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BRAIN IMAGING IN PRETERM INFANTS AT TERM EQUIVALENT AGE

VALUE AND COMPARISON OF MRI AND ULTRASOUND

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to my parents, Ulla & Dieter Horsch

ABBREVIATIONS

BPD	Bronchopulmonary Dysplasia
CPAP	Continuous Positive Airway Pressure
CT	Computed Tomography
cUS	Cranial Ultrasound
ELGA	Extremely Low Gestational Age Infants
GA	Gestational Age
GM	Grey Matter
GMH	Germinal Matrix Haemorrhage
IVH	Intraventricular Haemorrhage
MHz	Mega Hertz
MRI	Magnetic Resonance Imaging
PDA	Persistant Ductus Arteriosus
PHVD	Post Haemorrhagic Ventricular Dilatation
PVHI	Periventricular Haemorrhagic Infarction
PROM	Premature Rupture Of the Membranes
PVL	Periventricular Leukomalacia
RDS	Respiratory Distress Syndrome
WM	White Matter

ORIGINAL ARTICLES

This thesis is based on the original articles, listed in chronological order. Articles will be referred to by their Roman numerals:

I Horsch S, Muentjes C, Franz A, Roll C.
Ultrasound diagnosis of brain atrophy is related to neurodevelopmental outcome in preterm infants.
Acta Paediatrica 2005; 94:1815-21

II Horsch, S, Hallberg B, Leifsdottir K, Skiöld B, Nagy Z, Mosskin M, Blennow M, Ådén U.
Brain abnormalities in extremely low gestational age infants:
a Swedish population based study.
Acta Paediatrica 2007; 96:979–84

III Horsch S, Bengtsson J, Nordell A, Lagercrantz H, Ådén U, Blennow M.
Lateral ventricular size in extremely premature infants: 3D MRI confirms 2D ultrasound measurements.
Ultrasound in Medicine and Biology 2009; 35:360-6

IV Horsch S, Skiöld B, Hallberg B, Nordell B, Nordell A, Mosskin M, Lagercrantz H, Ådén U, Blennow M.
Cranial ultrasound and MRI at term in extremely preterm infants.
submitted manuscript

ABSTRACT

Cranial ultrasound (cUS) and magnetic resonance imaging (MRI) are the two most commonly used brain imaging techniques in preterm infants. cUS can be performed at the bedside and detects all major brain abnormalities (haemorrhages, infarctions, cysts, dilatation of the lateral ventricles) that are associated with severe neurodevelopmental disability. However, there are more subtle brain abnormalities that can be visualized with cUS, such as signs of brain atrophy and periventricular echodensities, for which the clinical relevance is less clear. Furthermore, there is no consensus how to quantify the lateral ventricular size on cUS, a procedure that is often necessary to monitor the progression of posthaemorrhagic ventricular dilatation or grade the extent of ventriculomegaly at term age. In comparison to MRI, cUs has been shown to be less sensitive for the detection of non-cystic white matter (WM) injury, the most common form of WM injury in preterm infants. Indeed, MRI at term age has been reported to be superior to cUS in detecting white matter (WM) abnormalities and predicting outcome in preterm infants. However, in that study cUS was performed during the first 6 weeks only and no late scan in parallel to MRI at term age was included. Furthermore MRI data from large population-based cohorts of extremely preterm infants are missing. Therefore, the aim of the present thesis was to study the relevance of subtle brain abnormalities on cUS (brain atrophy and periventricular echodensities) for neurodevelopmental outcome, to acquire and compare MRI and cUS data at term age in a population-based cohort of extremely preterm infants (< 27 weeks) and to determine which 2D linear cUS measurement of the lateral ventricular size is the best to estimate total ventricular volume using 3D MRI as the golden standard. Our main findings were, firstly, that sonographic signs of brain atrophy at term age, but not persistent periventricular echodensities, are related to neurodevelopmental outcome at 3 years of age, secondly that in the cohort of extremely preterm infants the incidence of brain abnormalities detected with MRI was unexpectedly low compared to previously published numbers from other regions, thirdly, that the 2D cUS measurements of the frontal horn and ventricular midbody correlate best to lateral ventricular volume, and finally that 40% of extremely preterm infants had a normal cUs at term age and that in these infants MRI at term age added no or only marginal clinically relevant information to the cUS result. In conclusion, our findings underline the important clinical role of cUs as a bedside imaging technique, but also highlight the potential of MRI as a complementary imaging tool in preterm infants.

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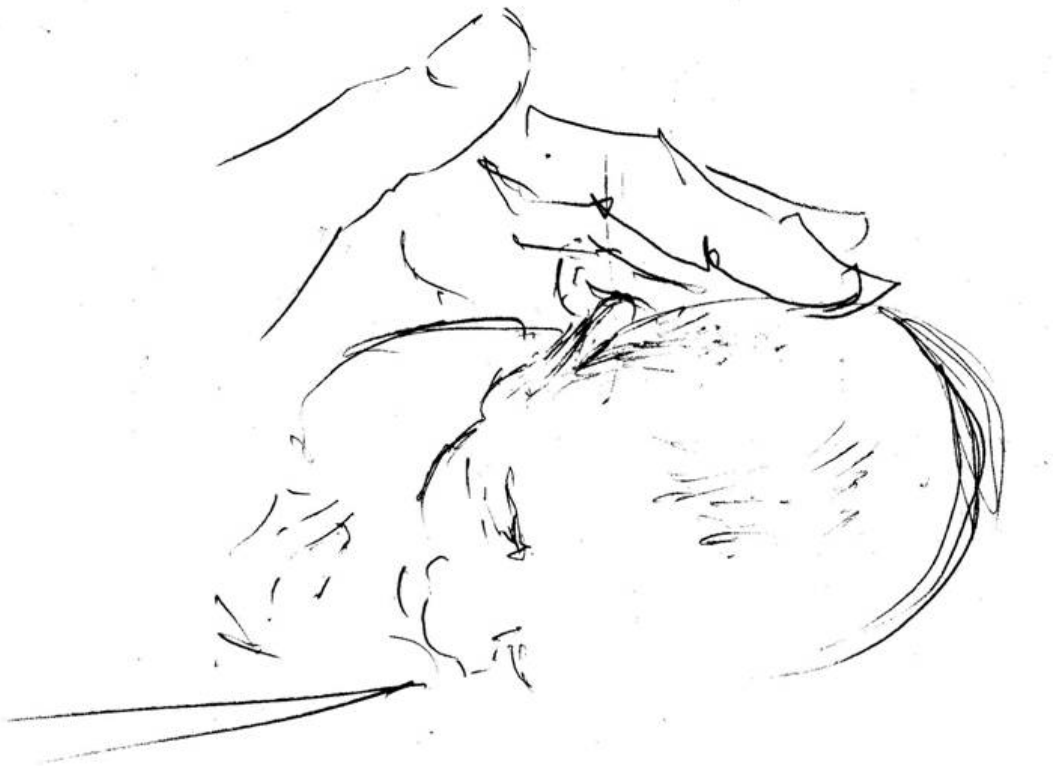


1 INTRODUCTION

1.1 Preterm birth and the threshold of viability

Preterm birth is one of the biggest challenges in perinatal medicine. In Europe, infants born with a birth weight below 1500g account to approximately 1% of all live births (0,77% in Sweden and 1,1,% in Germany), but to 30-50% of all neonatal deaths[1,2].

Neonatal intensive care medicine has developed fast in the last 25 years to meet the needs of these high risk infants and to improve outcome. Advances in obstetric care, antenatal referral to specialized centers in case of threatening extremely preterm birth, maternal corticosteroid treatment, exogenous surfactant application, improved respirator techniques, nutrition and nursing care have contributed to increasing survival rates amongst these vulnerable infants[1-10].

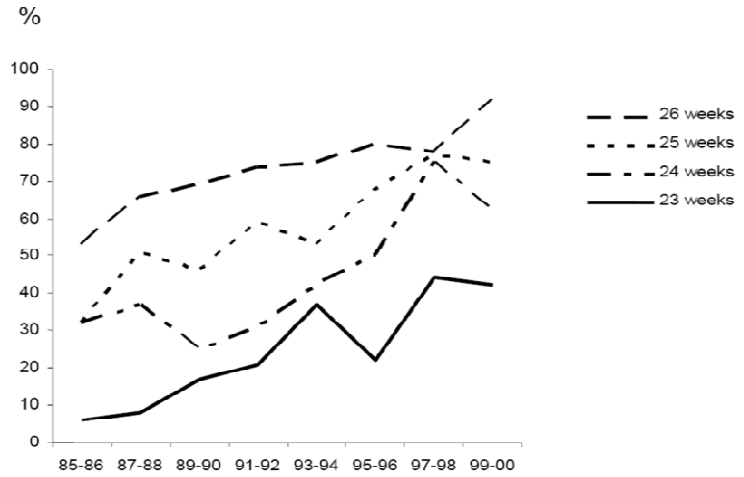


Figure 1: Survival rates of infants born at 23-25 weeks of gestational age in Sweden between 1985-2000. Data from the National Board of Health and Welfare (www. socialstyrelsen.se)[2]

The threshold of viability of extremely preterm infants has thereby decreased to 22-23 weeks of gestation. This development is impressively illustrated by a single center outcome study from the University College London, UK, where the survival rate of infants born 4 months early, with a gestational age of 22-25 weeks increased from 31% in 1981-85 to 71% in 1996-2000 without a concomitant increase in morbidity of surviving infants[4]. These results are in line with other promising results from Sweden (see figure 1) and Germany [2,6-12]. As a result of improved care, a decrease in the incidence of cerebral palsy, one of the most severe neurological sequela in preterm infants, has been observed in Sweden[13] and Canada[14].

Although this reads as a pure success story, not all reports on outcome after extremely preterm birth are positive [15-17]. The 6 years-outcome data of the EPICURE study, a study that collected data in all infants with a gestational age of 22 – 25 weeks born alive during a 10-months period in 1995 in the United Kingdom and Ireland, were less favorable, if not worrying: at the threshold of viability (≤ 23 weeks) only 37% of surviving infants survived without or with only mild overall disabilities[16]. At the age of 11 years this cohort was reevaluated for their school performance and it was revealed that survivors remain at high risk for learning impairments and poor academic attainment in middle childhood[17]. A significant proportion of these children require full-time specialist education and over half of those attending mainstream schools require additional health or educational resources in order to access the national curriculum.
In contrast, in a Swedish cohort of infants born before 26 weeks of gestation evaluated at 11 years of age, the majority of these extremely immature children (85%) were successfully attending mainstream schools without major adjustment problems[18].

Differences between countries and regions have been examined by the MOSAIC study that evaluated mortality rates and short term outcome of all infants born before 32 weeks of gestation in 10 regions of Europe[7,8]. The study disclosed that differences between the 10 regions in Europe were immense. Mortality rates for infants born before 28 weeks of gestation ranged from 18.3% in Hesse, Germany to 57.9% in the central and eastern regions of the Netherlands. These huge differences raise questions about variability in the treatment provided to these infants. Differences in ethical decision-making in delivery wards and neonatal units provide one explanation for the variations in outcome[19]. Opinions among neonatal health care providers vary widely regarding the benefits and disadvantages of active resuscitation of extremely preterm infants[19]. This is also reflected in high variability in guidelines between countries and even between centres within countries[20].

While there is consensus that infants with a gestational age of ≥ 26 weeks should nearly always be actively treated, resuscitation guidelines for infants born before 26 weeks of gestation vary[20].
In Germany, Austria and Sweden active treatment is nearly always initiated in infants with a gestational age of 24 and 25 weeks. In the grey zone of 22-23 weeks gestational age parental desire and individual factors are taken into account. In contrast, in the majority of centres in the Netherlands active treatment is usually not advised for infants < 25 weeks of

gestation and caesarean section on fetal indication is not performed < 26 weeks of gestation[21].

