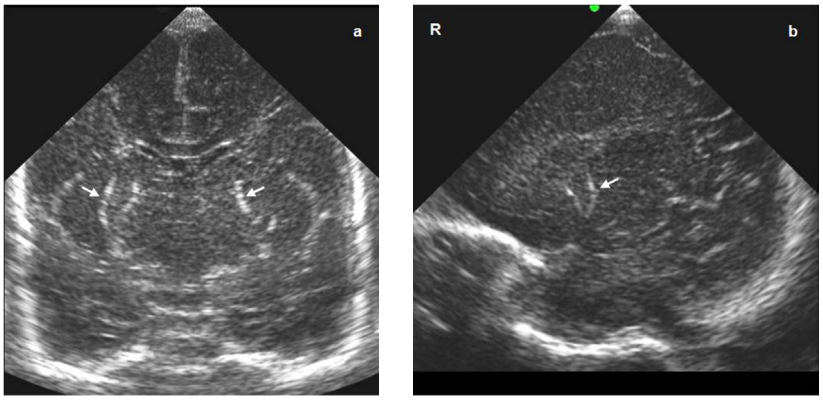
Cranial ultrasound

As part of the routine care, sequential cUS scans were performed by the attending (fellow) neonatologists, using an Aloka α10 scanner with multifrequency transducer (Biomedic Nederland B.V., Almere, the Netherlands), 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 (29). Of included infants, all cUS scans were assessed as recently described (30).

LSV was considered present when on at least one cUS examination, a punctate or linear echogenic structure was seen in the distribution of the thalamo-striatal vessels in the BGT region, on both coronal and (para)sagittal views (Figure 1). The side (left and/or right), appearance (punctate, linear and/or branching), and location (basal ganglia and/or thalamus) were recorded. The day LSV was first detected on sequential cUS and its evolution and duration (up to the day of the term equivalent cUS) were noted. As previous studies described differences between preterm infants with LSV presenting within the first 7-10 days of birth and thereafter (11), we divided LSV into early-onset (first seen on initial or subsequent cUS performed ≤ 7 days of birth) and late-onset (first seen on cUS performed > 7 days of birth).

Other changes, including echodensities in the frontal white matter (frontal echodensities), periventricular echodensities, cystic white matter lesions, intraventricular haemorrhage, post-haemorrhagic ventricular dilatation, and periventricular haemorrhagic infarction, were recorded (30).

Figure 1. Coronal (a) and sagittal (b) cUS scans of a preterm infant (gestational age 26.4 weeks), scanned at postmenstrual age 30.7 weeks, showing bilateral lenticulostriate vasculopathy having a branching appearance on the right side and a linear appearance on the left side.



MRI

MRI examinations were performed in all very preterm infants, preferably around or just after term equivalent age (TEA), according to our standard protocol, using a 3 Tesla Philips MR system (Philips Medical Systems, Best, the Netherlands) as recently described (31). For infants who were still unstable and/or ventilator dependent around that age, MRI was postponed. For this part of the neuro-imaging study, only the T_1-, T_2-, and susceptibility-weighted sequences were analyzed.

All MRIs were assessed as recently described (30). Special attention was paid to signal intensity changes in the BGT. The side (left and/or right), appearance, and location (basal ganglia and/or thalamus) were recorded. Myelination in the BGT region was compared to reference images, obtained with lower field strengths (32-35).

Clinical parameters

For all included infants the following perinatal clinical parameters were retrospectively collected: antenatal corticosteroid treatment; GA at birth; birth weight; gender; plurity and in case of monochorionic twins presence of twin-to-twin transfusion syndrome; congenital TORCH infection based on positive maternal serum IgM or PCR screening; respiratory distress syndrome requiring mechanical ventilation and surfactant treatment; bronchopulmonary dysplasia, if oxygen dependence ≥ 30% at 36 weeks'

postmenstrual age (PMA) (36); dexamethasone treatment for bronchopulmonary dysplasia; patent ductus arteriosus requiring medical and/or surgical treatment; hypotension requiring inotropic treatment; sepsis, if positive blood culture, and/or necrotizing enterocolitis, if grade ≥ 2a according to Bell et al. (37).

Data analysis

Statistical analyses were performed using SPSS software (version 14.0; SPSS inc., Chicago, Illinois, USA). For the analyses, only infants who were admitted to our unit for at least 7 days were included. The incidence of LSV was calculated. Incidences of (other) changes on cUS and MRI were compared between infants with and without LSV, using a Pearson χ^2 test. Subsequently, infants with LSV were divided into early-onset and late-onset groups. Characteristics of LSV and incidences of (other) changes on cUS and MRI were compared between both LSV groups, using a Pearson χ^2 test.

Incidences of clinical parameters were compared between infants with and without LSV and between the early-onset and late-onset groups, using a Pearson χ^2 test for categorical and an unpaired t-test for continuous variables. Clinical variables with $p < 0.1$ were entered into a stepwise logistic regression model to identify independent predictors of LSV. As several of the collected clinical parameters may be strongly related to GA at birth, this was always included in the model. Level of significance was $p \leq 0.05$.

Results

Patients

During the study-period, 182 very preterm infants were eligible for the LSV study, of whom 130 (80 male) were included. Fifty-two infants were excluded; three because of structural brain abnormalities and 49 because informed parental consent was not obtained. Reasons for not obtaining consent included transfer to another hospital or death within a very short period of birth, rejection of participation by the parents, and practical problems such as language barrier and travel distance to the hospital. Median GA and birth weight of included infants were 29.0 (range 25.6-31.9) weeks and 1141 (520-1960) grams, respectively. There were no significant differences in GA and weight at birth between infants with and without informed consent.

In 111 (83.5%; 68 male) infants, sequential cUS (median number 8, range 4-21) were performed during a period of at least 7 days, but in 12 of these infants no or inadequate cUS and/or MRI around TEA were obtained. In three infants, MRI was performed elsewhere, using different protocols. In two infants MR images were difficult to interpret due to movement artefacts, and in seven infants the parents withdrew participation from MRI. Therefore, in 99 infants (61 male) contemporaneous cUS and MRI were obtained at a median PMA of 43.4 (40.1-55.9) weeks. In 61 infants MRI was performed around TEA; in the other 38 between 44.0 and 55.9 weeks' PMA.

Cranial ultrasound (n=111)

LSV

LSV group

In 22 infants (19.8%; 11 male), LSV was detected on at least one cUS examination (median number 6, range 1-12). Median GA and birth weight were 27.9 (26.0-31.7) weeks and 1095 (620-1800) grams, respectively. Characteristics of LSV are shown in Table 1.

Early-onset and late-onset LSV

LSV was detected within the first 7 postnatal days in five infants (22.7%), while thereafter in 17 (77.3%). In three infants, LSV was seen on the first cUS scan performed within 24 hours of birth. Characteristics of LSV and differences therein between infants with early- and late-onset LSV are shown in Table 1. PMA at first detection of LSV was not different between both groups. In infants with early-onset LSV, LSV was significantly more often left-sided than in infants with late-onset LSV, in whom LSV was mostly right-sided. No other differences in characteristics were found.

Table 1. Characteristics of lenticulostriate vasculopathy for the lenticulostriate vasculopathy group and for the early-onset and late-onset lenticulostriate vasculopathy groups separately
(LSV, lenticulostriate vasculopathy; n, number of infants; NS, not significant; PMA, postmenstrual age; pn, postnatal)

Characteristics of LSV			LSV group (n=22)	Early-onset LSV group (n=5)	Late-onset LSV group (n=17)	Early-onset versus late-onset p-value
Detection	First, *median* (range)	Pn age (days)	17.0 (0-117)	0.0 (0-7)	20.0 (13-117)	0.034
		PMA (weeks)	30.5 (27.9-44.1)	30.0 (27.9-31.4)	31.0 (28.1-44.1)	NS
	Last, *median* (range)	Pn age (days)	97.0 (14-166)	62.0 (14-166)	106.0 (57-165)	NS
		PMA (weeks)	42.6 (31.9-55.1)	36.7 (31.9-55.1)	42.7 (35.0-50.4)	NS
	Duration (days), *median* (range)		69.5 (1-166)	62.0 (7-166)	71.0 (1-112)	NS
	On first cUS, *n* (%)		3 (13.6)	3 (60.0)	0 (0.0)	0.006
	On term cUS, *n* (%)		15 (68.2)	2 (40.0)	13 (76.5)	NS
At first detection	Laterality, *n* (%)	Unilateral	15 (68.2)	4 (80.0)	11 (64.7)	NS
		Right	11 (73.3)	1 (25.0)	10 (90.9)	0.022
		Left	4 (26.7)	3 (75.0)	1 (9.1)	
		Bilateral	7 (31.8)	1 (20.0)	6 (35.3)	
	Appearance, *n* (%)	Punctate	4 (18.2)	1 (20.0)	3 (17.6)	NS
		Linear	17 (77.3)	4 (80.0)	13 (76.5)	
		Branching	1 (4.5)	0 (0)	1 (5.9)	

Relation with other changes

In most very preterm infants other changes were detected on cUS (30). No association was found between LSV, or first detection of LSV, and other changes on cUS.

MRI (n=99)

In none of the infants with LSV, including infants with LSV seen on contemporaneous cUS, signal intensity changes were detected in corresponding areas on MRI. Myelination in the BGT region was normal in all infants as compared to reference images. No association was found between LSV and changes in signal or myelination in the BGT on MRI.

Relation between LSV and clinical parameters (n=111)

LSV group

Characteristics of perinatal clinical parameters for infants with and without LSV are shown in Table 2. Infants with LSV had significantly less episodes of hypotension than infants without LSV. Hypotension was identified as an independent variable. No differences were found for the other clinical parameters.

Early-onset and late-onset LSV

Characteristics of clinical parameters for the early- and late-onset LSV groups are shown in Table 2. Infants with late-onset LSV had a significantly lower GA and weight at birth than infants with early-onset LSV. Only GA was an independent variable. No differences were found for the other clinical parameters.