In the grey zone - independent of local definition - parental desires should be supported. It is therefore of crucial importance that parents receive timely, understandable, up-to-date and consistent information to make informed decisions. This information should include the estimated likelihood of the newborn infant to survive and to survive without major disabilites. The likelihood should preferably be based on local or regional data.

Major disabilities are to a high degree related to the occurrence of brain injuries. That is why brain imaging plays a central role in neonatal intensive care. Knowledge about cerebral lesions, their incidences, pathogenesis and relevance for neurodevelopmental outcome is of fundamental importance for

A) the treatment of the individual **patient** (e.g. avoiding known risk factors, withdrawal of treatment in severe cases),

B) antenatal counselling of **parents** on the basis of both local and regional data about likelihood of survival and survival without major disability,

C) critical evaluation of **quality of care** in every single centre, and

D) further **research** to be able to answer open questions such as: How can we optimize care to minimize neurological morbidity? Is there a possibility of early interventions?

1.2 Brain Imaging

Brain imaging in preterm infants has advanced as dramatically as the neonatal intensive care itself in the last 40 years. After early attempts of transillumination the development of computed tomography (CT) in the early 1970s allowed for the first time the detailed visualization of intracerebral lesions in preterm infants and understanding the correlation of these lesion to neurological outcome[22-24]. How important the achievements of this era are is illustrated by the fact that the classification system of germinal and intraventricular haemorrhages from 1978 has been in use for decades[22]. This system is still used by many despite the fact that it does not adequately account for up-to-date knowledge on

pathophysiology and morphological changes[25] (see also chapter 1.2.2). However, with the development of imaging methods that do not involve ionizing radiation - cranial ultrasound (cUS) and later magnetic resonance imaging (MRI) - CT is hardly used in preterm infants anymore. cUS and MRI are now the most commonly used imaging techniques in neonatology.

1.2.1 Cranial ultrasound

Since the late 1970s cUs is used for brain imaging in preterm infants[26-28]. cUS uses high-frequency sound waves (5-10MHz) transmitted through the open fontanelles (anterior, posterior or mastoid) of the infants' heads. The reflections of the sound waves are detected, processed and visualized. The differences in "*echogenicity"* or *"echodensitiy*" between tissues allow reliable identification of anatomical structures and brain abnormalities such as haemorrhages and cystic changes. Since its introduction the quality and especially the resolution of cUS images has continuously improved with the use of higher frequencies (today's standard for the preterm brain: ≥ 7.5 MHz) and advances in computer-based image processing techniques.

cUs is today the method of choice to assess the brain in preterm infants in neonatal intensive care units. The most obvious advantages are that cUS does not involve ionizing radiation and can be performed at the bedside, as opposed to CT and MRI. cUS is therefore an ideal method to sequentially study the developing brain, as frequently as clinically or scientifically indicated. Furthermore, cUS is non-invasive, fast, relatively cheap, available in nearly all hospitals and the expertise amongst neonatologist and radiologists in neonatal ultrasound is high.

1.2.2 cUS findings

cUs allows the early bedside detection of the major cerebral pathologies, such as intraventricular haemorrhage (IVH), haemorrhagic parenchymal infarction (PVHI), posthaemorrhagic ventricular dilatation (PHVD) and cystic periventricular leukomalcia (c-PVL), all strongly predictive of severe neurological impairment[29--41].

Germinal matrix and intraventricular haemorrhages

As previously mentioned the first classification of germinal matrix haemorrhages (GMH) and IVH was established by Lou Ann Papile in 1978[22]. This classification is based on CT findings in very low birth infants (table 1).

Grade	Extension of haemorrhage
I	Germinal matrix / subependymal haemorrhage
II	Intraventricular haemorrhage without ventricular dilatation
III	Intraventriular haemorrhage with ventricular dilatation
IV	Intraventricular haemorrhage with ventricular dilation and parenchymal extension

Table 1: Classification of GMH and IVH according to Papile.

This classification does not adequately account for some pathophysiological and morphological changes: the Grade IV lesion in the Papile classification is in fact not an "extension" of an intraventricular haemorrhage to the parenchyma as earlier assumed. We now know that the fan–shaped haemorrhagic necrosis in the periventricular WM just dorsal and lateral of the external angle of the lateral ventricle is indeed a *venous, haemorrhagic infarction* and therefore builds up its own entity[25] (figure 2). This fact is accounted for in the classification presented below (table 2) adapted from the classification according to Volpe[25] and national guidelines[42].

Grade	Definition
GMH	haemorrhage limited to the germinal matrix
IVH II	IVH (< 50% of ventricular area in parasagittal view)
IVH III	IVH (> 50% of ventricular area in parasagittal view)
PVHI	Periventricular haemorrhagic infarction

Table 2: Classification system for GMH/IVH and PVHI.

Periventricular haemorrhagic infarction (PVHI)

The pathogenesis of PVHI can be explained by looking at the venous system that drains the periventricular WM. The terminal vein that runs essentially within the germinal matrix drains the venous blood from medullary veins in the periventricular WM (figure 2 left). A large germinal matrix haemorrhage can therefore lead to an obstruction of the terminal

vein and it thus impairs blood drainage from the medullary veins, which results in the typical fan-shaped venous infarction in the periventricular WM (figure 2 right)

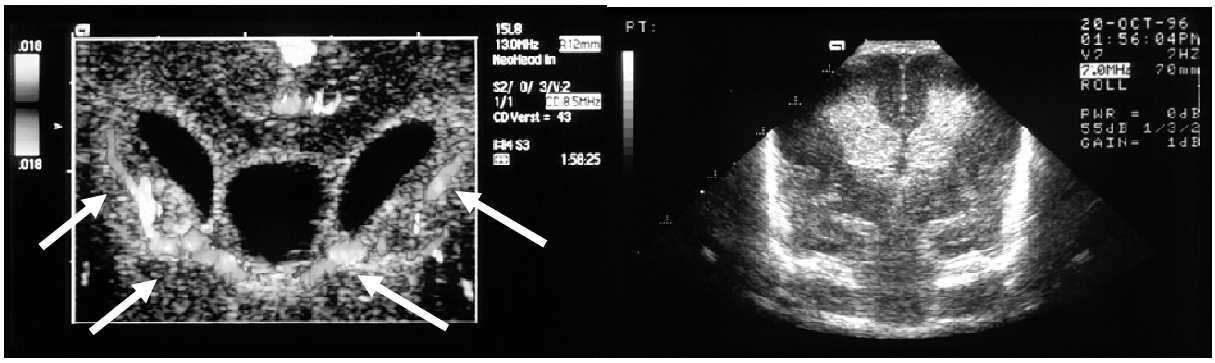


Figure 2: Left: Doppler sonography of terminal vein draining blood from medulary veins through the germinal matrix region (arrows), right: Bilateral IVH III plus bilateral periventricular haemorrhagic infarctions.

To grade the severity of PVHI Bassan et al introduced an extended topographic scoring system using cUS, with severity depending on bilateralism, midline shift and within-hemisphere extent[34]. High severity scores predict a worse outcome. Dudink et al have further refined the Bassan classification by categorizing PVHI according to the veins involved[35]. This subtype classification correlates well with both the topographical nature and severity of the neurological outcome.

The incidence of GMH/IVH and PVHI has decreased dramatically in the last 25 years in parallel with the improvements of neonatal care, especially the introduction of maternal corticosteroid treatment[36]. However, in infants with a gestational age below 27 weeks (or birth weight less than 1000g) approximately 20% still suffer from IVH and/or PVHI[12,37].

Many studies have shown that severe grades of IVH and PVHI are associated with severe motor and cognitive impairment[29-41], but the clinical relevance of low grade haemorrhages is less clear. Low grade haemorrhages have indeed been considered to be without significance for long term outcome in preterm infants. However, recent studies have shown that low grade haemorrhages (defined as GMH and/or uncomplicated IVH II) are actually associated with a reduction in cerebral grey matter volume, unfavourable neurodevelopmental outcome at 20 months of age and slightly higher prevalence of cerebral palsy[41,43,44]. This might be explained by the destruction of glial precursor cells and astrocytes located in the germinal matrix and destined for the supragranular cortical layers. Their destruction may result in the disruption of cortical organization and ultimately in the

reduction of grey matter volume. In the case of extension of the haemorrhage into the lateral ventricles, proinflammatory cytokines and elevated free iron that catalyzes hydroxyl radical formation in the cerebrospinal fluid contribute to subsequent white matter injury[45,46].

Posthaemorrhagic ventricular dilatation and measurement of lateral ventricle size

Posthaemorrhagic ventricular dilatation (PHVD) occurs in approximately 25% of infants with IVH[25,47] (figure 3). The vast majority of PHVD cases (80%) occur after severe grade IVH (IVH III/ PVHI) and are associated with a high mortality rate [25,47.48]. PHVD can be self-limiting, but in 40-60% of infants PHVD proceeds to shunt dependent hydrocephalus[47,48].

In parallel to the decline in the incidence of IVH[35], the incidence of its complication PHVD has decreased[49]. In a population-based study in Sweden, Persson et al showed a 50% decline of the incidence of PHVD that required shunt surgery in very preterm infants over a ten years period of time (1989-98, incidence in 96-98 7/1000 live borns)[49]. However, PHVD still plays a clinically important role as affected infants suffer from major impairments, such as mental and motor retardation, epilepsy and cerebral palsy[50]. Infants with PHVD can be identified earlier with sequential ultrasound scans. The infants suffer from severe brain injuries that are caused by the combinations of pressure, distortion, ischaemia, inflammation, and free radical-mediated injury[51]. Therapeutic interventions strategies ranging from frequent lumbar punctures to drainage, irrigation, and fibrinolytic therapy have failed to improve outcome so far [53-55].

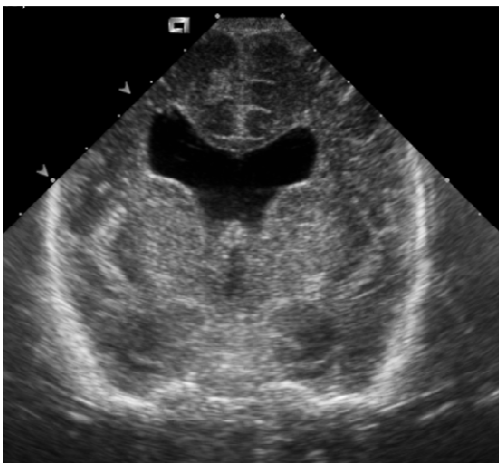


Figure 3 cUs at term, coronal view, infant with shunt dependent hydrocephalus after bilateral IVH II

The presence of cerebral ventriculomegaly at term equivalent age (independent of its cause: PHVD or brain atrophy) is an important and independent predictor of adverse cognitive and motor development in preterm infants[56]. Ventriculomegaly can be easily detected by cranial 2D ultrasound at the bedside. To quantify ventricular size, a variety of ultrasound measurements have been suggested by

different authors[56-60]. The width of the frontal horns in the coronal plane and the width of the ventricular midbody in the sagittal plane are the most commonly used parameters in daily routine in neonatal intensive care units. However, there is no consensus as to which is the best parameter to use. Furthermore, interobserver variability has been a matter of concern, as well as correlation of 2D measurements with actual ventricular volume[61]. Reliable ultrasound measurements are important to monitor clinical courses and to time interventions. This problem is addressed in *study III.*

Cystic periventricular leukomalacia (c-PVL) and non-cystic white matter injury

C- PVL refers specifically to regions of coagulation necrosis and liquefaction in the periventricular white matter that are usually small, multiple, bilateral and easy to detect using cUS[25] (figure 4). Cystic PVL is a strong predictor of severe neurological impairment. The size and location of cysts relates to a certain degree to the severity of later neurological outcome[25,62]. Although cystic lesions can be reliably visualized with cUS, small localized cysts may collapse over time and remain undetected if cUS is not performed frequently after the first weeks of life. Fortunately, a decline in the incidence of c-PVL could be observed in the last decade. In a representative study, Hamrick et al could demonstrate a 6.1 fold decrease in the incidence of c-PVL over a 10 years period of time (1992-2002) [63].

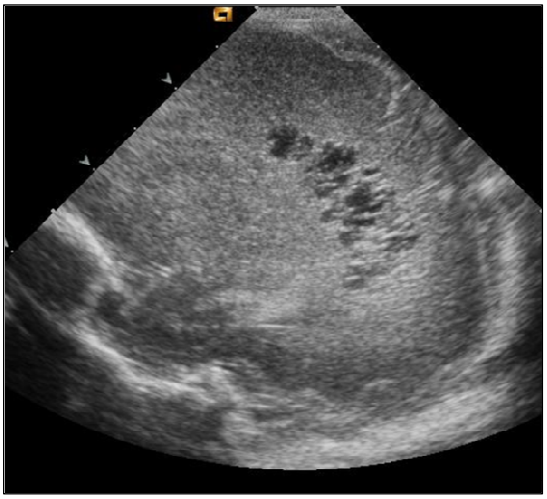


Figure 4: Parasagittal view through the periventricular WM in infant with c-PVL

The diffuse, **non-cystic** form of WM injury, which is milder and more common, is characterized by a more uniform spreading of the damaged tissue in the periventricular WM. This spreading is also referred to as periventricular echodensities or flaring and can lead to ventriculomegaly and a reduction in white matter volume[64].

Govaert and de Vries proposed a grading system of PVL, ranging from persisting echodensities up to extensive c-PVL that facilitates the accurate description of cystic and non-cystic WM disease[58](table 3).

Grade	Definition
I	Transient periventricular echodensities persisting 7 days or longer
II	Periventricular echodensities evolving into small localized frontoparietal cystic lesions
III	Periventricular echodensities, evolving into extensive periventricular cystic lesions
IV	Echodensities extending into the deep white matter evolving into extensive cystic lesions

Table 3: Grading system of PVL according to Govaert and de Vries[58]

Persisting periventricular echodensities have been associated with a higher incidence of minor motor disabilities[65-67]. However, other authors have failed to show this association[68]. This might be due to differences in definition of periventricular echodensities, since accurate diagnosis and quantification of periventricular echodensities remains a problem. Although cellular histopathology causes flaring, it is not abnormal for unaffected newborns to develop mild transient physiological flaring, partly related to normal white matter maturation. To delineate between normal and abnormal periventricular echodensities is difficult. The clinically most accepted definition of pathological flaring is that the periventricular tissue appears more echodense than the choroid plexus, persisting for longer than 7 days. Recently, Vansteenkiste et al have presented an interactive algorithm to segment flaring on cUS images[69]. If this technique turns out to be clinically applicable, it might overcome the problem of high user dependency in the diagnosis of periventricular echodensities.

Impaired brain growth/ brain atrophy

Enlarged subarachnoidal spaces, widened interhemispheric fissure, ventricular dilatation and reduction in complex gyral folding can be indirect sonographic signs of impaired brain growth, also referred to as global brain atrophy. Using MRI Inder et al found a unique pattern of cerebral abnormalities consisting of significant diffuse white matter atrophy, ventriculomegaly, immature gyral development, and enlarged subarachnoidal spaces in 10 of 11 of their infants with gestational age of < 26 weeks[70]. Although signs of impaired brain growth can be visualized by cUS the incidence and relevance of brain atrophy as a

pattern (and not single measurements) on neurogical outcome has not yet been systematically studied with cUS. This issue is addressed in *study I*.

1.2.3 MRI

In the past 20 years MRI has been increasingly used as a research and clinical imaging tool in neonatology and neonatal intensive care, complementary to cUS[70-100]. MR image quality has improved remarkably, but still adaptation of the standard MRI pulse sequences provided from the manufacturer is required to achieve optimal contrast in the immature preterm and term neonatal brain. This is due to the high water content of the neonatal brain and thereby longer T1 and T2 relaxation times in comparison to those in adults and older children. Thus, performing a high quality neonatal MRI is still a challenge that requires a lot of expertise and team work of radiologists, physicists and NICU nurses and doctors. Unfortunately, these optimal conditions are rare and usually found only in tertiary care centers with focus on neonatal neurology. Nevertheless, MRI-compatible equipment (ventilators, incubators, infusion pumps etc.) is increasingly available, acoustic noise shielding has improved[7] and an increasing number of centers have succeeded to scan neonates in natural sleep without any sedative medication. This has led to rising numbers of clinically indicated neonatal MRIs and a growing field of neonatal research within the MRI field.

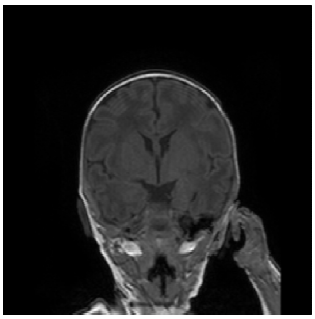


Figure 5: T1-weighted 3D Gradient Echo sequence of preterm infant scanned at term.

1.2.4 MRI findings

With conventional MRI good contrast between grey and white matter can be achieved. Thanks to the high image resolution anatomical structures as well as myelination can be reliably visualized, both supra- and infratentorial. All major brain abnormalities described in chapter 1.2.2 can be detected by MRI. Moreover, MRI has been shown to have a higher sensitivity in detecting non-cystic white matter injury in preterm infants as compared to cUS[71-74].

Non-cystic white matter injury

While the incidence of cystic PVL is decreasing, MRI has attracted the attention to more subtle changes in the WM. This non-cystic form of WM injury that can be detected on term/near-term MRI scans is by far more prevalent than the cystic form: the incidence in very preterm infants ranges between 35%-79% [70-77]. In 1999, the Hammersmith group in London described these changes as "excessive" high signal regions on T2 fast spin echo images, the regions being diffusely distributed in the periventricular and subcortical WM[71]. These DEHSI ("diffuse excessive high signal intensities", figure 6) were different from the normal cellular layers forming anterior caps and posterior arrowheads. In subsequently performed studies Counsell et al showed that the subjective findings of DEHSI on conventional MRI were indeed associated with quantifiable changes in water diffusion measured by Diffusion Weighted Imaging (DWI)[78]. The abnormal values present in regions of DEHSI were similar to values in preterm infants with major focal lesions, suggesting that DEHSI were neuroimaging correlates to diffuse WM abnormality. Since then several studies have been able to show the association of non-cystic WM injury to reduction in cerebellar, cortical grey and deep grey matter volume and, most importantly, to neurodevelopmental outcome[77,80-81].

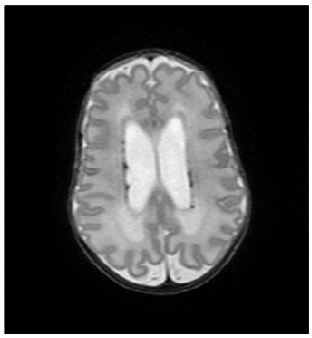


Figure 6: MRI at term age, T2 weighted axial image. DEHSIs in frontal and occipital WM.

Myelination

One of the great advantages of MRI over cUS is that the development of myelination in the preterm brain can be assessed[82,83]. Myelin in the vermis and cerebellar hemispheres is already present at less than 37 weeks of gestation. Myelin reaches the posterior limb of the internal capsule (PLIC) and the lenticular nucleus and thalamus at a gestational age of 37-38 weeks. Around 38-39 weeks of gestation it reaches the central corona radiate and the caudate nucleus and at 40-42 weeks of gestation it proceeds to the centrum semiovale. The normally myelinated PLIC appears as a region of high signal intensity on T1-weighted spin echo and inversion recovery images. In infants with PVHI and c-PVL, asymmetrical myelination in the PLIC or even bilateral absence of normal PLIC signal at term age is associated with severe motor impairment[84,85]. The myelination stage is also one of five WM parameters included in a MRI scoring systems published by Inder et al that has been

demonstrated to be strongly predictive of adverse neurodevelopmental outcomes at two years of age[76].

Cerebellar Injury

One of the advantages of MRI over cUS is the complete and detailed visualization of the posterior fossa. MRI has made essential contributions to the understanding that cerebellar pathology is much more common in preterm infants than earlier assumed[86-93]. Cerebellar injury resulting in reduced cerebellar volume has been observed in up to 14% of preterm infants[86,87]. This reduction in cerebellar volume may occur as a result of a primary injury, such as infarction or haemorrhage. The incidence of cerebellar haemorrhages in very preterm infants ranges between 2.5-3.8% in recent imaging studies[91-93]. However, in the absence of a direct cerebellar insult, cerebellar growth may also be compromised as a secondary effect related to damage in remote but connected areas of the brain. A number of recent studies have performed volumetric analyses, correlating reduced cerebellar volume with supratentorial injury, including white matter injury, IVH, PHVD and PVHI[88,89,90]. These data suggest that both reduction in contralateral cerebellar volume with unilateral cerebral parenchymal injury and reduction in total cerebellar volume with bilateral cerebral lesions are related to trophic transsynaptic effects[91]. Cerebellar injury is of clinical relevance as it has been associated with adverse developmental outcome, including motor, cognitive, communication and behavioral impairments[89].

Advanced MR techniques

Advanced MR techniques and image post-processing techniques like MR spectroscopy, DWI, diffusion tensor imaging (DTI), functional MRI and fibre tracking are currently used in preterm infants in research settings. Although not used in the studies included in this thesis, their immense input into neonatal MRI research has to be acknowledged. They have enhanced and will further enhance our knowledge about physiology and pathophysiology of the developing newborn brain[77,78,80,81,88-90,94-97]. Future implementation of these more advanced techniques into the clinical setting might improve the information gained by MRI at term age.

1.2.5 Comparison of cUS and MRI

Several studies have compared cUS and MRI in preterm and term infants[71-6,98-103], but the heterogeneity in patient characteristics, timing of imaging and definition of brain abnormalities makes comparison difficult and preclude a single conclusion.

Some authors report good agreement between the two imaging methods regarding the presence, degree and duration of transient WM echodensities, IVH, PVHI and cysts[98,99,100]. Roelants-van Rijn demonstrated in a selected group of preterm infants that in infants with normal cUS, early and late MRI images were in complete agreement with the cUS result. Also, in infants with IVH and periventricular echodensities the late MRI did not provide any additional information to the cUS[85].

However, other authors found that cUS lacks sensitivity in detecting small punctuate parenchymal haemorrhages[73], cerebellar haemorrhages and most importantly, non-cystic WM injury, the most common form of brain abnormality amongst these three pathologies[71-76]. In a study of Childs et al only one third of non-cystic WM abnormalities on MRI were also detected by CUS[72]. Similarly, Miller found cUS to be an insensitive predictor of the milder spectrum of MRI-defined white matter abnormalities, although it is noteworthy that the predictive value improved when cUS was performed after the first week of life[74].

Furthermore, with MRI (but not with cUS), myelination of the posterior limb of the internal capsule (PLIC) can be reliably evaluated. This can be important as signal asymmetries/abnormalities in the PLIC help to predict hemiplegia in children with unilateral parenchymal abnormalities and in predicting diplegia in infants with bilateral PVL[84,85].