Table 2. Characteristics of clinical parameters for the total group, the lenticulostriate vasculopathy group, the non-lenticulostriate vasculopathy group, and the early-onset and late-onset lenticulostriate vasculopathy groups, and comparison of clinical parameters between groups

(*, independent variable; BPD, bronchopulmonary dysplasia; GA, gestational age; LSV, lenticulostriate vasculopathy; n, number; NEC, necrotizing enterocolitis; NS, not significant; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; TORCH, Toxoplasmosis, Other, Rubella, Cytomegalovirus, Herpes (including Parvo B19); TTTS, twin-to-twin transfusion syndrome)

Clinical parameters		Total group (n=111)	LSV group (n=22)	Non-LSV group (n=89)	LSV versus non-LSV group p-value	Early-onset LSV group (n=5)	Late-onset LSV group (n=17)	Early- versus late-onset p-value
Antenatal corticosteroids, *n* (%)		66 (59.5)	16 (72.7)	50 (56.2)	NS	5 (100)	11 (64.7)	NS
GA (weeks), *median* (range)		28.7 (25.6-31.9)	27.9 (26.0-31.7)	29.0 (25.6-31.9)	NS	29.9 (27.9-31.4)	27.3 (26.0-31.7)	0.041*
Birth weight (g), *median* (range)		1072 (520-1960)	1095 (620-1800)	1065 (520-1960)	NS	1410 (1066-1750)	1030 (620-1800)	0.045
Male, *n* (%)		68 (61.3)	11 (50.0)	57 (64.0)	NS	2 (40.0)	9 (52.9)	NS
Plurity, *n* (%)	Singleton	74 (66.7)	14 (63.6)	60 (67.4)	NS	2 (40.0)	12 (70.6)	NS
	Twin / triplet	37 (33.3)	8 (36.4)	29 (32.6)		3 (60.0)	5 (29.4)	
Monochrionicity, *n* (%)	Total	9 (24.3)	2 (25.0)	7 (24.1)	NS	1 (33.3)	1 (20.0)	NS
	TTTS	6 (66.7)	2 (100)	4 (57.1)	NS	1 (100)	1 (100)	NS
	Donor / recipient	4 / 2	1 / 1	3 / 1	NS	0 / 1	1 / 0	NS
Congenital TORCH, *n* (%)	Performed	24 (27.9)	10 (45.5)	14 (20.9)	NS	2 (40.0)	8 (88.9)	NS
	Positive	0 (0)	0 (0)	0 (0)	NS	0 (0)	0 (0)	NS
Sepsis / NEC, *n* (%)		51 (45.9)	11 (50.0)	40 (44.9)	NS	2 (40.0)	9 (52.9)	NS
RDS, *n* (%)		61 (55.0)	15 (68.2)	46 (51.7)	NS	4 (80.0)	11 (64.7)	NS
BPD, *n* (%)		5 (4.5)	1 (4.5)	4 (4.5)	NS	1 (20.0)	0 (0)	NS
Postnatal dexamethasone, *n* (%)		16 (14.4)	2 (9.1)	14 (15.7)	NS	0 (0)	2 (11.8)	NS
Hypotension, *n* (%)		37 (33.3)	3 (13.6)	34 (38.2)	0.042*	1 (20.0)	2 (11.8)	NS
PDA, *n* (%)		36 (32.4)	5 (22.7)	31 (34.8)	NS	1 (20.0)	4 (23.5)	NS

Discussion

To our knowledge, this is the first prospective study describing the incidence, evolution and association with clinical parameters of LSV in a large cohort of very preterm infants. Our incidence (20%) is higher than previously reported (3-9,11-16). Chamnanvanakij et al. (8) found an incidence of 5.1% in a small group of preterm infants with birth weight < 1250 grams, and in a retrospective study in preterm infants < 35 weeks' GA, an incidence of 4.6% was reported (11). Possible explanations for our higher incidence may be differences in study-populations and ultrasound techniques. We included only very preterm infants, assessed with sequential cUS over a longer period, up to TEA, and also included infants with a punctate appearance of LSV. Ultrasound equipment and techniques have improved considerably over recent years, resulting in higher image quality and possibly better detection of subtle changes. In a study by Paczko et al. (10) in a group of preterm infants up to 37 weeks' GA with otherwise normal cUS in the first postnatal week, an incidence of 31.6% was described. Higher incidences have been reported in full-term than in preterm neonates, probably explaining their high incidence. As we included a large cohort of unselected infants born very prematurely, assessed with frequent high-quality cUS, our data probably reflect the true incidence of LSV in very preterm infants.

LSV was mostly detected after the first few weeks of birth, and persisted for several months, at least up to TEA. At first detection, LSV was mostly unilateral (mainly right-sided) and linear, but often became bilateral and more complex in appearance on subsequent scans before fading towards TEA. These findings are largely consistent with recent studies, describing a mean postnatal age at first detection of 4 to 5 weeks, and LSV to be mostly unilateral (right-sided) and have a progressive or static appearance (4-9,12-13). We and others do not have an explanation for the right-sided predominance of LSV.

In agreement with previous studies (4,9,11,16), the majority (77%) of our preterm infants had late-onset LSV. Only in studies mainly consisting of full-term neonates, LSV was generally present within the first week of life (7,12-13). These findings further indicate that in preterm infants LSV mostly presents after the first postnatal week(s).

Similar to Hemanchandra et al. (11), we found infants with late-onset LSV to be younger

at birth than those with early-onset LSV. However, despite the differences in GA and postnatal age at first detection of LSV between the early- and late-onset groups, the PMA at first detection was not significantly different. In most infants, LSV was first seen between 30 and 31 weeks' PMA. This may indicate that PMA is an important factor in the development of LSV, rather than GA at birth and postnatal age at first detection, and that the lenticulostriate vessels are most vulnerable or prone for LSV before or around this PMA. This hypothesis is supported by the fact that in full-term neonates LSV mostly presents at birth, while in preterm neonates mostly after several weeks (4,7,9,11-13,16).
LSV has been associated with a variety of perinatal conditions. We found a tendency towards more multiple pregnancies in the early-onset group, being in agreement with several previous studies, reporting LSV to occur more often in infants of multiple pregnancies, particularly monochorionic twin pregnancies (12-13,25-26). As we did not find differences in incidence of monochorionic twins between infants with and without LSV, we cannot confirm this finding.
We did not find an association between LSV and congenital TORCH infection: in all infants, both with and without LSV, in whom TORCH screening was performed, results were negative. Our findings are consistent with recent studies, only occasionally describing TORCH infection in neonates with LSV (7,11,13). Therefore, we do not consider TORCH screening warranted in very preterm infants with LSV, unless there are symptoms suggestive of infection.
The aetiology and clinical significance of LSV remain largely unclear (8,13,15). While initial studies suggested an infectious origin (1-3,19), more recent studies have suggested (a combination of) a variety of infectious and non-infectious origins (6-7,9). In addition, late-onset LSV may be due to a perinatal insult to the developing brain, while early-onset LSV may reflect an in utero insult (11).
Histological studies on changes in thalamo-striatal vessels in infants with LSV reported inconsistent findings, possibly partly due to sampling differences and to different stages of LSV (5,9). Some studies found no (peri)vascular abnormalities in involved vessel walls, while others reported depositions of basophilic material as solitary finding or in combination with iron (mineralisation), diffuse microcalcifications and/or calcium (2-3,5,9,13). LSV was therefore thought to represent a vasculopathy, but its underlying pathogenesis is unclear and several potential pathways have been suggested, including vasculitis, hypoxia-ischaemia, and changes in blood flow.

We only found a significant association between LSV, particularly late-onset, and less episodes of hypotension, and do not have an explanation for this finding. We did not find associations with (other) changes on cUS or MRI, and, as expected, no equivalent was found for LSV on MRI (2-6,13,21-22,28). An explanation for this may be that ultrasound and MR imaging are based on different technologies, making detection of vascular deposits and/or calcifications difficult with MRI. In addition, LSV seems to be of vascular origin and does not represent tissue changes. Therefore, the MRI techniques included in this study may not be sensitive to the changes underlying LSV. Possibly, studies on blood flow in and vasculature of involved vessels, including MR angiography, may elucidate vascular changes resulting from LSV and/or may help to study its origin. Based on our results and recent findings, we suggest that a combination of factors underlies LSV.

We appreciate some limitations of our study. In several infants early transfer limited sequential cUS to the early postnatal period. As in most infants LSV was still seen at discharge, it was not always possible to assess its exact duration, and we may have underestimated its duration in four infants in whom it was no longer detected around TEA. We excluded infants with congenital malformations and chromosomal and/or metabolic disorders. Consequently, we cannot comment on the association between LSV and these disorders, and may have slightly underestimated the incidence of LSV in the general preterm population. Finally, no outcome data are, as yet, available for our study-population. Favourable outcome has been found in infants with isolated LSV (13).

In conclusion, this study shows that LSV is a frequent finding in very preterm infants. It often first presents several weeks after birth and persists for several months. PMA, rather than GA and postnatal age, is an important factor in the development of LSV. The aetiology and clinical significance remain unclear and we did not find associations with perinatal clinical parameters, including congenital infections. Our findings suggest that LSV, when encountered in otherwise healthy preterm infants, may be a benign temporary phenomenon.

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Part VI

Discussion

Chapter 13

General discussion and Future perspectives

General discussion

Infants who are born very prematurely are at risk of brain injury. Although advances in neonatal care have greatly improved the survival and outcome of very preterm infants, this still poses major challenges (1-8).

Cranial ultrasonography (cUS) and magnetic resonance imaging (MRI) are the preferred techniques for imaging the newborn infant's brain. Sequential cUS is an excellent tool to image and follow the very preterm infant's brain throughout the neonatal period (5) (Chapters 2 and 3). MRI provides invaluable additional information on growth and development of and injury to the preterm brain (5,9-11) (Chapters 4, 5 and 9). cUS and MRI techniques and protocols have improved considerably over recent years.

Although the incidences of intraventricular haemorrhage (IVH), periventricular haemorrhagic infarction and cystic periventricular leukomalacia have markedly decreased over the past decades, the overall incidence of brain injury in very preterm infants has not. Nowadays, more subtle and diffuse white matter (WM) changes and deviant and/or delayed growth and development of the WM and deep and cortical grey matter (GM) are more frequently reported, and their importance is becoming more widely appreciated (8-10,12-23). As these subtle changes may have consequences for the neurodevelopmental outcome of very preterm infants, distinction from maturational phenomena, normally occurring in the very preterm infant's brain, is important.

The general aim of this thesis was to study and describe brain imaging findings in very preterm infants, including normal maturational phenomena as well as pathological changes, using sequential high-quality cUS throughout the neonatal period and a single high field strength MRI obtained with adapted neonatal protocols. We focused on the immature WM and deep GM. The immature WM is very vulnerable to injury and/or deviant development, being the major constituents of neurodevelopmental problems in very preterm infants (8). In addition, although the importance of injury to and/or deviant development of the deep GM in full-term neonates is well appreciated (24-26), so far, studies on the deep GM in very preterm infants are limited.

Several studies have described the prevalence and clinical relevance of various brain abnormalities in very preterm infants (9-11,27-29). However, since then, cUS and

MRI techniques and protocols have improved and higher field strength MR systems have become more widely available for clinical imaging. We showed in Chapter 5, assessing the very preterm infant's brain using frequent, sequential high-quality cUS throughout the neonatal period and 3 Tesla MRI around term equivalent age (TEA), that nowadays periventricular echodensities (PVE) and IVH are the most frequent cUS findings during the early neonatal period, while around TEA ventricular dilatation, widening of extracerebral spaces, and decreased complexity of gyration are frequently seen. Additional, frequent findings in very preterm infants seen on MRI around TEA are punctate WM lesions (PWML) and diffuse and excessive high signal intensity (DEHSI). While cUS seems less sensitive for detecting more subtle and diffuse WM changes, MRI does not depict lenticulostriate vasculopathy (LSV) and calcifications and is less reliable for detection of germinolytic cysts and choroid plexus cysts.

Besides increasing our knowledge on brain imaging findings and the accuracy of modern, high-quality cUS and MRI for detecting abnormalities and showing brain growth and development, it is desirable to identify risk factors for brain abnormalities in very preterm infants. This may contribute to early detection and intervention, and possibly to prevention of injury and neurological sequelae. In Chapter 6 we, in consistence with others (30-42), identified several potential risk factors for the most frequent and/or clinically relevant brain imaging findings in very preterm infants during the early neonatal period, including male gender for PVE and IVH, lower gestational age (GA) for post-haemorrhagic ventricular dilatation, and postnatal dexamethasone treatment for cystic WM lesions. Despite the advances in neonatal care and changes in the distribution of WM injury over the past decades, these risk factors have largely remained unchanged. In consistence with scarce previous studies (9,43-45), no risk factors were identified for abnormalities frequently detected around TEA, including PWML, severe ventricular dilatation and decreased complexity of gyration, and for DEHSI. As for several abnormalities the number of infants was small, we may not have reached statistical significance. In addition, as we only assessed perinatal clinical factors previously identified as risk factors for brain abnormalities, we cannot exclude other clinical risk factors.

White matter

In very preterm infants, the brain WM is vulnerable to injury and/or deviant growth and development. This is mainly related to the maturational processes that need to take place after birth (including myelination, glial cell migration and volume increase), leading to a high metabolic demand, and to the immaturity and anatomy of the vasculature supplying the WM and impaired cerebrovascular autoregulation. These maturational-dependent factors render the immature WM susceptible to ischaemia and inflammation, probably being the main initiating factors of WM injury (7-8,46). Injury to and deviant growth and development of the WM may lead to neurodevelopmental problems. As shown by us (Chapter 5) and others (10,13-14,17,19,22,44,47-49), cUS is not a good tool to detect subtle and diffuse WM changes as seen on MRI of very preterm infants, and, so far, no cUS-correlates have been established for PWML and DEHSI.

In our retrospective study (Chapter 8), assessing the predictive value of WM changes seen on sequential, neonatal cUS for those seen on MRI performed within the first 3 postnatal months, we found cUS to be predictive not only of severe WM changes but also of mild to moderate changes. However, in this study, 1.5 Tesla MRI was performed within the first 3 months of birth, mostly well before TEA, and at different postnatal ages, possibly limiting its reliability. Nowadays, we preferably perform MRI around TEA in very preterm infants, particularly as term equivalent MRI is highly predictive of outcome (9-11,29,49-50). In consistence with several other studies assessing the WM in very preterm infants (10,13,17,44,47), additional limitations of the study were its retrospective design, the relatively small number of infants, and the fact that changes suggested to be associated with WM injury, including ventricular dilatation, were not assessed in combination with WM injury. We therefore additionally performed a prospective study on WM injury in a large consecutive cohort of very preterm infants (Chapter 9).

We designed a new classification system for grading WM injury on frequent, sequential high-quality cUS in very preterm infants throughout the neonatal period, not only including changes within the WM but also other changes thought to be related to WM injury (i.e. abnormality in size and shape of lateral ventricles), and assessed its reliability, using a classification system for MRI (3 Tesla) around TEA as reference standard. We confirmed that sequential, neonatal cUS is reliable for detecting severely abnormal

WM, but, despite using the classification system, less reliable for detecting mildly and moderately abnormal WM as seen on MRI. In some cases cUS underestimated, while in others it overestimated WM injury on MRI. These results show that MRI around TEA is needed to reliably detect WM injury in very preterm infants with mild to moderately abnormal WM. In addition, in infants with severely abnormal WM on sequential, neonatal cUS, additional MRI helps to assess the site and extent of lesions more precisely. When MRI is performed around TEA, contemporaneous cUS does not contribute to detecting WM injury. As MRI is more burdening and repetitive MRI examinations are undesirable, sequential cUS throughout the neonatal period remains necessary to evaluate the timing, origin and evolution of WM lesions, to depict transient changes, and to follow brain maturation in these vulnerable patients. We therefore consider sequential cUS throughout the neonatal period and a single MRI around TEA warranted in all very preterm infants, enabling optimal detection of (transient) WM injury.

There are several possible explanations for the lower sensitivity of cUS for mild to moderate WM changes. One is that MRI provides higher resolution images and better coverage of the brain than cUS, enabling detection of smaller and more peripheral lesions. Another explanation for our study in specific may be the apparent discrepancy between contemporaneous cUS and MRI for detecting ventricular dilation (Chapters 5 and 9). This may indicate that visual scoring of ventricular size, as done for the WM classification systems, is not reliable (enough). Quantitative measurements may improve the agreement between cUS and MRI and the reliability of cUS for detecting moderate WM changes.

The fact that, despite advances in neonatal cUS, modern, high-quality cUS is still not a good tool for detecting mild to moderate WM changes as seen on MRI raises questions about the significance of its lower sensitivity for these WM changes. The clinical importance of separate WM changes, including PVE without cystic involution on cUS and PWML and more diffuse signal intensity changes on MRI, and of changes probably resulting from WM injury, including ventricular dilatation and widening of extracerebral spaces, has as yet not fully been established (9-10,13-15,20). It can be hypothesized that the improvements in cUS and MR imaging techniques and protocols over recent years, providing higher resolution cUS and MR images, have resulted in (better) detection of more subtle and diffuse (WM) changes. Some of the particularly

milder changes in the WM as depicted by modern, high-quality cUS and/or MRI may represent normal maturational rather than pathological processes in the immature WM. We have shown (Chapter 7) that bilateral, symmetrical echogenic areas in the frontal and parietal periventricular WM, being less echogenic than the choroid plexus and not evolving into lesions, on cUS of apparently well preterm infants during the early neonatal period most probably reflect (normal) maturational processes in the WM. In some cases, they may however reflect delayed or even abnormal maturation, comparable to persistence of echogenic areas in the frontal WM in high-risk fetuses (51). The echogenic areas are correlated with areas of altered signal intensity in the WM, previously described as maturational processes, on MRI. These results indicate that modern, high-quality cUS shows maturational processes in the preterm brain WM, and that it is important to distinguish these WM phenomena from pathological changes.

We found an incidence of PVE of 80% in our consecutive cohort of very preterm infants (Chapters 5 and 9), having an inhomogeneous appearance in the majority of infants. Some authors have suggested that the grade of PVE is an indicator of the severity of WM injury and predictor of neurodevelopmental outcome (52), while others found the duration to be the most important (53-55). Based on the results of our retrospective study (Chapter 8) and that of Sie et al. (22) on WM injury in very preterm infants, showing that homogeneous grade 1 PVE are mostly associated with normal or only mildly abnormal early MRI and short-term outcome findings, we hypothesize that the appearance of PVE is an important indicator of the severity of WM injury. Homogeneous grade 1 PVE may represent normal (maturational) phenomena in the immature WM, while inhomogeneous PVE, regardless of grade and duration, may reflect WM injury.

We (Chapter 5) and others (9-10,16,43) found an incidence of DEHSI of up to 80% on MRI of very preterm infants around TEA. DEHSI is considered to reflect WM injury, and has been associated with smaller WM volumes, changes in diffusivity in the WM, and less optimal neurodevelopmental outcome (9,15-16,43,56-57). However, recent studies, applying high-quality MR techniques and protocols, did not find associations with ventricular dilatation, widening of extracerebral spaces or smaller total brain volumes (9,58). In our opinion, a distinction should be made between DEHSI having a subtle, homogeneous appearance and more prominent, diffuse, inhomogeneous signal intensity changes on T_2-weighted images. The latter may indeed reflect WM injury,

while subtle, homogeneous DEHSI may be a maturational rather than pathological phenomenon of the immature WM.

PWML were detected in 24% of our infants (Chapters 5 and 9), which is consistent with recent studies (9,14,20). So far, their aetiology and, as mentioned above, clinical significance remain unclear. Some studies have described a favourable neurodevelopmental outcome in preterm infants with isolated or few PWML (9,14,23). In our very preterm cohort, a distinction could be made between infants with PWML being few, mostly isolated in organization and located in the periventricular WM at the level of the centrum semiovale and/or adjacent to the optic radiation, and infants with PWML being multiple, widely distributed in the WM and organized linearly and/or in clusters (Chapter 9). The latter probably reflect more severe injury to the WM.

Changes around TEA considered to reflect WM injury and/or volume loss, including ventricular dilatation and widening of extracerebral spaces, were detected on MRI in respectively 61% and 81% of our very preterm infants (Chapter 5). Previous studies described that posterior widening of extracerebral spaces can be considered normal until term age, and that in preterm infants extracerebral spaces may be wide without clinical implications (9,50,59). In preterm infants, quantified severe dilatation of lateral ventricles around TEA, particularly when combined with parenchymal lesions or IVH, predicted cerebral palsy, while mild dilatation of lateral ventricles seen as solitary finding and widening of extracerebral spaces did not (9,49-50). These data and the high incidence of widening of extracerebral spaces suggest that solitary, mild ventricular dilatation and widening of extracerebral spaces may be benign phenomena in the very preterm infant's brain around TEA, while severe lateral ventricular dilatation is a sign of WM injury.