On the other hand, a disadvantage of MRI over cUS is that it does not depict lenticulostriate vasculopathy and calcifications, and is less reliable for germinolytic and plexus cysts[98]. If this is of clinical relevance has not yet been shown.

A few studies have systematically evaluated the predictive value of both methods for neurodevelopmental outcome. Van de Bor found ultrasound-defined PVL the best and MRI defined delay of myelination the second best predictor of abnormal

neurodevelopmental outcome at the age of 3 years[103]. In contrast, Woodward et al and Mirmiran et al, found conventional MRI to be superior to cUS in predicting adverse neurodevelopmental outcome at the age of 2 years and cerebral palsy[76,102].
However, in both Woodward's and Mirmiran's studies the sensitivity of cUS for predicting cerebral palsy (sensitivity/specificity: Woodward 18%/95%; Mirmiran 29%/86%) was inferior compared to results published by other groups, e.g. de Vries et al (79%/95%)[29]. This is likely due to a major difference in study design. While van de Bor et al and de Vries et al scanned infants once or twice weekly from birth until term age, Woodward et al performed only 3 cUS scans during the first six weeks of life and Mirmiran et al 2 scans during the first two weeks of life. Thus, information that can be generated from frequent serial cUS after six/two weeks of life were not taken into account in any of these studies.

In summary, there is so far no study that has examined a large unselected, populations-based cohort of extremely low gestational age infants with cUS and MRI at term age. In many studies the study population was selected or cUS was not serially performed after the first weeks of life. Moreover, very often cUS evaluation was limited to the presence of major brain abnormalities, and minor abnormalities (enlarged subarchnoidal spaces, reduced complexity of gyral folding etc) were not taken into account. It could therefore be the case that serial high quality cUSs carefully performed from birth up to term age predict brain abnormalities on MRI and outcome well.

Nevertheless, the high resolution of MRI and thus its capability to depict the extent of lesions in detail and to visualize myelination stage is with no doubt very helpful in some preterm infants. Therefore it would be desirable to know in which preterm infants MRI adds valuable information and thus is indicated as a complementary diagnostic imaging tool and in which it is not. This would help to save time, manpower and money and even more importantly, ward off unnecessary stress of MRI imaging (transport, noise, etc) for the infants.

2 AIMS OF THE THESIS

The overall aim of the thesis was to study brain abnormalities with cUS and MRI at term age in very preterm infants.

The specific aims of the included studies were:

Study I

The aim of *study I* was to correlate periventricular echodensities and signs of brain atrophy on cUS at discharge to neurodevelopmental outcome at three years of age in a one year cohort of very preterm infants.

Study II

The aim of *study II* was to acquire population based MRI data on brain abnormalities in ELGA infants from the Stockholm region and to relate the MR findings to perinatal data, in order to identify protective and risk factors.

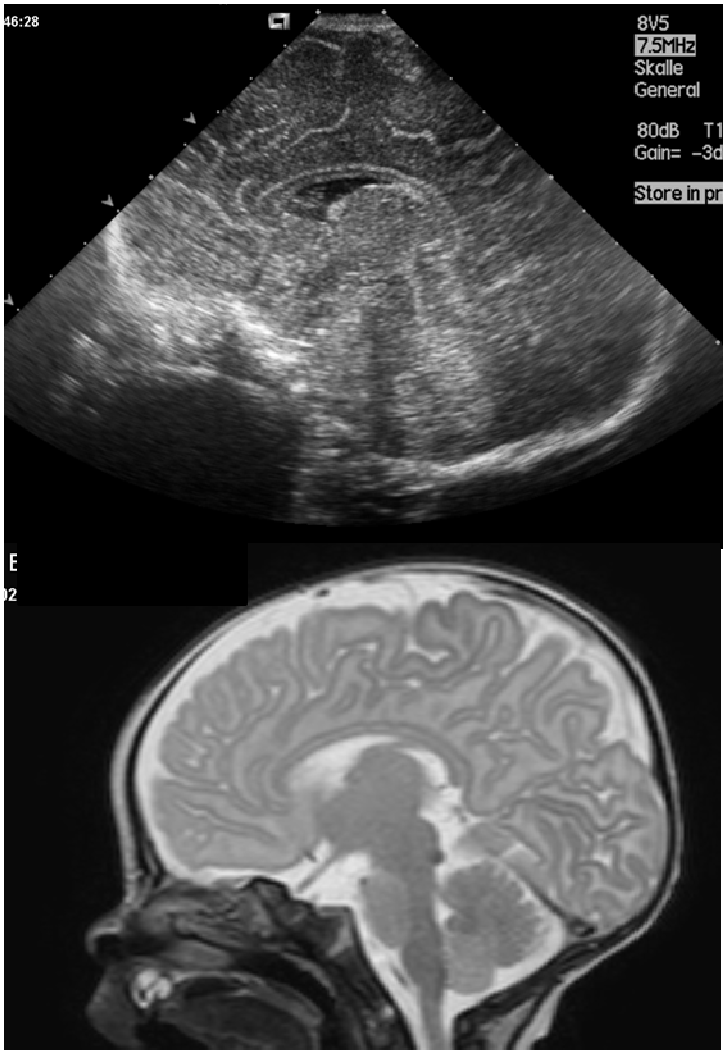
Study III

The aim of *study III* was to correlate 5 common linear 2D ultrasound measurements of lateral ventricular size and the frontal horn product to the lateral ventricular volume assessed by 3D MRI. Thereby we wanted to determine the best ultrasound parameter to use in clinical practice to quantify ventricular size.

Study IV

The aim of *study IV* was to compare cUS and conventional MRI performed on the same day at term age, in a population based cohort of ELGA infants. We wanted to determine if conventional MRI adds clinically important information to the results from cUS at term age and if conventional MRI therefore should be recommended as a screening tool for ELGA infants at term age in a clinical setting.

Methods



3 METHODS

3.1 Overview on methods used in the thesis

	STUDY I	STUDY II	STUDY III	STUDY IV
inclusion criteria	birth weight <1500g or GA <32 weeks	GA < 27 weeks	GA < 27 weeks	GA < 27 weeks
cUS performed	day 1,2,3,5,7,14, every 2nd week until term age	None	at term age	at term age
cUS 2D measurements performed	None	None	yes	yes
MRI performed	None	at term age	at term age	at term age
MR image post processing	None	None	segmentation of lateral ventricles	none

Table 4: Overview on methods used in the thesis

3.2 Patients and Methods Study I

3.2.1 Patients

Preterm infants with a gestational age below 33 weeks and/or a birth weight below 1500 g admitted in 1997 to the Neonatal Intensive Care Unit of the University Children's Hospital of Essen, Germany, were included. Infants with chromosomal disorders, congenital abnormalities, congenital infections and proven metabolic disorders were excluded from further analysis.

3.2.2 Cranial ultrasound

cUS was performed according to clinical routine as soon as possible after admission, on days 2, 3, 5 and 7, at the end of week 2, and then every second week until discharge (postmenstrual age at discharge ranged from 35 to 44 weeks, median value 39 weeks). If

discharge was before 37 weeks postmenstrual age, cUS was repeated in the outpatient clinic at term equivalent age and included in the analysis (four infants). Infants were scanned by two experienced investigators using a 128 XP Acuson (Mountain View, CA, USA) scanner equipped with a multi-frequency sector transducer (5–6–7 MHz). cUS was performed in the coronal and sagittal/ parasagittal planes through the anterior fontanelle, obtaining sequential sections according to Levene[104] (figure 7,8). The images were printed and assessed for clinical diagnosis. Later, they were reviewed by three investigators (Claudia Roll, Carsten Muentjes, Sandra Horsch) and diagnosis was agreed upon by consensus. Images were judged according to the following criteria: presence of GMH; IVH (classified according to Volpe[25]; table 2); PVHI; PVL (classified according to Govaert and de Vries[58], table 3); periventricular echodensities (classified according to Govaert and de Vries[58] into two groups: persisting less than 7 days and persisting longer than 7 days), width of interhemispheric fissure, size of subarachnoid spaces, size of the lateral ventricles, gyral folding/maturation and other abnormalities. Brain atrophy was defined as the combination of enlarged subarachnoid spaces, widened interhemispheric fissure, and reduction in complex gyral folding with or without concomitant ventriculomegaly.

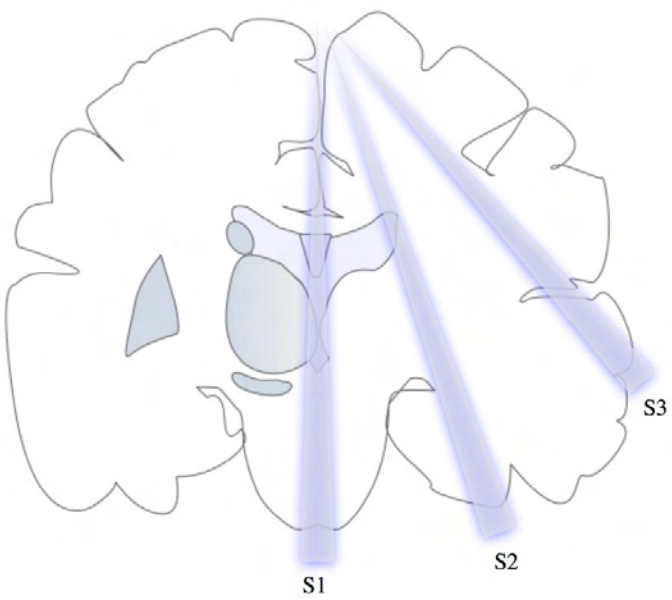


Figure 7: Sagittal and parasagittal planes performed and documented in all infants on both sides.

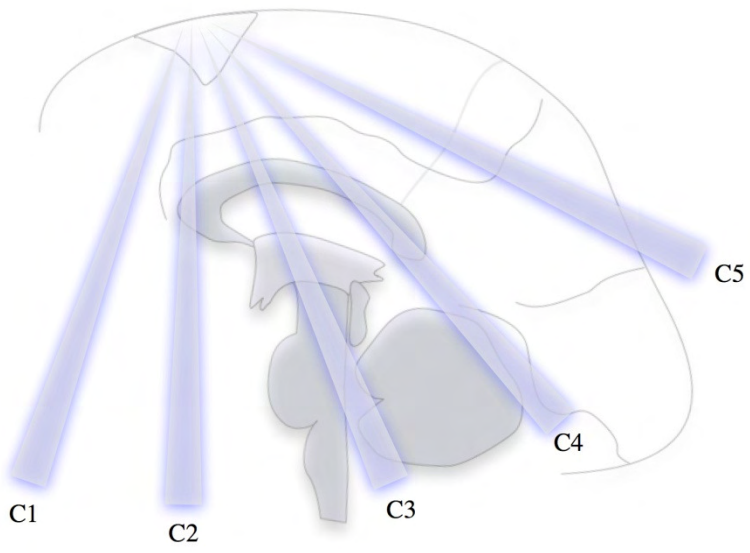


Figure 8: Coronal planes performed and documented in all infants.

3.2.3 Neurodevelopmental Follow-Up

Neurodevelopmental follow-up was performed at a corrected age of 3 years. The assessment consisted of a semi-structured interview with the caregivers, a clinical examination including neurological assessment, functional classification of hearing and visual ability, and growth assessment. Development was assessed by Bayley Scales of Infant Development (II) testing, yielding scores for mental (MDI) and psychomotor development (PDI) with a standardization mean of 100 and a standard deviation of 15 points. Development was considered severely delayed when a score was less than 70, and mildly delayed when it was 70–84. Severely impaired children that did not reach the minimum index score of 50 in the Motor Scale and Mental Scale were given a score of 45. Behavior (orientation and engagement, emotional regulation and motor quality) during examination was assessed with the Behavior Rating Subscale of Bayley Scale. Percentile scores less than 10 were considered non-optimal, between 11 and 25 questionable, and above 26 normal.

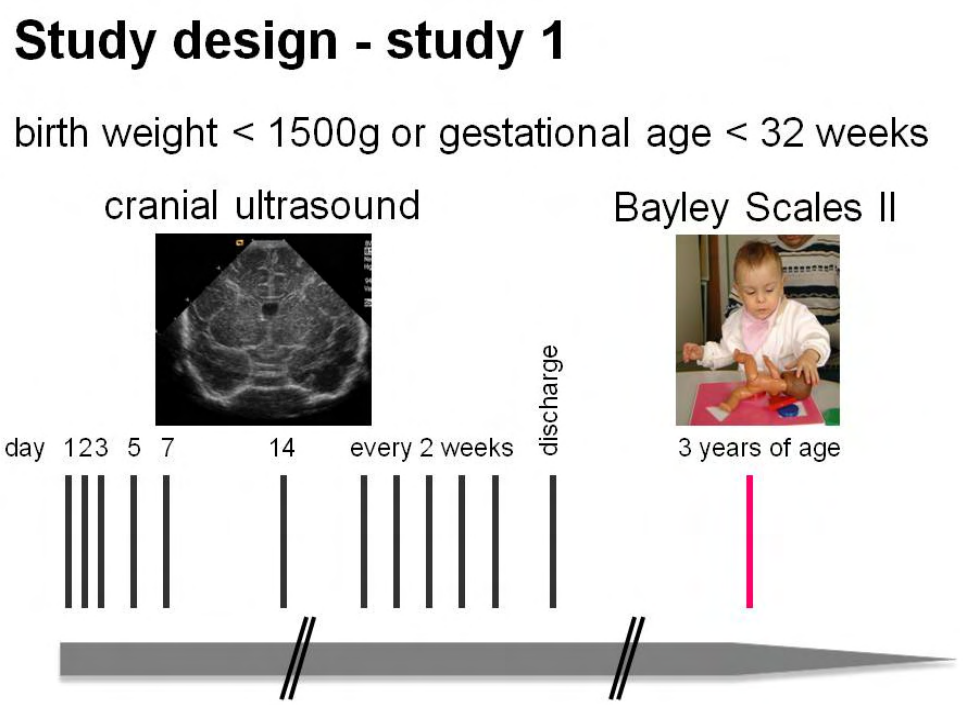


Figure 9: Study design study I

3.3 Patients and Methods study II, III and IV

3.3.1 Patients

All patients in study II, III and IV belong to a population based cohort of extremely low gestational age (gestational age below 27 weeks) infants from the Stockholm region, Sweden. From January 2004 until November 2006 all infants with a gestational age below 27 weeks were included, their clinical data were prospectively collected, coded and stored in a computerized data base. Due to the centralized care in the great Stockholm region all included infants were born at the Astrid Lindgren Children´s Hospital at Karolinska University Hospital or, if antenatal transport was impossible, were transported immediately after birth to the Neonatal Intensive Care Unit of the Astrid Lindgren Children´s Hospital. After discharge, all infants were scheduled for a cranial MRI at corrected term age at the Paediatric Radiology Department at Astrid Lindgren Children´s Hospital and from August 2004 and onwards a cranial ultrasound scan was performed in parallel to the MRI scan on the same day at term age by one of two investigators (Béatrice Skiöld, Sandra Horsch).

In *study II* the MRI scoring data of the patients included between January 2004 and August 2005 were analyzed.

In *study III* the 2D ultrasound measurements and 3D MRI volume measurements of the lateral ventricles were analyzed in the infants that were included between August 2004 and August 2005.

In *study IV* the results of the cranial ultrasound and MRI scan at term age were analyzed of infants included between January 2004 and November 2006.

The studies were approved by the regional ethical committee in Stockholm. Informed consent was obtained from all parents of infants included in the study.

3.3.2 MRI at term age

All MRI scans were performed at the Astrid Lindgren Children´s Hospital at Karolinska University Hospital in Stockholm, Sweden, using a 1.5 Tesla MRI system (Philips Intera, Philips, Best Holland). According to the standard clinical protocol for neonatal MRI during the time the studies were carried out, infants were fed and given chloral hydrate (30 mg/kg orally or rectally) 15-30 min prior to the examination. However, if infants were already deeply asleep prior to the examination or if the parents did not give consent to the use of sedative medication, infants were scanned during natural sleep. The following MRI sequences were performed in all infants (table 5):

Pulse Sequence	TR (ms)	TI (ms)	TE (ms)	Flip Angle	NSA	Scan Matrix	Slice Thickness (mm)	FOV (mm)	ETL	SENSE
T1-w. Turbo Spin Echo. (sagittal)	600	-	9.2	90	3	256 x 206	3 (3.3mm spacing)	180	3	R=1.5
T1-w. Spin Echo (axial)	600	-	9.2	90	2	192 x 154	4 (5mm spacing)	180	-	NO
T2-w. Turbo Spin Echo (axial and sagittal)	5000	-	100	90	2 ax 4 sag	240 x 192 ax 224 x 179 sag	4 (5mm spacing)	180	16	R=1.5
T1-w. IR Turbo Spin Echo (axial)	3500	400	15	90	2	192 x 154	4 (4.8mm spacing)	180	5	NO
T2*-w. Gradient Echo (axial)	583	-	23	18	2	256 x 206	5 (5mm spacing)	180	-	R=1.5
T1-w. 3D Gradient Echo (coronal)	40	-	4.6	30	2	256 x 206	2 (1mm spacing)	180	-	R=1.5

Table 5: MRI pulse sequence protocol

In order to reduce the acoustic noise for the infant in the scanner, we used a combination of three passive hearing protections: commercially available dental putty (Affinis dental putty soft, ColteneAG, Switzerland*)* and pediatric ear muffs (Bilsom Junior) as well as an in-house developed acoustic hood that reduces noise levels by 16-22 dBA depending on the pulse sequence[79] (figure 10).

Figure 10: Neo Hood – acoustic noise reduction device

3.3.3 MRI scoring system

MR images were evaluated independently by three observers blinded to the clinical course of the infants. We used a previously described scoring system to evaluate and grade grey and white matter abnormalities[70,76]. Discrepancies between observers were resolved by discussion and consensus was reached in all cases. Five different WM-variables were assigned a score of 1, 2 or 3 (see also table 6): I- WM signal abnormality [on T1 and/or T2 images], II- reduction in WM volume, III- cystic abnormalities, IV- lateral ventricular size and V- corpus callosum size/myelination stage.

ITEM	GRADE I	GRADE II	GRADE III
WM signal abnormality	nil	focal (one region only)	extensive (≥2regions)
Reduction in WM volume	normal	mild-moderate loss	diffuse loss
Cystic abnormalities	nil	focal cystic changes	extensive cystic changes
Lateral ventricle size	normal	mild-moderate dilatation	marked ventricular dilatation
C. callosum and myelination	normal or isolated partial thinning	marked thinning of corpus callosum	marked thinning of CC and impared PLIC myelinatoin
Subaranoidal spaces	normal	mild enlargement	moderate – severe enlargement
Cortical grey matter signal abnormalities	nil	focal (one region only)	extensive (≥2regions)
Gyral maturation	normal for GA age	delay 2-4 weeks	delay > 4 weeks

Table 6: MRI scoring system

The myelination stage was defined as followed: myelination stage 1 (M1): myelin in the brainstem, vermis and cerebellar hemispheres corresponding to a maturation less than 37 weeks GA, myelination stage 2 (M2): myelin reaching the posterior limb of the internal capsule (PLIC) and the lenticular nucleus and thalamus corresponding to 37-38 weeks GA, myelination stage 3 (M3): myelin reaching the central corona radiate and the caudate nucleus (38-39 weeks GA) and myelination stage 4 (M4): myelin reaching the centrum semiovale, corresponding to 40-42 weeks GA .

WM abnormalities were further classified by the composite score of these five categories (potential range of composite WM score: 5–15) into no WM abnormality (composite score 5–6), mild WM abnormality (composite score 7–9), moderate WM abnormality (composite score 10–12), or severe WM abnormality (composite score 13–15). Further, three different grey matter (GM) abnormalities were assigned a score 1, 2 or 3 (table 6): I- cortical grey matter signal, II- gyration maturation and III- size of the subarachnoidal spaces. In analogy to the WM score, GM scores were added to a composite GM score (potential range of composite GM score: 3–9) and GM appearance was divided into two groups: normal (composite score 3–5) or abnormal (composite score 6–9) grey matter.

3.3.4 MR Image Postprocessing (study III)

To segment the lateral ventricles, an image-processing software was developed and implemented in Matlab 7.0 (Mathworks, Michigan, USA). The software uses a semi-automatic Gradient Vector Flow Active Contour mode[105,106] that is attracted to the ventricle edges. Dedicated software provided by Xu et al was used to calculate the Gradient Vector Flow field[105]. Apart from reducing inter- and intraobserver variability compared to fully manual segmentation, the edge-based segmentation approach is beneficial due to the large amount of choroid plexus present within the lateral ventricles. Using intensity-based segmentation methods such as thresholding and region growing, it is difficult to differentiate between the choroid plexus and white matter on T1-weighted MR images since their image intensities can be similar. The edge-based active contour model suffers less from this problem and therefore reduces the risk of underestimating the ventricular volume because of choroid plexus misclassification. The contours were placed in the coronal and axial planes and merged to create a final segmentation result. To secure quality, the segmentation result was reviewed in all three planes by two observers (Johan Bengtsson, Sandra Horsch). When necessary, manual adjustments were performed. Finally,

the total lateral ventricular volume was automatically calculated based on the segmentation result.

3.3.5 cUS at term age (study III and IV)

cUS was performed the same day as the MRI scan. Infants were scanned by one of two examiners (Béatrice Skiöld, Sandra Horsch,) experienced in neonatal cUS using the ACUSON Sequoia ultrasound system (Siemens Medical Solutions, Germany) equipped with a multifrequency sector transducer (5-8 MHz). cUS was performed in the coronal and sagittal/parasagittal planes through the anterior fontanelle obtaining sequential images according to Levene[104] (see figures 7 and 8). The images were stored digitally.

In study III the following 5 ventricular measurements were obtained for both lateral ventricles on the digitally stored ultrasound images:

- in the coronal plane at the level of the 3rd ventricle:
the width of the frontal horn in the short (measurement 1) and long axis (measurement 2) were measured, see figure 11.

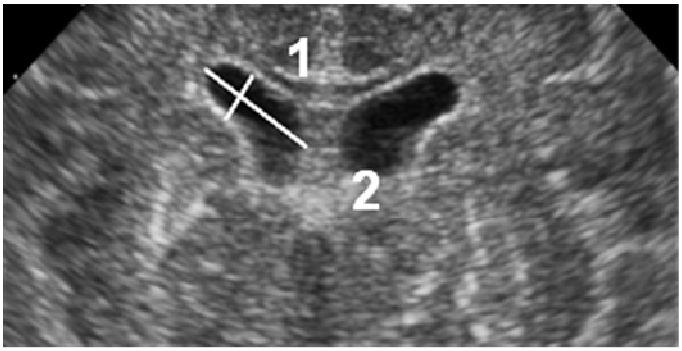


Figure 11: Coronal measurements of lateral ventricle size

- in the parasagittal plane: the height of the frontal horn (measurement 3), width of the ventricular midbody (measurement 4), and the thalamo-occipital horn distance (measurement 5), see figure 12.