No clear and strict definition has, so far, been given to the nowadays frequently used term 'diffuse WM injury', and the ideas about what it reflects seem to differ. In our studies on WM injury (Chapters 8 and 9), we considered diffuse WM injury to reflect PVE without cystic involution on cUS and PWML and more diffuse signal intensity changes (e.g. DEHSI) on MRI. However, based on the experiences over the past several years, we feel that the term should be refined to inhomogeneous PVE on cUS during the neonatal period, and/or multiple PWML and/or prominent, inhomogenous DEHSI on MRI, combined with decreased WM volume around TEA. We therefore define 'diffuse

WM injury' as diffuse, mostly subtle abnormalities in the WM of very preterm infants, consisting of inhomogeneous PVE (regardless of duration and grade) on neonatal cUS and/or multiple PWML with or without prominent, inhomogeneous DEHSI on MRI, combined with WM volume loss around TEA.

Deep grey matter

Like the WM, the deep GM (i.e. basal ganglia and thalami (BGT)) of very preterm infants is vulnerable to injury and/or deviant growth and development. Although the exact aetiology still needs to be elucidated, this is probably mainly related to the maturational processes that need to take place in the deep GM during the perinatal and neonatal period (including myelination), leading to a high metabolic demand, and to the close connections of the deep GM with the immature and vulnerable WM (7-8,60).

We have observed increased echogenicity of the deep GM on cUS in the majority of apparently well very preterm infants. While a similar finding may indicate injury to these structures in (near) full-term neonates, with possible (serious) consequences for neurological outcome, we hypothesized that it may be normal in very preterm infants. This observation and the scarce data on imaging of the deep GM in very preterm infants prompted us to systematically study the deep GM, as shown by modern, high-quality imaging techniques, in large consecutive cohorts of very preterm infants.

In our retrospective (Chapter 10) and subsequent prospective (Chapter 11) study, assessing the deep GM with sequential, neonatal cUS and MRI around TEA, we showed that bilateral, diffuse and subtle echogenicity in the BGT (EG-BGT) on cUS, seen in nearly all very preterm infants before TEA, is a prematurity-related finding. It probably represents a normal maturational phenomenon of the immature deep GM. However, if persisting beyond TEA, it may reflect delayed or even abnormal maturation, comparable to persistence of echogenic areas in the frontal WM in high-risk fetuses (51). No MRI-correlate was found and its origin remains unclear. It can be hypothesized that the echogenic appearance of the BGT results from a relative difference in echogenicity between the immature deep GM and WM related to differences in water content and/or myelination. The immature WM is not yet myelinating during the early preterm period and has a very high water content, while myelination in the BGT starts at the beginning of the third trimester of pregnancy (61-63). The echogenic appearance may also be

related to differences in cell content and/or density of fibres between the immature deep GM and WM.

Another ultrasound finding in the deep GM that, when encountered in otherwise healthy preterm infants, may be a benign temporary phenomenon is LSV. We showed (Chapter 12) that LSV is a frequent finding (20%) on sequential, high-quality neonatal cUS in very preterm infants, mostly presenting after the first few weeks after birth and persisting for several months. Although LSV has been associated with a variety of fetal and neonatal conditions, its aetiology remains largely unclear. No correlate was found for LSV on high-quality MRI. We hypothesize that LSV is of a vascular origin, representing vasculopathy of the thalamo-striatal vessels, and does not reflect tissue changes. The MRI techniques used in our study may not be sensitive to the vascular changes underlying LSV. Based on our study, showing that LSV was first detected between 30 and 31 weeks' postmenstrual age in nearly all infants, we suggest that the postmenstrual age, rather than the GA at birth and postnatal age at first detection of LSV, is important in the development of LSV. In consistence with recent studies (64-66), we did not find an association between LSV and congenital infections, indicating that LSV is not (solely) caused by infectious factors. We only found an association with less episodes of hypotension, suggesting that hypotension may have a preventive effect on LSV development.

As recent studies, although performed in small and/or selected study-populations, have shown that injury to and changes in growth and development of the deep GM are associated with neurodevelopmental and visual deficits in preterm infants (12,21,67), it is important to recognize these pathological processes. Our prospective study (Chapter 11) showed that focal lesions in the deep GM, mostly ascribed to haemorrhage or infarction, are rare in very preterm infants on both cUS and MRI.

The study also showed that in very preterm infants without moderate/severe WM injury, growth and development of the deep GM are ongoing around TEA. In consistence with others (8-9,12,21,60,67-70), we additionally showed that very preterm infants with moderate/severe WM injury have smaller deep GM volumes around TEA than infants without WM injury. This indicates that (moderate/severe) WM injury has a negative effect on growth of the deep GM, already during the neonatal period. It has been postulated that injury to the developing WM induces axonal and neuronal

damage and, consequently, disturbances in the thalamo-cortical connectivity. This may lead to direct injury and/or secondary developmental disturbances, and thereby volume reductions, of the deep GM and possibly other brain tissues (8,60,67,69-70). Previous quantitative studies have reported smaller BGT volumes in preterm neonates in comparison with full-term neonates, being persistent up to adulthood (18,67-68,70-72). The above data suggest that preterm birth has a negative effect on brain growth during the neonatal period, being more prominent in case of WM injury. As in very preterm infants maturational processes in the deep GM and WM are ongoing after TEA, and differences in BGT volumes between preterm and full-term neonates are persistent, we hypothesize that the negative effects of preterm birth and WM injury on brain growth are not restricted to the neonatal period but are ongoing after TEA.

In summary, we performed a neuro-imaging study of the WM and deep GM in very preterm infants. Several conclusions can be drawn from the results of this thesis:

- Frequent, sequential cUS, when performed according to our standard protocol and using appropriate and modern, high-quality equipment and techniques, is an excellent tool to image and follow the preterm infant's brain throughout the neonatal period. It enables assessment of the timing and origin of lesions, following brain maturation and the evolution of lesions, and detection of transient (WM) changes.

- Single MRI, when performed around or shortly after TEA and using optimized scan protocols and modern, high-quality equipment, provides invaluable and detailed additional information on growth and development of and injury to the preterm infant's brain.

- Sequential high-quality cUS in very preterm infants during the neonatal period predicts WM injury as seen on MRI performed well before TEA, but is less predictive of mild to moderate WM injury on MRI around TEA.

- MRI is necessary to detect mild and moderate WM injury. In addition, if performed around or shortly after TEA, MRI helps to define the site and extent of lesions in case of severe WM injury.

- When MRI is performed around TEA, additional contemporaneous cUS does not contribute to detecting WM injury.

- Sequential cUS throughout the neonatal period and a single MRI around TEA are warranted in all very preterm infants.

- Although the incidence of some forms of brain injury in very preterm infants has declined over the past decades, the overall incidence of brain injury has not. The distribution of WM injury has shifted to more diffuse and subtle changes.

- Despite advances in perinatal care and the shift towards more diffuse and subtle WM changes, the risk factors for frequent and clinically relevant forms of brain injury in very preterm infants have largely remained unchanged. Risk factors for diffuse WM injury in very preterm infants around TEA have, so far, not been demonstrated.

- Bilateral, symmetrical echogenic areas in the frontal and parietal periventricular WM and bilateral, diffuse and subtle echogenicity in the BGT (EG-BGT) on cUS of very preterm infants during the early neonatal period reflect (normal) maturational processes in the immature brain. When persisting, they may indicate delayed or even abnormal maturation.

- LSV is a frequent ultrasound finding in very preterm infants and, when encountered in otherwise healthy infants, may be a benign temporary phenomenon.

- Focal lesions in the deep GM, mostly ascribed to haemorrhage or infarction, are rare in very preterm infants, and need to be distinguished from physiological or benign phenomena in the deep GM.

- In very preterm infants, growth and development of the deep GM are ongoing around TEA. (Severe) WM injury has a negative effect on growth of the deep GM, already before TEA.

Based on the results of this thesis, we further hypothesize that in very preterm infants:

- Quantitative measurements of ventricular size will improve our classification systems for grading WM injury, and thereby the reliability of cUS for detecting moderate WM injury as seen on MRI.

- Homogeneous grade 1 PVE represent normal (maturational) phenomena in the immature WM, while inhomogeneous PVE, regardless of grade and duration, reflect WM injury.

- Subtle, homogeneous DEHSI is a maturational rather than pathological phenomenon of the immature WM, while prominent, inhomogeneous DEHSI reflects diffuse WM injury.

- Few PWML, isolated in organization and located in the periventricular WM at the level of the centrum semiovale and/or adjacent to the optic radiation, have a benign nature, while multiple PWML, widely distributed in the WM and organized linearly and/or in clusters, reflect diffuse WM injury.

- Around TEA, widening of extracerebral spaces and isolated, mild lateral ventricular dilatation are benign phenomena, while severe dilatation of the lateral ventricles is a sign of WM injury.

- Diffuse WM injury is reflected by inhomogeneous PVE on cUS during the neonatal period and/or multiple PWML with or without prominent, inhomogeneous DEHSI on MRI, combined with decreased WM volume around TEA.

- LSV is of vascular origin and does not reflect tissue changes. Hypotension may have a preventive effect on the development of LSV.

Future perspectives

Considerable progress has been made over recent decades to optimize cUS and MRI techniques and protocols for imaging the very preterm infant's brain throughout the neonatal period. These advances have greatly contributed to our knowledge on brain injury in very preterm infants. The reviews and studies reported in this thesis shed light on neuro-imaging in very preterm infants and on normal and abnormal phenomena in the immature WM and deep GM. Resulting from this thesis, several issues require further investigation:

- So far, no cUS-correlates have been found for diffuse WM injury as seen on MRI, and the origin and significance of diffuse WM injury and changes to the brain resulting from WM injury (including dilatation of the lateral ventricles) have not been fully established. Therefore, studies comparing cUS and MRI for the separate WM changes, and assessing the implications of these changes for long-term neurodevelopmental outcome are needed. Quantitative measurements of volumes of the WM and lateral ventricles, in combination with follow-up studies, need to be performed, and WM changes need to be related to volumes of the WM and lateral ventricles. In addition, studies including histological examinations of the immature WM and modern MRI techniques (such as diffusion-weighted, diffusion-tensor and susceptibility-weighted imaging) are required. These studies may help to explore the aforementioned lacks in knowledge, and to assess the clinical significance of the lower sensitivity of cUS for some of these changes. In addition, they may help to check the accuracy of our hypotheses on PVE, DEHSI, PWML and widening of cerebrospinal fluid spaces.

- Future study should focus on identifying risk factors for diffuse WM injury, especially as this may contribute to prevention of brain injury in very preterm infants.

- Echogenic areas in the frontal and parietal periventricular WM and echogenicity in the BGT (EG-BGT) reflect (normal) maturational processes in the immature WM and deep GM of very preterm infants, but may, if persisting beyond TEA, reflect delayed or even abnormal maturation. Approaches to understanding the origin of these cUS

phenomena include histological examinations of the WM and deep GM in infants who die before TEA. Studies on the maturation and the evolution of the ultrasound appearance of the WM and deep GM in normal fetuses will contribute to designate the normal evolution of these phenomena.

- Quantification of ventricular size may optimize our classification system for grading WM injury on cUS, and follow-up studies may help to establish the clinical significance of our cUS and MRI WM classifications. The optimal number of and interval between cUS examinations during the neonatal period for optimal detection of WM injury still need to be elucidated.

- The aetiology and clinical significance of LSV are still largely unclear. Histological studies and studies on blood flow in and vasculature of involved vessels, including MR angiography, may help to elucidate the vascular changes resulting from LSV and/or study its origin. Long-term follow-up studies are needed to assess the clinical significance.

- To explore growth and development of the BGT and their relation with age after TEA, long-term neuro-imaging studies are necessary.

- Long-term neuro-imaging studies may help to explore the relation between growth and development of the BGT and WM injury after TEA. In addition, long-term follow-up studies in large cohorts of unselected (very) preterm infants are needed to reliably assess the clinical significance of deviant growth and development of the deep GM.

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Chapter 14

Summary

Part I

In the Netherlands, each year approximately 2,500 infants are born very prematurely, at a gestational age (GA) of less than 32 weeks. Although advances in the care of very preterm infants have greatly improved their survival and outcome, very preterm infants are still at risk of brain injury and neurodevelopmental problems.

Imaging the preterm brain during the neonatal period has become an essential, basic part of the modern care of very preterm infants. Sequential cranial ultrasonography (cUS) is an excellent tool to image and follow the very preterm infant's brain throughout the neonatal period, while magnetic resonance imaging (MRI) provides invaluable additional information on brain growth and development and brain injury. cUS and MRI techniques and protocols have improved considerably over recent years.

While the incidence of some forms of brain injury, including intraventricular haemorrhage (IVH) and cystic white matter (WM) lesions, has markedly decreased over the last decades, the overall incidence of brain injury in very preterm infants has not. Nowadays, more subtle and diffuse WM changes and deviant growth and development of the WM and deep and cortical grey matter (GM) are more frequently reported, and their importance is becoming more widely appreciated.

The general aim of this thesis was to study and describe brain imaging findings in very preterm infants, including normal maturational phenomena as well as pathological changes, using modern, high-quality imaging techniques.

Part II reviewed the currently used and preferred techniques for neonatal neuro-imaging.

Chapter 2 discussed the value of modern, high-quality cUS imaging in both preterm and full-term neonates, and addressed issues on technical aspects, appropriate timing and protocols, diagnostic accuracy, and safety. Techniques to optimize its performance, including the use of additional acoustic windows and different transducer types, and adapting transducer frequencies and focus points, were described in **Chapter 3**.

In **Chapter 4** we shared our experience on neonatal brain MR imaging, and addressed its challenges with regard to safety, patient preparation and transportation, monitoring of vital functions, and feeding and sedation. Indications and appropriate timing, technical aspects and sequences, and optimized scan protocols for different field strength MR systems were discussed.

In **Part III** an overview of brain imaging findings, and their potential risk factors, in very preterm infants was presented.

In **Chapter 5** we studied the incidence and evolution of brain imaging findings in a consecutive cohort of 133 very preterm infants, as detected with frequent, sequential cUS throughout the neonatal period and MRI (3 Tesla) around term equivalent age (TEA). The accuracy of modern, high-quality cUS and MRI was compared. We showed that nowadays periventricular echodensities (PVE; 80%) and IVH (30%) are the most frequent cUS findings during the early neonatal period, while around TEA ventricular dilatation (43% on cUS, 61% on MRI), widening of extracerebral spaces (76% on cUS, 81% on MRI), and decreased complexity of gyration (35% on cUS, 8% on MRI) are frequently encountered. Additional, frequent findings seen on MRI around TEA are punctate WM lesions (24%) and diffuse and excessive high signal intensity (DEHSI; 79%). While cUS seems less sensitive for detecting more subtle and diffuse WM changes, MRI does not depict lenticulostriate vasculopathy (LSV) and calcifications and is less reliable for detection of germinolytic cysts and choroid plexus cysts.

In **Chapter 6** we assessed the relation between frequent and clinically relevant brain imaging findings in very preterm infants and several perinatal clinical parameters, previously associated with brain injury in preterm infants. We also evaluated whether risk factors had changed over recent decades. Several potential, independent risk factors were identified for the most frequent and/or clinically relevant findings on cUS during the early neonatal period (i.e. PVE, IVH, post-haemorrhagic ventricular dilatation, cystic WM lesions). Male gender was a risk factor for PVE ($p=0.01$) and IVH ($p=0.04$), lower GA for post-haemorrhagic ventricular dilatation ($p=0.00$), and postnatal dexamethasone treatment for cystic WM lesions ($p=0.02$). Despite advances in neonatal care and changes in the distribution of WM injury over the past decades, these risk factors have largely remained unchanged. No risk factors were identified for abnormalities frequently detected around TEA, including subtle and/or diffuse WM injury, severe ventricular dilatation and decreased cortical complexity on MRI.

Part IV focused on imaging of the WM.

In **Chapter 7** we aimed to determine whether bilateral, symmetrical echogenic areas in the frontal and parietal periventricular WM, frequently seen on cUS scans of apparently

well preterm infants and being less echogenic than the choroid plexus and not evolving into obvious lesions, reflect maturational, rather than pathological, processes in the newborn infant's brain. Forty-four sets of contemporaneous cUS and T_2-weighted MR images (3 Tesla) of 26 preterm and eight full-term neonates without overt brain injury were assessed for echogenic areas in the periventricular WM on cUS, and for correlates for these areas in the WM on MRI. The echogenic areas were more frequently and better seen in preterm neonates than in full-term neonates, and on early preterm cUS scans than on scans nearer to term age. They correlated well with areas of altered signal intensity in the WM, previously described as maturational processes, on MRI. The study showed that bilateral, symmetrical and subtle echogenic areas in the frontal and parietal periventricular WM on cUS of very preterm infants during the early neonatal period most probably reflect (normal) maturational processes in the immature WM. In some cases they may, however, reflect delayed or even abnormal maturation.

Concerns have been raised that cUS may not be a good tool to detect subtle and diffuse WM changes, nowadays frequently reported in very preterm infants. In the retrospective study in **Chapter 8**, we assessed the value of sequential, neonatal cUS and MRI (1.5 Tesla) within the first 3 months after birth for detecting WM changes and for predicting short-term neurodevelopmental outcome based on WM changes in very preterm infants. In 40 very preterm infants findings in the WM on cUS were compared to WM findings on MRI, and in 32 infants cUS and MRI findings were related to outcome at 2 years corrected age. cUS and MRI were classified as normal/mildly abnormal, moderately abnormal or severely abnormal. Sequential cUS was predictive of WM changes on MRI. Severely abnormal WM on cUS/MRI was predictive of adverse outcome, and normal/mildly abnormal WM on cUS/MRI of favourable outcome. Moderately abnormal WM on cUS/MRI was associated with variable outcome. Additional early MRI was only of significance for depicting WM changes more precisely and for more accurate prediction of outcome in infants with severely abnormal WM on cUS. This study thus showed that in very preterm infants, sequential, high-quality cUS throughout the neonatal period is predictive not only of severe WM changes but also of mild to moderate WM changes as seen on MRI performed well before TEA.

However, nowadays, in very preterm infants MRI is preferably performed around TEA, particularly as term equivalent MRI is highly predictive of outcome. In addition,

changes suggested to be associated with WM injury, including ventricular dilatation, were not assessed in the retrospective study. We therefore performed a prospective study in our large consecutive cohort of very preterm infants (**Chapter 9**). We designed and evaluated the reliability of a new classification system for grading WM injury on frequent, sequential high-quality cUS in very preterm infants throughout the neonatal period. This classification not only included WM changes but also other changes thought to be related to WM injury (i.e. abnormality in size and shape of the lateral ventricles). A WM classification system for MRI (3 Tesla) around TEA was used as reference standard. In 110 very preterm infants, repetitive cUS during admission and a single cUS and MRI around TEA were performed. cUS during admission were assessed for WM changes, and cUS and MRI around TEA additionally for abnormalities of the lateral ventricles. Sequential, neonatal cUS and MRI around TEA were classified as normal/mildly abnormal, moderately abnormal or severely abnormal. The positive predictive value of the cUS classification for the MRI classification was high for severely abnormal WM (0.79), but lower for normal/mildly (0.50) and moderately (0.65) abnormal WM. In some cases cUS underestimated but in others it overestimated WM injury. In infants with severely abnormal WM, MRI assessed the site and extent of lesions more precisely. Additional cUS around TEA did not contribute to detecting WM injury. This study confirmed that in very preterm infants sequential, neonatal cUS is reliable for detecting severely abnormal WM, but less reliable for mildly and moderately abnormal WM. We concluded that in very preterm infants, MRI around TEA is necessary to reliably detect WM injury and/or to precisely define the site and extent of injury. When MRI around TEA is performed, contemporaneous cUS has no additional value.