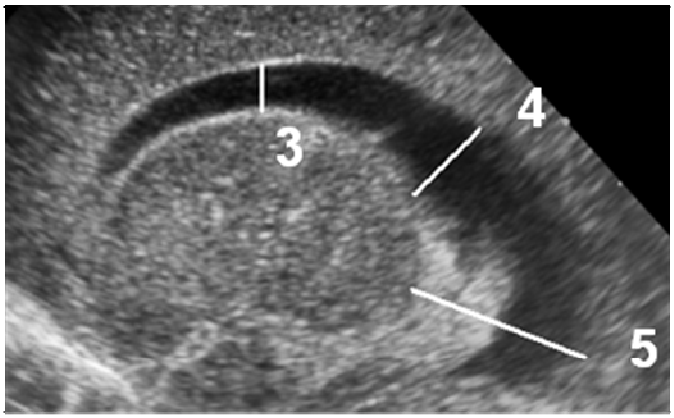


Figure 12: Sagittal measurements of ventricular size

Furthermore, in order to get an estimate of the frontal horn area the short and long axis measurement of the frontal horn were multiplied resulting in the frontal horn product (frontal horn product = short axis measurement * long axis measurement).
To study the interobserver variability, and thereby the reliability of the ventricular measurement, the digitally stored images were reanalysed by a second independent observer (Mats Blennow) for all patients. Both observers (Sandra Horsch, Mats Blennow) were blinded to clinical data.

In study IV the digitally stored ultrasound images were analyzed by three independent observers blinded to clinical data. All three observers performed all measurements mentioned below. The mean of the measurements of the three observers was used for further analysis for all parameters. The cUS was considered **normal** if none of the 8 measured or scored items (A: frontal horn size, B: ventricular midbody size, C: interhemispheric fissure, D: subarachnoidal spaces, E: cysts, F: corpus callosum size, G: gyral folding, H: cortical grey matter signal abnormalities) was abnormal/outside of the normal range.

A. The *frontal horn size* as an indirect sign of frontal white matter loss was measured in the following way:
   The short (*1*) and the long (*2*) axis of the frontal horn in the coronal view on the height of the 3rd ventricle (C3 in figure 8, and (*1*) and (*2*) in figure 11) and the frontal horn height (*3,* figure 12) in the parasagittal view (S2 in figure 7) were measured bilaterally. A cut-off level of 3 mm was chosen for (*1)* and (*3)*, and 13 mm for (*2)*[57]. The frontal

horn size was considered **normal**, when none or only one of the 6 measurements were above the cut-off level.

B. The size of *ventricular midbody* (*4*) as an indirect sign of parieto-occipital white matter loss was measured in the parasagittal view [S2 in figure 7, and *4* in figure 12). The size of the ventricular midbody was considered **normal** when bilaterally < 10mm[56].

C. The width of the *interhemispheric fissure* (IF see figure 13) was measured in the coronal view at the height of the 3rd ventricle as a mean distance between hemispheres. The width of the interhemispheric fissure was considered **normal** when < 3mm.

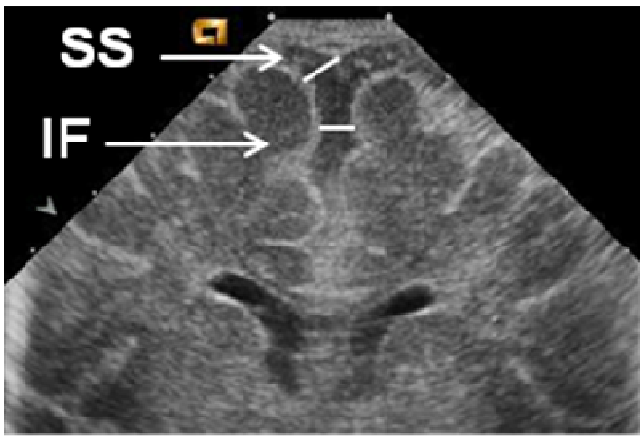


Figure 13: Measurements of subarchnoidal spaces and interhemispheric fissure

D. The width of the *subachnoidal spaces* (SS see figure 13) was measured as the sino-cortical width in the coronal view in 3 different positions (C1, C3, C5, see figure 14). The width of the subarchnoidal space was considered **normal** when < 4mm in all three measurements[107].

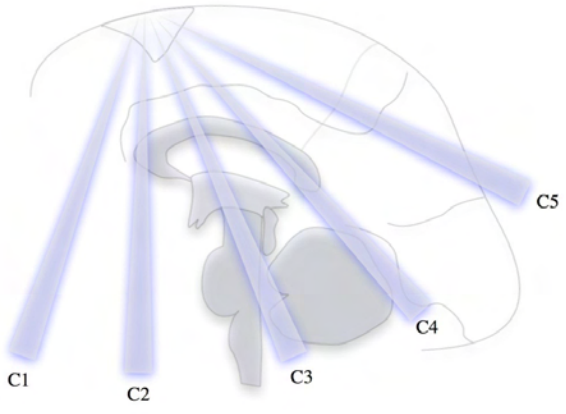


Figure 14: Subarachnoidal space measurements

E. Only the absence of cysts in the grey and white matter was considered **normal**.

F. The body of the *corpus callosum* was measured in the sagittal midline view. The size of the corpus callosum was considered **normal** when > 1,5mm[108].

G. The complexity of gyral folding was considered **normal** when appropriate for gestational age in coherence with the definition of the MRI scoring system published by Inder et al/ Woodward et al [70,76].

H. Only the absence of grey matter signal abnormalities was considered **normal**.

Severe abnormalities were predefined as cystic periventricular leukomalacia, cystic defects/white matter loss after periventricular haemorrhagic infarctions and global white and/or grey matter loss without focal lesion, usually coinciding with severe ventriculomegaly.

3.3 Statistical Analysis

In study I statistical analysis was performed with Stat View version 4.5 and SPSS version 10.5 and was based on nonparametric tests and linear regression analysis, with $p<0.05$ indicating significance.

In study II statistical analysis was performed with SYSTAT® Version 10.0 (Systat Software, Inc., Point Richmond, CA; USA). Univariate and multiple logistic regressions, ANOVA with Bonferroni correction were performed to correlate perinatal data to MRI findings. For parameters that were not Gaussian distributed the Kruskal-Wallis-test was applied. A significance level of $p < 0.05$ was chosen for all tests. To simplify statistical analysis, infants were divided into two groups: 1/ infants with no or mild abnormalities and 2/ infants with moderate or severe abnormalities.

In study III statistical analysis was performed with SYSTAT® Version 11. Simple correlations and linear regressions were calculated for ultrasound measurements and MRI volumes. To assess the interobserver variability, the intraclass correlation coefficient (ICC) was calculated for each ultrasound parameter and the strength of agreement scale of Brennan and Silman was used for interpretation[109]. The strength of agreement or reliability was considered poor if the ICC was less than 0.2, fair if between 0.21 and 0.4, moderate if between 0.41 and 0.6, good if between 0.61 and 0.8 and very good if more than 0.8.

Results

4 RESULTS

4.1 Results Study I

Out of the 87 patients included, six had died, one was excluded because of trisomy 21, parents of two patients did not want to participate in the study, and 14 infants had moved outside the region and could not be traced for follow-up. Sixty-four infants (79% of all survivors) were examined. Patient characteristics are presented in table 7.

	infants born n= 87	survived until discharge n=81	examined at 3 years n=64
Gestational age	29wk (24-35w)	29wk (24-35w)	29wk (24-35w)
Birth weight	1200g (430-2500g)	1200g (430-2500g)	1200g (430-2500g)
Male	47 (54%)	42 (52%)	35 (55%)
Caesarean	83 (95%)	83 (95%)	60 (94%)
Singleton	70 (81%)	65 (80%)	50 (78%)
Antenatal steroids	74 (85%)	70 (86%)	53 (83%)
Inborn	70 (81%)	64 (79%)	50 (78%)
Small for GA	24 (28%)	22 (27%)	17 (27%)
Mechanical ventilation	54 (62%)	48 (59%)	40/(63%)
Days on ventilator	2d (0-36)	2d (0-36)	2d (0-36)
Surfactant	47 (54%)	42 (52%)	35 (55%)
Inotropes	13 (15%)	11 (14%)	11 (17%)
Indomethacin	19 (22%)	19 (24%)	15 (23%)
Postnatal steroids	5 (6%)	5 (6%)	5 (8%)
Threshold ROP	8 (9%)	8 (10%)	6 (9%)
GMH	11 (13%)	11 (14%)	9 (14%)
IVH II	7 (8%)	6 (7%)	6 (9%)
IVH III	1 (1.1%)	1 (1.2%)	1 (1.6%)
IVH III+PVHI	3 (3%)	0	0
c-PVL	0	0	0
Periventrular flares	42 (48%)	38 (47%)	30 (47%)
detectable < 7d	12(14%)	9 (11%)	6 (9%)
detectable > 7d	30 (35%)	29 (36%)	24 (38%)
Brain atrophy (discharge)		18 (22%)	14 (22%)

Table 7: Patient characteristics study I

4.1.1 Neurodevelopmental outcome

Follow-up was performed in 64 infants at 3 years of age (median 36 months, range 32–42 months). Neurodevelopmental outcome was classified as normal in 45 (70%), mildly delayed in 17 (27%), and severely delayed in two (3%) infants according to the results of the Bayley Scales and the clinical and neurosensory assessments.

4.1.2 cUS and neurodevelopmental outcome

Infants who presented with signs of brain atrophy at discharge had significantly lower MDI, PDI and Behaviour Rating Scale scores than infants without signs of brain atrophy (Figure 15).

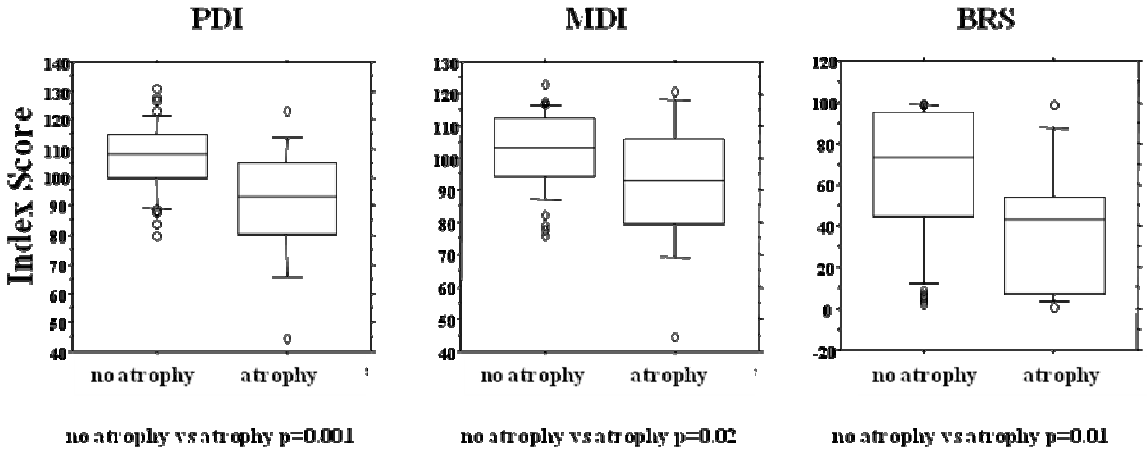


Figure 15: Results of the Bayley Scales of infants with and without signs of brain atrophy at term age.

In contrast, the presence of periventricular echodensities - independent of the duration of their persistence – was not associated with adverse neurodevelopmental outcome.

4.1.3 Brain atrophy and perinatal data

Details of the comparison of perinatal data between infants with and without brain atrophy are given in table 8.