Part V focused on imaging of the deep GM (i.e. basal ganglia and thalami (BGT)).
In the retrospective study in preterm infants (GA < 35 weeks) in **Chapter 10**, we assessed the incidence, clinical significance and origin of bilateral, subtle and diffusely increased echogenicity in the BGT region (EG-BGT), frequently seen on cUS scans of very preterm infants and fetuses and, so far, of largely unclear origin and clinical significance. We additionally explored whether this cUS phenomenon reflects a maturational, rather than pathological, process in the immature brain. Sequential cUS of 359 preterm infants, of whom 143 were born at less than 32 weeks of gestation, were evaluated for EG-BGT

and other brain findings. EG-BGT was related to findings in the BGT on neonatal MRI (1.5 Tesla), and to clinical and short-term neurological outcome data in infants with GA of less than 32 weeks, who participated in an ongoing standardized follow-up program. EG-BGT was seen in 11% (39/359) of infants of less than 35 weeks, and in 26% (37/143) of infants of less than 32 weeks. Infants with EG-BGT were significantly younger and smaller at birth and had a more complicated neonatal clinical course than those without this finding. EG-BGT was always associated with other brain findings on cUS, and MRI, available in 12 infants with EG-BGT, showed changes in the BGT in five infants. Neurological development around TEA was less favourable in very preterm infants with EG-BGT than in those without EG-BGT, but comparable at 1 year corrected age. The study showed that EG-BGT mainly occurs in very small and sick very preterm infants, with appropriate neurodevelopment at 1 year corrected age, and is only occasionally associated with changes in the BGT on MRI. These findings suggest that EG-BGT is a prematurity-related finding, probably reflecting a normal maturational phenomenon of the immature deep GM.

However, as MRI was only available in some of the infants and EG-BGT always co-existed with other cUS findings, the origin and clinical implications of EG-BGT could not be established. In addition, previous neuro-imaging data on the BGT in preterm infants were limited. In the prospective study in **Chapter 11,** we systematically described imaging findings of the deep GM, as seen on sequential cUS throughout the neonatal period and MRI (3 Tesla) around TEA, in our large cohort of very preterm infants. We assessed the relation between EG-BGT and quantitative measurements (diffusivity values and volumes), indicative of growth and development, of the BGT and between quantitative measurement and age and WM injury. Sequential, neonatal cUS of 130 very preterm infants were evaluated for echogenicity of the BGT, and MRI, obtained in 110 infants, for changes in myelination and signal in the BGT and for WM injury. Diffusivity values of the BGT were obtained from diffusion-tensor images and BGT volumes were measured by manual segmentation. Bilateral, diffuse and subtle EG-BGT was seen in nearly all very preterm infants (92%), predominantly in the youngest and smallest infants. It gradually faded with age and was no longer seen after 1 month post-term. There was no association with changes in signal, myelination, diffusivity values or volumes of the BGT on MRI. None of the 130 infants had focal lesions in the BGT on cUS,

while only one infant had BGT changes on MRI. Quantitative measurements correlated with age at MRI, but not with age at birth. WM injury negatively correlated with BGT volumes, but not with diffusivity values. This study further showed that diffuse, subtle EG-BGT is a frequent and prematurity-related finding in very preterm infants. Like the echogenic areas in the periventricular WM (**Chapter 7**), it probably represents a normal maturational phenomenon of the immature brain, but, if persisting beyond TEA, may reflect delayed or even abnormal maturation. Focal BGT lesions are rare in very preterm infants and should be regarded as non-physiological. In very preterm infants, growth and development of the BGT are ongoing around TEA but WM injury negatively influences BGT growth.

Another cUS finding that we frequently encountered in the deep GM of very preterm infants was LSV. So far, its aetiology and clinical significance were largely unclear and studies on LSV in large and unselected cohorts of very preterm infants were scarce. In **Chapter 12** we prospectively studied the incidence, evolution, aetiology and clinical significance of LSV, as seen on frequent, sequential cUS throughout the neonatal period, in our cohort of very preterm infants. cUS, performed for at least 7 days during admission and again around TEA, were assessed for LSV and other changes, and MRI, obtained around TEA, for changes in signal and myelination in the BGT. LSV was divided in early-onset (≤ 7 postnatal days) and late-onset (> 7 postnatal days). For all infants, several relevant perinatal clinical parameters were collected. LSV was related to other cUS findings, MRI findings and clinical parameters. In 22 of 111 (20%) infants LSV was detected; early-onset in five and late-onset in 17. LSV mostly presented some weeks after birth and persisted for several months. It was not associated with other cUS findings or with changes in the BGT on MRI. Infants with late-onset LSV were younger and smaller at birth than infants with early-onset LSV. The postmenstrual age at first detection (mostly 30-31 weeks) was comparable for both LSV groups. No association was found between LSV and perinatal clinical parameters (including congenital infection), but infants with LSV had less episodes of hypotension than infants without LSV. The study showed that LSV is a frequent finding on cUS in very preterm infants, but does not show on MRI. The postmenstrual age, rather than GA and postnatal age, seems important in the development of LSV. When encountered in otherwise healthy preterm infants, LSV is probably a benign temporary phenomenon.

In conclusion, modern, high-quality cUS and MRI are excellent tools to image the preterm infant's brain. cUS shows maturational processes in the immature WM and deep GM of very preterm infants. MRI around TEA remains necessary to detect mild and moderate WM injury, and helps to define the site and extent of lesions more precisely. In addition, unlike cUS, it depicts myelination and shows other maturational processes in more detail. As MRI is more burdening and repetitive MRI examinations are undesirable, sequential cUS throughout the neonatal period is necessary to assess the timing and origin of lesions, to follow brain maturation and the evolution of lesions, and to depict transient (WM) changes. Sequential cUS throughout the neonatal period and a single MRI around TEA are therefore warranted in all very preterm infants.

Chapter 15

Samenvatting

Deel I

In Nederland worden ieder jaar ongeveer 14.000 kinderen te vroeg (prematuur) geboren, dat wil zeggen bij een zwangerschapsduur van minder dan 37 weken. Ongeveer 2.500 van deze kinderen worden veel te vroeg (zeer prematuur) geboren, bij een zwangerschapsduur van minder dan 32 weken. Belangrijke vooruitgangen in de zorg en behandeling van pasgeborenen gedurende de afgelopen decennia hebben geleid tot een hogere overlevingskans en gunstigere uitkomst van zeer premature pasgeborenen. Desondanks hebben zeer premature pasgeborenen nog steeds een verhoogde kans op schade aan de hersenen en problemen met de motorische en mentale ontwikkeling.

Beeldvorming van de hersenen tijdens de neonatale periode (t.w. de eerste weken na geboorte) is een essentieel onderdeel van de zorg voor zeer premature pasgeborenen. De twee technieken die hiervoor worden gebruikt, zijn schedelechografie en 'magnetic resonance imaging' (MRI). Herhaalde schedelechografie tijdens de neonatale periode is een goede methode voor het in beeld brengen en vervolgen van de hersenen, en eventuele schade daarin, bij zeer premature pasgeborenen. MRI geeft echter meer gedetailleerde informatie over de groei en ontwikkeling van de hersenen en eventuele hersenschade, maar is, in tegenstelling tot echografie, ongeschikt voor herhaalde beeldvorming. De technieken en protocollen voor het vervaardigen van schedelecho- en MRI-onderzoeken bij premature pasgeborenen zijn de afgelopen jaren sterk verbeterd.

Ondanks het feit dat bepaalde vormen van hersenschade, zoals bloedingen en cysteuze lesies in de witte stof (de verbindingsbanen), steeds minder vaak voorkomen, is de incidentie van hersenschade bij zeer premature pasgeborenen niet gedaald. Tegenwoordig worden vaker meer subtiele en diffuse veranderingen in de witte stof en afwijkende groei en ontwikkeling van de witte stof en diepe en corticale grijze stof (de hersenkernen en de hersenschors) gezien. Het belang van deze laatste vormen van veranderingen in de hersenen wordt steeds meer onderkend.

Het belangrijkste doel van dit proefschrift was het bestuderen en beschrijven van de bevindingen, waaronder zowel normale rijpingsprocessen als pathologische veranderingen, bij beeldvorming van de hersenen van zeer premature pasgeborenen met behulp van moderne, kwalitatief hoogstaande echo- en MRI-technieken.

In **Deel II** werden de huidige technieken voor beeldvorming van de hersenen bij pasgeborenen uitvoerig besproken.
In **Hoofdstuk 2** werd de waarde van moderne, kwalitatief hoogstaande schedelechografie bij zowel premature als voldragen (à terme) pasgeborenen besproken en werd ingegaan op technische aspecten, protocollen, optimale timing, betrouwbaarheid en veiligheid. De mogelijkheden om schedelecho-onderzoeken te optimaliseren, onder andere door het gebruik van verschillende akoestische vensters en echotransducers en het aanpassen van de echofrequenties en focuspunten, werden uitvoerig besproken in **Hoofdstuk 3**.
In **Hoofdstuk 4** werden onze ervaringen met het maken van MRI van de hersenen bij pasgeborenen besproken en werden belangrijke aspecten van de gehele MRI-procedure, zoals veiligheid, voorbereiding, vervoer van en naar de MRI-ruimte en bewaking van vitale functies, beschreven. Daarnaast werden technische aspecten, sequenties, indicaties, optimale timing en geoptimaliseerde protocollen besproken.

Deel III gaf een overzicht van de bevindingen, en de mogelijke risicofactoren voor deze bevindingen, bij beeldvorming van de hersenen van zeer premature pasgeborenen met behulp van moderne, kwalitatief hoogstaande technieken.
In **Hoofdstuk 5** hebben we de incidentie en evolutie van bevindingen in de hersenen in een aaneengesloten cohort van 133 zeer premature pasgeborenen bestudeerd met behulp van frequent herhaalde echografie tijdens de neonatale periode en MRI met een sterk magnetisch veld (3 Tesla) rond de uitgerekende (à terme) leeftijd. De betrouwbaarheid van echo en MRI voor het aantonen van de bevindingen werd vergeleken. We hebben aangetoond dat echodensiteiten in de witte stof rond de laterale ventrikels (periventriculaire witte stof; 80%) en bloedingen in de laterale ventrikels (intraventriculaire bloedingen; 30%) tegenwoordig het meest frequent voorkomen op echo tijdens de vroege neonatale periode, terwijl rond de à terme leeftijd verwijding van de laterale ventrikels (43% op echo, 61% op MRI), verwijding van de extracerebrale ruimten (76% op echo, 81% op MRI) en verminderde complexiteit van de gyratie (vouwing van de hersenschors; 35% op echo, 8% op MRI) de meest frequente bevindingen zijn. Andere frequente bevindingen op MRI rond de à terme leeftijd zijn puntvormige witte stof lesies (24%) en diffuus verhoogd signaal in de witte

stof op T_2-gewogen opnamen (DEHSI; 79%). Echografie lijkt minder betrouwbaar voor het aantonen van subtiele en diffuse veranderingen in de witte stof. MRI toont echter geen lenticulostriatale vasculopathie (LSV) en verkalkingen en is minder betrouwbaar dan echo voor het aantonen van cysten in de germinale matrix en plexus choroïdeus.
In **Hoofdstuk 6** hebben we de relatie onderzocht tussen frequente en klinisch relevante bevindingen in de hersenen van zeer premature pasgeborenen en een aantal perinatale klinische factoren, welke eerder geassocieerd bleken met hersenschade. Daarnaast zijn we nagegaan of de risicofactoren voor hersenschade in de afgelopen decennia zijn veranderd. Een aantal potentiële en onafhankelijke risicofactoren werd gevonden voor de meest frequente en/of klinisch relevante bevindingen op echo tijdens de vroege neonatale periode; mannelijk geslacht voor echodensiteiten in de periventriculaire witte stof (p=0.01) en intraventriculaire bloedingen (p=0.04), kortere zwangerschapsduur voor post-hemorragische ventrikel verwijding (p=0.00) en postnatale behandeling met corticosteroïden voor cysteuze witte stof lesies (p=0.02). Ondanks belangrijke vooruitgangen in de zorg van pasgeborenen en veranderingen in de aard van witte stof schade, zijn deze risicofactoren grotendeels hetzelfde gebleven ten opzichte van een aantal decennia geleden. Er werden geen risicofactoren gevonden voor de veranderingen in de hersenen die frequent gezien werden op MRI rond de à terme leeftijd, zoals subtiele en/of diffuse witte stof schade, ernstige ventrikel verwijding en verminderde complexiteit van de gyratie.

Deel IV was gericht op beeldvorming van de witte stof.
Het doel van **Hoofdstuk 7** was om vast te stellen of bilaterale, symmetrische echodense gebieden in de frontale en pariëtale periventriculaire witte stof, die regelmatig gezien worden op schedelecho's van klinisch stabiele premature pasgeborenen en die minder echorijk zijn dan de plexus choroïdeus en niet overgaan in duidelijke afwijkingen, een uiting zijn van normale rijpingsprocessen in de hersenen van pasgeborenen of van schade. Vierenveertig sets van op dezelfde dag gemaakte schedelecho- en T_2-gewogen MRI-onderzoeken (3 Tesla), afkomstig van 26 premature en 8 à terme pasgeborenen zonder hersenschade, werden beoordeeld op aanwezigheid van echodense gebieden in de periventriculaire witte stof op echo en van hiermee correlerende gebieden op MRI. De echodense gebieden werden frequenter en duidelijker gezien bij premature

pasgeborenen dan bij à terme pasgeborenen en op echo's gemaakt tijdens de vroege premature periode dan rond de à terme leeftijd. De echodense gebieden waren sterk gecorreleerd aan gebieden met veranderd signaal in de witte stof op MRI, welke beschouwd worden als rijpingsprocessen. Met deze studie hebben we aannemelijk gemaakt dat de bilaterale, symmetrische en subtiele echodense gebieden in de frontale en pariëtale periventriculaire witte stof op echo van zeer premature pasgeborenen tijdens de vroege neonatale periode (normale) rijpingsprocessen in de nog onrijpe witte stof weerspiegelen. Echter, in sommige gevallen kunnen ze ook een uiting zijn van vertraagde of zelfs afwijkende rijping van de witte stof.

Eerdere studies en de studie in hoofdstuk 5 hebben beschreven dat schedelechografie mogelijk geen goede techniek is voor het aantonen van subtiele en diffuse veranderingen in de witte stof, welke tegenwoordig frequent gezien worden op MRI-onderzoeken van zeer premature pasgeborenen. In de retrospectieve studie in **Hoofdstuk 8** hebben we de waarde van herhaalde echografie tijdens de neonatale periode en MRI (1.5 Tesla) in de eerste 3 maanden na geboorte voor het aantonen van veranderingen in de witte stof en het naar aanleiding daarvan voorspellen van de neurologische ontwikkeling bestudeerd bij premature pasgeborenen. De bevindingen in de witte stof op echo en MRI van 40 zeer premature pasgeborenen werden vergeleken en bij 32 van deze kinderen werden de echo- en MRI-bevindingen gerelateerd aan de ontwikkeling op de gecorrigeerde leeftijd van 2 jaar. De echo- en MRI-bevindingen werden geclassificeerd als normaal/mild afwijkend, matig-ernstig afwijkend of ernstig afwijkend. Herhaalde echografie was voorspellend voor veranderingen in de witte stof zoals gezien op MRI. Ernstig afwijkende bevindingen in de witte stof op echo en/of MRI waren voorspellend voor een afwijkende neurologische ontwikkeling en normale/mild afwijkende bevindingen voor een gunstige neurologische ontwikkeling. Matig-ernstig afwijkende bevindingen in de witte stof op echo en/of MRI waren geassocieerd met uiteenlopende ontwikkeling. Het maken van een vroege MRI, naast herhaalde schedelecho's, had alleen meerwaarde voor het nog gedetailleerder aantonen van witte stof veranderingen en het voorspellen van de ontwikkeling van prematuren met ernstig afwijkende bevindingen op echo. Deze studie heeft dus aangetoond dat bij zeer premature pasgeborenen herhaalde, kwalitatief hoogstaande echografie tijdens de neonatale periode niet alleen voorspellend is voor ernstige witte stof veranderingen,

maar ook voor milde tot matig-ernstige veranderingen zoals gezien op MRI gemaakt voor de à terme leeftijd.

MRI van de hersenen wordt tegenwoordig bij premature pasgeborenen bij voorkeur gemaakt rond de à terme leeftijd, met name omdat het dan een zeer goede voorspellende waarde lijkt te hebben voor de neurologische ontwikkeling. Daarnaast werd in de bovengenoemde studie alleen gekeken naar aanwezigheid van veranderingen in de witte stof en niet naar andere veranderingen in de hersenen, zoals verwijding van de ventrikels, die mogelijk het gevolg zijn van witte stof schade. Met het oog hierop hebben we een prospectieve studie naar witte stof schade verricht in ons grote, aaneengesloten cohort van zeer premature pasgeborenen (**Hoofdstuk 9**). In het kader van deze studie hebben we een nieuw classificatiesysteem ontwikkeld voor het graderen van witte stof schade zoals gezien op frequent herhaalde, kwalitatief hoogstaande echografie bij zeer premature pasgeborenen tijdens de neonatale periode. Deze classificatie omvatte zowel witte stof veranderingen als veranderingen in de hersenen die mogelijk het gevolg zijn van witte stof schade (t.w. afwijkingen in grootte en vorm van de laterale ventrikels). De betrouwbaarheid van de echo-classificatie werd getest, waarbij een classificatiesysteem voor het graderen van witte stof schade op MRI (3 Tesla) gemaakt rond de à terme leeftijd gebruikt werd als referentie. Bij 110 zeer premature pasgeborenen werden herhaalde echo-onderzoeken tijdens opname en een echo- en MRI-onderzoek rond de à terme leeftijd gemaakt. De echo's gemaakt tijdens opname werden beoordeeld op aanwezigheid van witte stof veranderingen en de echo's en MRI's rond de à terme leeftijd op aanwezigheid van witte stof veranderingen en afwijkingen van de laterale ventrikels. Voor iedere prematuur werden de echo's tijdens de gehele neonatale periode en de MRI rond de à terme leeftijd geclassificeerd als normaal/mild afwijkend, matig-ernstig afwijkend of ernstig afwijkend. De positief voorspellende waarde van de echo-classificatie voor de MRI-classificatie was hoog in geval van ernstig afwijkende witte stof (0.79), maar lager in geval van normaal/mild afwijkende (0.50) en matig-ernstig afwijkende (0.65) witte stof. De ernst en uitgebreidheid van de witte stof veranderingen werden in enkele gevallen onderschat op echo, maar in andere gevallen juist overschat. Bij prematuren met ernstig afwijkende witte stof toonde MRI de plaats en uitgebreidheid van de veranderingen in meer detail. De echo rond de à terme leeftijd leverde ten opzichte van de MRI geen extra informatie op. Deze studie

bevestigde dat bij zeer premature pasgeborenen herhaalde echografie tijdens de neonatale periode een betrouwbare methode is voor het aantonen van ernstige witte stof afwijkingen, maar minder betrouwbaar voor milde tot matig-ernstige witte stof afwijkingen. We concludeerden hieruit dat bij zeer premature pasgeborenen MRI rond de à terme leeftijd nodig is voor het betrouwbaar aantonen van witte stof schade en/ of de exacte plaats en uitgebreidheid van schade. Indien deze MRI wordt verricht, is echografie op dezelfde leeftijd niet waardevol.

Deel V was gericht op beeldvorming van de diepe grijze stof (t.w. basale kernen en thalami (BKT)).

In de retrospectieve studie in premature pasgeborenen (zwangerschapsduur < 35 weken) in **Hoofdstuk 10** hebben we de incidentie, klinische consequenties en oorzaak van bilateraal, subtiel en diffuus verhoogde echogeniciteit in het BKT gebied (EG-BKT), regelmatig gezien op schedelecho's van zeer premature pasgeborenen en foetussen en met nog grotendeels onbekende oorzaak en klinische betekenis, bestudeerd. Tevens wilden we vaststellen of dit echofenomeen een uiting is van een normaal rijpingsproces in de nog onrijpe hersenen van prematuren of van schade. Herhaalde schedelecho-onderzoeken van 359 premature pasgeborenen, van wie 143 geboren bij een zwangerschapsduur van < 32 weken, werden beoordeeld op aanwezigheid van EG-BKT en van andere veranderingen. Beschikbare MRI's (1.5 Tesla), gemaakt tijdens de neonatale periode, werden beoordeeld op aanwezigheid van veranderingen in de BKT. De bevindingen in de BKT op echo en MRI werden vergeleken. Daarnaast werd in de subgroep van zeer premature pasgeborenen, deelnemend aan een lopend en gestandaardiseerd follow-up programma, EG-BKT gerelateerd aan klinische gegevens tijdens de neonatale periode en aan de neurologische ontwikkeling rond de à terme leeftijd en de gecorrigeerde leeftijd van 1 jaar. EG-BKT werd gezien bij 11% (39/259) van de premature pasgeborenen en zelfs bij 26% (37/143) van de zeer premature pasgeborenen. De prematuren met EG-BKT waren significant jonger en kleiner bij geboorte en hadden een meer gecompliceerd klinisch beloop tijdens de neonatale periode dan de prematuren zonder dit echofenomeen. EG-BKT ging altijd gepaard met andere veranderingen in de hersenen op echo. MRI, beschikbaar van 12 prematuren met EG-BKT, toonde veranderingen in de BKT bij 5 prematuren. De neurologische

ontwikkeling rond de à terme leeftijd was minder gunstig voor de zeer premature pasgeborenen met EG-BKT dan voor die zonder EG-BKT, maar vergelijkbaar voor beide groepen op 1-jarige leeftijd. Deze studie heeft dus aangetoond dat EG-BKT voornamelijk voorkomt bij de kleinste en ziekste zeer premature pasgeborenen, met een adequate neurologische ontwikkeling bij 1 jaar. EG-BKT gaat slechts sporadisch gepaard met veranderingen in de BKT op MRI. Deze resultaten suggereren dat EG-BKT een bevinding is die gerelateerd is aan prematuriteit en waarschijnlijk een normaal rijpingsproces in de nog onrijpe diepe grijze stof weerspiegelt.