Infants survived until discharge	with atrophy n=18	without atrophy n=83	p- value
Birth weight (g)	785g (550–2500g)	1230g (530–2100g)	0.004
Gestational age (w)	28+5w (25+1–35w)	30+1w (24+1–34)	0.009
1 min APGAR	4.5 (2–9)	7 (0–10)	0.001
5 min APGAR	7 (3–10)	8 (6–10)	0.006
10 min APGAR	8.0 (3–10)	9 (7–10)	0.04
Haemoglobin (mg/dl)	14.8 (9.2–21.4)	16.4 (10.8–22.4)	0.01
Cord blood pH (arterial)	7.22 (7.09–7.37)	7.26 (6.8–7.44)	ns
pH of first BGA	7.25 (7.0–7.37)	7.28 (6.8–7.43)	ns
First arterial CO_2 (mmHg)	45 (27.1–69.5)	49.1 (22–73.3)	0.04
Elevated CRP first 3 d	7 (39%)	12 (19%)	ns
Days on ventilator	5 (0–36)	1 (0–23)	0.008
Postnatal steroids	4 (22%)	1 (1.2%)	0.004
in infants examined at 3 years			
Head circumference(SDS)	70.8 (74.2 to 0.8)	70.55 (74.7 to 2.1)	ns
Body mass index (SDS)	71.8 (74.0 to 0.1)	70.6 (73.5 to 2.9)	0.003
Height (SDS)	70.7 (72.8 to 2.8)	70.45 (72.7 to 3.3)	ns

Table 8: Brain atrophy and perinatal data at 3 years. Values are presented as median (range) or n (%).

When linear regression analysis was performed to assess the effect of brain atrophy at discharge on outcome at 3 years after adjusting for gestational age and birth weight, only atrophy at discharge remained an independently significant risk factor (atrophy, p=0.024; birth weight, p=0.113; gestational age, p=0.162).

4.2 Results Study II

During the study period 81 infants with a gestational age $\leq$ 26 weeks were born alive. Twenty-two infants (27%) died before term equivalent age. Four infants were excluded (two with congenital CMV infection, one with trisomy 21, one with haemophagocytic lymphohistiocytosis), one infant emigrated from Sweden and for two infants parental consent was not obtained. Fifty-two infants were scanned and included into the analysis, representing 95% of the eligible survivors. Details of perinatal data and clinical courses are presented in table 9.

	all patients n=52	no-mild WM abnormalities n=42% (82%)	moderate-severe WM abnormalities n= 9 (18%)	p
Birth weight	775g ± 154g	788g ± 152g	742g ± 138g	ns
Gestational age	25+3wks± 9days	25+3 wks ± 8days	25+0 wks ± 9days	ns
Boys	27/52 (52%)	22/42 (52%)	5/9 (56%)	ns
Singletons	40/52 (77%)	31/42 (74%)	8/9 (88%)	ns
Prenatal steroids	48/52 (92%)	38/42 (90%)	9/9 (100%)	ns
PROM	16/52 (31%)	15/42 (35%)	1/9 (11%)	ns
CRIB Score	6.73 ± 3.3	6.2 ± 3.3	9.0 ± 2.5	0,039
IVH/ PVHI	6/52 (12%)	2/42 (5%)	4/9 (44%)	0,005
PHVD	4/52 (8%)	0/42 (0%)	4/9 (44%)	0,000
PVL	2/52 (4%)	1/42 (2%)	1/9 (11%)	ns
Indometacin	32 (63%)	26/42 (62%)	6/9 (66%)	ns
PDA ligation	15/52 (28%)	13/42 (31%)	2/9 (22%)	ns
Inotrope use	30/52 (58%)	22/42 (52%)	8/9 (89%)	0.044
Ventilator days	16,5 ± 14.4 d	15.3 ± 14.4 d	23.1 ± 13.3	ns
Postnatal steroids	13/52 (25%)	10/42 (24%)	3/9 (33%)	ns
BPD (O_2 at 36 GA)	27/52 (52%)	19/42 (45%)	7/9 (78%)	ns
CPAP only	8/52 (15%)	7/42 (16%)	0/9 (0%)	

Table 9: Patient characteristics in study II, grouped in all infants, infants with no-mild WM abnormalities and infants with moderate.severe WM abnormalities.

4.2.1 Grey and white matter abnormalities

In seventeen infants WM was normal (33%). WM abnormalities were found in 34 infants (67%). The abnormalities were classified as mild (score 7 - 9) in 25 infants (49%), moderate (scores 10 - 12) in 8 infants (16%), and severe (scores 13 - 15) in 1 infant (2%). GM was classified as abnormal in 4 infants (8%).

4.2.2 Correlation to perinatal data

Gestational age and birth weight did not differ significantly between the groups with different severity of white matter abnormalities (see table 9). However, a trend towards higher white matter scores in infants with lower gestational age was observed. Elevated CRIB score, sonographic findings of high grade IVH (IVH III and/or parenchymal hemorrhagic infarction (PVHI)), posthemorrhagic ventricular dilatation and inotrope use were identified as univariate predictors for moderate-severe WM abnormalities. More details of all 15 perinatal variables are presented in table 9.

4.3 Results Study III

During the study period (August 2004 - August 2005), fifty ELGA infants were born and subsequently enrolled in the study. Fifteen infants died before reaching term equivalent age. For one child, parental consent was not obtained. Thirty-four infants were scanned representing 97% of the eligible survivors. Due to MRI image movement artefacts 6 infants had to be excluded from analysis.

US parameter	**US values**		**reliability**			**correlation to MRI ventricular volume**
	mean	SD	mean diff	Variability	ICC	
	(mm)	(mm)	(mm)	(mm)		r/r^2
coronal:						
left frontal horn short axis	2.89	2.50	0.12	0.27	0.97	0.93/0.87
right frontal horn short axis	2.77	3.20	0.19	0.29	0.98	0.94/0.88
left frontal horn long axis	11.68	2.20	1.17	0.65	0.86	0.76/0.57
right frontal horn long axis	11.65	2.53	0.58	0.70	0.79	0.8/0.64
left frontal horn product	38.19	43.65				0.97/0.95
right frontal horn product	39.14	64.03				0.97/0.94
sagittal:						
left frontal horn height	2.90	2.84	0.10	0.33	0.97	0.88/0.78
right frontal horn height	2.53	3.01	0.11	0.26	0.98	0.96/0.93
left thalamo-occipital horn distance	18.19	4.91	0.17	1.80	0.73	0.61/0.37
right thalamo-occipital horn distance	17.85	5.44	0.01	1.59	0.83	0.7/0.40
left ventricular midbody	6.12	4.22	0.18	0.50	0.97	0.86/0.73
right ventricular midbody	5.67	4.31	0.24	0.55	0.96	0.93/0.87

Table 10: cUS measurements and cUS/MRI correlation

4.3.1 cUS measurements and cUS-MRI correlation

2D ultrasound measurements of the frontal horns and ventricular midbody correlated consistently well to lateral ventricular volume measured by 3D MRI, whereas the measurements of the thalamo-occipital horn distance showed a poor correlation to MRI measurements (see table 10). The best correlation between 2D ultrasound measurements and ventricular volume measured by 3D MRI was achieved by combining the coronal

frontal horn measurements to a frontal horn product (long axis times short axis; correlation to MRI volume on the left side $r^2 = 0.95$; right side $r^2 = 0.94$).

4.4 Results Study IV

During the study period 132 infants were live-born with a gestational age (GA) below 27 weeks (w) in the Stockholm region. Of the surviving infants (n=84) three infants met the exclusion criteria (one meningomyelocele, one oesophageal atresia, one haemophagocytic lymphohistiocytosis). For 5 infants parents did not give consent. 76 infants were scanned, representing 94% of all eligible survivors. In 4 infants full data analysis was not possible, due to MRI motion artifacts (n=2) or incomplete cUS (n=2) leaving 72 infants for analysis. Patient characteristics are presented in table 11.

Patient characteristics	**all infants included into analysis (n=72)**
birth weight (median, range)	849g (494-1161g)
gestational age (median, range)	25+4 weeks (23+3w-26+6w)
Singleton	56/72 (77%)
prenatal steroids	68/72 (94%)
Cesarean	30/72 (42%)
Boys	36/72 (50%)
days on ventilator (median, range)	8 days (0-50 days)
postnatal steroids (betamethasone)	15/72 (21%)
BPD (O_2 at 36w GA)	28/72 (38%)
IVH III/PVHI	10/72 (14%)
NEC	4/72 (5.6%)

Table 11: Patient characteristics in study IV

4.4.1 MRI Scoring Results

No or only mild abnormalities were found in 83% of the infants, while 17% had moderate or severe white matter abnormalities. Abnormal grey matter was found in 8 (11%) infants. Four infants had a small punctual cerebellar haemorrhage. Three of the four infants with cerebellar haemorrhage also had supratentorial abnormalities, while in one infant the cerebellar haemorrhage was the only pathological finding.

4.4.2 cUS Results

In 28/72 (39%) of the infants the cUS at term age was found to be normal. Mild-moderate abnormalities (not normal, not severe) were found in 41/72 infants (57%) and severe abnormalities in 3 infants (4%).

4.4.3 MRI and cUS comparison

All infants with severe abnormalities (n=3) were scored as severely abnormal on cUS and MRI. Out of 28 infants with normal cUS at term age, 18 (64%) had a completely normal MRI and 10 (36%) had only mild WM abnormalities on MRI. Thus, none of the infants with normal cUS had moderate or severe WM abnormalities or abnormal grey matter (figure 16). Ten infants who were scored as normal on MRI were scored as mild-moderate (=not normal/not severe) on cUS. In 5.6% (4/72) of infants small punctual cerebellar haemorrhage was diagnosed with MRI. None of these were diagnosed with cUS via the anterior fontanelle.

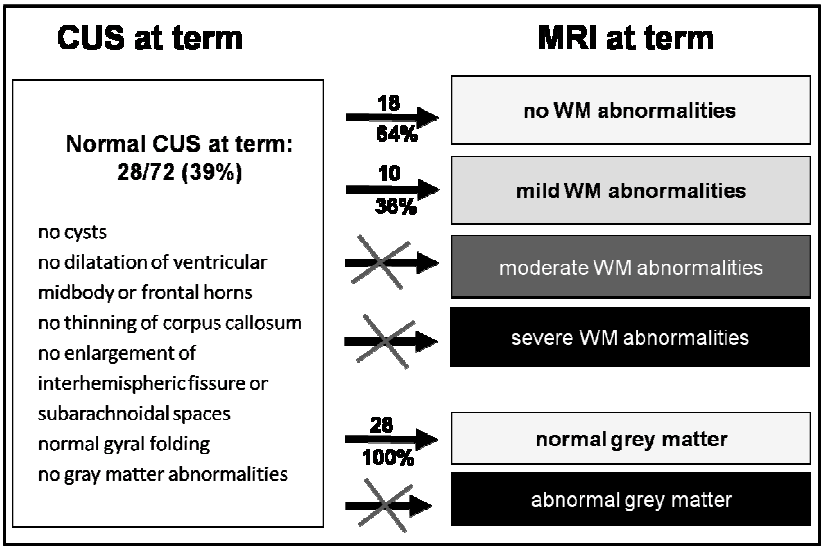


Figure 16: cUS - MRI comparison

Discussion

5 DISCUSSION

In *study I* we demonstrate that sonographic signs of **impaired brain growth/brain atrophy** at term age are associated with adverse outcome at the age of three years. We therefore suggest that brain atrophy should be added to the list of cerebral abnormalities associated with poor outcome. Infants with signs of brain atrophy had lower gestational age and birth weight and higher incidence of morbidity than infants without brain atrophy. These risk factors are identical to those identified for IVH, PVHI and c-PVL[110,111]. Interestingly, head circumference did not differ significantly between infants with and without brain atrophy, neither at discharge nor at three years of age. In contrast, the body mass index was significant lower in infants with brain atrophy at three years than in those without brain atrophy. This observation is in line with earlier reports on the association of postnatal growth retardation and adverse neurodevelopmental outcome[112-114]. However, the limitation of *study I* is that the diagnosis brain atrophy was based on a visual recognition pattern. The width of the subarachnoidal spaces, interhemispheric fissure, lateral ventricles and the grade of gyral maturation were not quantified. Although the diagnosis of brain atrophy was always a consensus decision among three experienced observers, it is desirable that the observed association between brain atrophy and adverse outcome will be confirmed in a prospectively conducted study including more objective and quantifiable parameters.