Mede doordat slechts voor een klein deel van de premature pasgeborenen MRI beschikbaar was en EG-BKT altijd gepaard ging met andere veranderingen op echo, konden de oorzaak en klinische consequenties van EG-BKT niet achterhaald worden met de bovengenoemde, retrospectieve studie. Daarnaast waren tot dusver studies naar beeldvorming van de BKT bij premature pasgeborenen schaars. Om deze redenen hebben wij in de prospectieve studie in **Hoofdstuk 11** de bevindingen bij beeldvorming van de diepe grijze stof met behulp van herhaalde echo's tijdens de neonatale periode en MRI (3 Tesla) rond de à terme leeftijd systematisch beschreven voor ons grote cohort van zeer premature pasgeborenen. Tevens hebben we de relatie tussen EG-BKT en kwantitatieve metingen (t.w. diffusie waarden en volumes) van de BKT en tussen kwantitatieve metingen en de leeftijd van de prematuur bij geboorte en op de dag van de MRI en witte stof schade bestudeerd. De diffusie waarden werden verkregen van diffusie-gewogen MRI opnamen en de volumes werden berekend middels manuele segmentatie. De herhaalde echo's, gemaakt bij 130 zeer premature pasgeborenen tijdens de neonatale periode, werden beoordeeld op aanwezigheid van EG-BKT. De MRI, gemaakt bij 110 prematuren, werd beoordeeld op aanwezigheid van veranderingen in myelinisatie en signaal van de BKT en witte stof schade. Bilaterale, diffuse en subtiele EG-BKT werd gezien op de echo's van vrijwel alle zeer premature pasgeborenen (92%), met name de kleinste en jongste prematuren. De echogeniciteit van de BKT vervaagde geleidelijk met het vorderen van de leeftijd en werd niet meer gezien na 1 maand na de à terme leeftijd. EG-BKT ging niet gepaard met veranderingen in signaal, myelinisatie, diffusie waarden en volumes van de BKT op MRI. Geen van de 130 prematuren had lokale veranderingen in de BKT op echo en slechts 1 kind had BKT veranderingen op MRI. De kwantitatieve metingen van de BKT waren gecorreleerd aan de

postconceptionele leeftijd op de dag van de MRI, maar niet aan de zwangerschapsduur bij geboorte. Witte stof schade op MRI was negatief gecorreleerd aan de BKT volumes, maar was niet gecorreleerd aan de diffusie waarden. Deze studie toont nogmaals aan dat bilaterale, diffuse en subtiele EG-BKT een frequente bevinding is bij zeer premature pasgeborenen, die gerelateerd is aan prematuriteit. Vergelijkbaar met de echodense gebieden in de periventriculaire witte stof (hoofdstuk 7), weerspiegelt het waarschijnlijk een normaal rijpingsproces in de nog onrijpe hersenen. Indien het echter nog na de à terme leeftijd aanwezig is, is het mogelijk een uiting van vertraagde of zelfs afwijkende rijping. Lokale lesies in de BKT zijn zeldzaam bij zeer premature pasgeborenen en dienen als afwijkend beschouwd te worden. Bij zeer premature pasgeborenen gaan de groei en ontwikkeling van de BKT door rond de à terme leeftijd, maar witte stof schade heeft een negatief effect op de groei van de BKT.

Een andere echo-bevinding die we frequent zagen in de diepe grijze stof van zeer premature pasgeborenen was LSV. Tot dusver waren de oorzaak en klinische consequenties van LSV nog grotendeels onbekend en waren studies naar LSV in grote, ongeselecteerde groepen zeer premature pasgeborenen schaars. In **Hoofdstuk 12** hebben we de incidentie, evolutie, oorzaak en klinische consequenties van LSV, zoals gezien op herhaalde echo's tijdens de neonatale periode, prospectief onderzocht in ons cohort van zeer premature pasgeborenen. De echo's, gemaakt tijdens opname en rond de à terme leeftijd, werden beoordeeld op aanwezigheid van LSV en van andere veranderingen. De MRI's, gemaakt bij bijna alle prematuren rond de à terme leeftijd, werden beoordeeld op aanwezigheid van veranderingen in signaal en myelinisatie van de BKT. LSV werd onderverdeeld in 'early-onset' (gezien binnen 7 dagen na geboorte) en 'late-onset' (gezien na de eerste 7 dagen na geboorte). Voor alle prematuren werd een aantal relevante perinatale klinische factoren (zoals congenitale infecties) verzameld. De relatie tussen LSV en andere veranderingen op echo, veranderingen op MRI en klinische factoren werd bestudeerd. LSV werd gezien bij 20% (22/111) van de prematuren; 'early-onset' bij 5 en 'late-onset' bij 17 prematuren. Het was meestal pas na enkele weken na geboorte zichtbaar en bleef gedurende een aantal maanden aanwezig. LSV ging niet gepaard met andere veranderingen op echo of BKT veranderingen op MRI. De prematuren met 'late-onset' LSV waren jonger en kleiner bij geboorte dan die met 'early-onset' LSV. De postconceptionele leeftijd op de dag dat

LSV voor het eerst gezien werd (meestal tussen 30 en 31 weken), was vergelijkbaar voor de prematuren met 'early-onset' en 'late-onset' LSV. LSV was niet geassocieerd met perinatale klinische factoren, maar zeer premature pasgeborenen met LSV hadden minder vaak hypotensie dan die zonder LSV. Deze studie heeft aangetoond dat LSV een frequente bevinding is op schedelecho's van zeer premature pasgeborenen. Op MRI zijn geen veranderingen aantoonbaar die correleren met LSV. De postconceptionele leeftijd lijkt een belangrijkere rol te spelen bij het zichtbaar worden van LSV dan de zwangerschapsduur bij geboorte en de postnatale leeftijd. Als LSV gezien wordt bij klinisch stabiele premature pasgeborenen, is het waarschijnlijk een goedaardig en voorbijgaand fenomeen.

Concluderend zijn moderne, kwalitatief hoogstaande echografie en MRI uitstekende technieken voor het in beeld brengen van de hersenen van premature pasgeborenen. Echografie toont rijpingsprocessen in de nog onrijpe witte en diepe grijze stof van zeer premature pasgeborenen. MRI rond de à terme leeftijd blijft echter nodig voor het aantonen van milde tot matig-ernstige witte stof schade en draagt bij aan het vaststellen van de exacte plaats en uitgebreidheid van hersenschade. Daarnaast toont MRI, in tegenstelling tot echo, myelinisatie en brengt andere rijpingsprocessen meer gedetailleerd in beeld. Aangezien MRI meer belastend is en herhaalde MRI-onderzoeken niet wenselijk zijn, zijn frequent herhaalde schedelecho-onderzoeken tijdens de neonatale periode nodig voor het bepalen van het moment en de oorzaak van schade, het vervolgen van hersenrijping en de evolutie van veranderingen en het in beeld brengen van voorbijgaande (witte stof) veranderingen. Herhaalde echografie tijdens de neonatale periode in combinatie met een MRI rond de à terme leeftijd zijn daarom gewenst bij alle zeer premature pasgeborenen.

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List of abbreviations

ADC	Apparent diffusion coefficient
AF	Anterior fontanel
BG	Basal ganglia
BGT	Basal ganglia and/or thalamus
BPD	Bronchopulmonary dysplasia
CBFV	Cerebral blood flow velocity
CI	Confidence interval
CP	Cerebral palsy
CT	Computed tomography
cUS	Cranial ultrasonography / ultrasound
CV	Convex
DEHSI	Diffuse and excessive high signal intensity (in the periventricular and/or subcortical white matter)
DTI	Diffusion-tensor imaging
DWI	Diffusion-weighted imaging
ECS	Extracerebral spaces
EG-BGT	Echogenicity of the basal ganglia and/or thalami region
FA	Fractional anisotropy
FLAIR	Fluid-attenuated inversion recovery
GA	Gestational age
GM	Grey matter
HC	Head circumference
HIE	Hypoxic-ischaemic encephalopathy
HPI	Parenchymal haemorrhage
IHF	Interhemispheric fissure
IPE	Intraparenchymal echodensity
iv	Intravenous
IVH	Intraventricular haemorrhage
LA	Linear array
LSV	Lenticulostriate vasculopathy
LV	Lateral ventricles

MCA	Middle cerebral artery
MDI	Mental developmental index
MF	Mastoid fontanels
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NEC	Necrotizing enterocolitis
NPV	Negative predictive value
OR	Odds ratio
PA	Phased array
PDA	Patent ductus arteriosus
PDI	Psychomotor developmental index
PF	Posterior fontanel
PHVD	Post-haemorrhagic ventricular dilatation
PI	Pulsatility index
P/IVH	Peri- and intraventricular haemorrhages
PLIC	Posterior limb of the internal capsule
PMA	Postmenstrual age
PPV	Positive predictive value
PVE	Periventricular echodensities / echogenicity
PVHI	Periventricular haemorrhagic infarction
PVL	Periventricular leukomalacia
PWML	Punctate white matter lesions
RDS	Respiratory distress syndrome
RI	Resistance index
ROI	Region of interest
SI	Signal intensity
SNR	Signal-to-noise ratio
TE	Echo time
TEA	Term equivalent age
TORCH	Toxoplasmosis, Other, Rubella, Cytomegalovirus, Herpes (includingParvo B19)
TR	Repetition time
TW	Temporal windows
WM	White matter

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