Furthermore, we could not to find a correlation of **persistent periventricular echodensities (flares)** to neurodevelopmental outcome at three years of age. Our findings oppose earlier finding by Lai et al, Ringelberg et al, and Jongman et al who were able to demonstrate that infants with persistent echodensities are at higher risk for minor motor disabilities[65-67], but are in line with the results of Bennett et al and O'Shea et al[37,68]. The definition of periventricular echodensities regarding location, intensity and duration differed between the studies and might explain the controversial results. Quantification of echodensities in the white matter, though possible[69], is not used in clinical routine, and the variability between observers is probably high. In our cohort, the rate of periventricular echodensities persisting longer than 7 days was 35%, which is well above rates reported by others (Lai: 8.9% Ringelberg: 8.2%). Possibly, flares were overestimated and we therefore failed to show the association to neurodevelopmental outcome. Recently, Vansteenkiste et al have presented an interactive algorithm to segment flaring on cUS images[69]. If this technique turns out to be clinically applicable, it might overcome the problem of high user dependency in the diagnosis of periventricular echodensities.

In *study II* we acquired **population-based MRI data of brain abnormalities** in 52 infants born with a gestational age below 27 weeks. At the time of publication, this cohort of 53 premature infants, born ≤ 26 weeks gestation, was to our knowledge the largest population-based cohort of extremely preterm infants studied by MRI at term age.

MRI data on brain abnormalities at term age in this high risk group of preterm infants are thus scarce and often the definition of GM and WM abnormalities vary between studies which makes comparison difficult. We therefore chose to apply the same MRI scoring system as used by Inders group that has been shown to correlate well to later neurodevelopmental outcome[70,76]. Inder et al further described a unique pattern of global brain atrophy in 91% of extremely immature infants with a gestational age below 26 weeks[70]. This pattern could be found neither in the cohort studied by Miller[115], nor in our cohort. Thirty infants in our cohort had a gestational age of < 26 weeks, but 80% of them (n=24) had normal WM or only mild abnormalities. Only two infants (7%) showed a pattern partly similar to the pattern described by Inder et al. In general, the incidence of GM and WM abnormalities in our cohort was relatively low in comparison to previously published cohorts. The reasons for this more favorable outcome can only be speculated upon. Several studies have shown immense differences in mortality and morbidity of extremely low gestational age infants between countries and regions[1,7,8]. The reasons for these differences are multifactorial and still not fully understood. Possible beneficial factors in our cohort might be the centralized care in the great Stockholm region with a strict policy of intrauterine referrals to one single center in case of threatening extreme preterm birth (outborn rate 1%) and the high rates of antenatal steroid therapy (92% during the study period). Another beneficial factor might be that non-invasive treatment strategies like early nasal CPAP and the newborn individualized developmental care and assessment program (NIDCAP) are well established in the region. In the present cohort, eight (15%) infants could be managed with nasal-CPAP alone. None of these infants had moderate-severe white matter abnormalities on the full term MRI scan. Moreover all infants were treated in neonatal units where individualized care and minimal handling are routinely performed. One previous study, that however included only a small number of infants, indicates that these care strategies (NIDCPAP) result in measurable improvements in brain structure and function of preterm infants[116]. However, in order to make any conclusions regarding the impact of different therapy traditions, the neurodevelopmental outcome data of this cohort and further studies specifically targeting these issues are needed.

In *study III* we were able to show that **2D ultrasound measurements** of the frontal horns and ventricular midbody are good estimates of **lateral ventricular volume** measured by **3D MRI**. In contrast, the measurement of the occipital horn showed a poor correlation to MRI measurements. This might be explained by the fact that correct visualization of the posterior borders of occipital horn through the anterior fontanelle can be difficult, and might result in high interobserver variability.

In addition to the most common linear ventricular measurements, we also included the frontal horn product (= short axis measurement times long axis measurement of the frontal horn in the coronal view) into our analysis. We included this parameter since we assumed that the frontal horn area correlates well to the total lateral ventricular volume. However, area measurements are not easily performed with all ultrasound devices. Therefore we decided to measure an estimate of the frontal horn area (called frontal horn product) by multiplying two perpendicular linear measurements of the frontal horns, the short and the long axis of the frontal horn. Our results confirmed the assumption: the frontal horn product showed indeed the best correlation to lateral ventricular volume measured by 3D MRI. To our knowledge, there are no publications about normal values of the frontal horn product in term infants or in preterm infants. Our findings encourage studying this parameter further in a large cohort of term and preterm infants, in order to establish normal values and thresholds that predict adverse outcome.

In this study we studied preterm infants at term only. In clinical practice, ventricular size and its quantification are also of interest in the first weeks of life when posthaemorrhagic ventricular dilatation (PHVD) may occur. Especially in infants with PHVD reliable measurement of ventricular size is important in order to institute and monitor the success of timely interventions. We did not study preterm infants during the acute phase of PHVD but speculate that our results can be applied also in this patient group.

The study underlines the accuracy, reliability and value of 2D cranial ultrasound in quantifying lateral ventricle size in clinical practice

In study IV we **compared cUS and conventional MRI** performed on the same day **at term age** in a cohort of extremely low gestational age infants. We found that infants with normal cUS at term age had a normal MRI (64%) or only mild (36%) WM abnormalities on MRI. Thus, none of the infants with a normal cUS at term age had moderate-severe WM abnormalities or abnormal GM on MRI. Secondly, all infants with severe abnormalities were scored as severe both with conventional MRI and ultrasound. cUS and conventional

MRI have been systematically compared before. Both Woodward et al and Mirmiran et al found conventional MRI to be superior to cUS in predicting adverse neurodevelopmental outcome at 2 years and cerebral palsy, respectively[76,102]. This has initiated an ongoing discussion if conventional MRI should be introduced as a screening tool for preterm infants at term age.

However, in both these studies the sensitivity of cUS for predicting cerebral palsy (sensitivity/specificity: Woodward 18%/95%; Mirmiran 29%/86%) was inferior compared to results published by other groups, e.g. de Vries et al (79%/95%)[29]. This is likely due to a major difference in study design. While de Vries et al scanned infants weekly from birth until term age, Woodward et al performed only 3 cUS scans within the first six weeks of life and Mirmiran et al 2 scans in the first two weeks of life. Thus, information generated from cUS after six/two weeks of life were not taken into account any of these studies. As shown in *study I* cUS can provide valuable information about impaired brain growth/brain atrophy. Therefore, we argue that the superiority of MRI at term age to sequential cUS carefully performed from birth to term age still needs to be proven.

Our data show that approximately 40% of the extremely low gestation age infants had a completely normal cUS at term age and that none of these infants had moderate or severe WM abnormalities or abnormal GM on conventional MRI. Consequently, all infants with normal cUS have either a normal MRI (64%) or only mild (36%) WM abnormalities on MRI. This raises the question if the mild WM abnormalities on MRI found in one third of infants are of clinical relevance; does the knowledge about these mild WM abnormalities change our clinical decision making and/or influence parental counseling? Neurodevelopmental follow-up of this cohort has not been completed yet, thus at this moment we cannot answer this questions on the basis of our outcome data.

Woodward et al demonstrated that infants with mild WM abnormalities had a 7.2 points lower mean MDI and a 3.9 points lower mean PDI score compared to infants with normal white matter[76]. However, the specificity for predicting severe cognitive and motor delay, cerebral palsy and neurosensory delay decreased from 82-84% (for moderate to severe WM abnormalities) to 30-31% when all WM abnormalities - including mild WM abnormalities - were taken into account. Considering that these data were acquired in centers of excellence in neonatal MRI, it can be assumed that sensitivity and specificity might be reasonably lower in centers with less experience in neonatal MRI.

From our results, we hypothesize that in infants with normal cUS at term age, conventional MRI adds no or only marginally relevant clinical information. Consequently, in this group of infants it is unlikely that MRI at term age will change clinical decisions making or influence parental counseling. This implies that cUS can be used as a screening method to identify infants with low risk of brain injury and thereby reduce the number of MRIs. This is important as MRI is at this moment an expensive technique with limited access and sometimes logistic challenges (such as transport and sedation).

Nevertheless, it has to be emphasized that our results refer to conventional MRI in preterm infants at term in a clinical setting only. The high impact of neonatal MRI in a research setting is certain and undisputed. Conventional MRI and more advanced MR methods (incl. image post-processing techniques) like diffusion tensor imaging, tractography, volumetry, MR spectroscopy and functional MRI have enhanced and will further enhance our knowledge about physiology and pathophysiology of the developing newborn brain [78,80,81,88-90,94-97]. Implementing the more advanced techniques into the clinical setting might improve the information gained by MRI at term age in the future.

Conclusion

6 CONCLUSION

The main conclusions of the thesis are

- Signs of impaired brain growth/brain atrophy (enlarged subarachnoid spaces, widened interhemispheric fissure, reduction in complex gyral folding, ventriculomegaly) can be detected on cUS at term equivalent age and relate to adverse neurodevelopmental outcome at 3 years of age. Thus, brain atrophy should be added to the list of cerebral abnormalities associated with poor outcome.

- We provided unique population-based data on brain abnormalities in preterm infants born before 27 weeks gestation detected by conventional MRI at term age. Incidences of brain abnormalities were relatively low compared with previous publications from other countries/regions. High CRIB scores, sonographic findings of high grade IVH/PVHI, PHVD and inotrope use were identified as predictors for moderate-severe WM abnormalities at term age.

- Lateral ventricle volume can be reliably estimated using 2D ultrasound measurements of the frontal horns and ventricular midbody. The highest correlation between 2D ultrasound measurements and ventricular volume measured by 3D MRI can be achieved by combining the coronal frontal horn measurements to a frontal horn product (long axis x short axis).

- In clinical settings, cUS at term age can be used as a screening method to identify those preterm infants in which conventional MRI at term adds no or only marginally clinically relevant information to the cUS result. Thereby the number of MRI scans can be reduced in centers with limited MRI access.

Future Perspectives

7 FUTURE PERSPECTIVES

With technical advances MRI scanners are going to be faster, higher field strengths will bring even higher resolution and most importantly MRI scanners will hopefully become cheaper in the future. This will increase their general availability, the level of MRI-expertise amongst radiologist and neonatologist and thus the use of MRI in neonatal intensive care medicine. Moreover, advanced MR techniques like diffusion weighted imaging, volumetric measurements, fibre tracking and MR spectroscopy that are now nearly exclusively used in research settings, might then become part of clinical routine. This will increase the clinically relevant information derived from MRI for every single patient. However, it is doubtful if MRI can ever be a bedside technique. Therefore, cUS will keep its central role in brain imaging of preterm infants. When carefully and frequently performed from birth until term age, cUS provides most of the clinically relevant information on brain development and injury. Furthermore, also cUS techniques improve and the resolution of ultrasound images increases steadily. Even quantitative measurements of the detected ultrasound signals are possible today and might help to overcome the drawback that cUS is until now still highly operator dependent.
For both methods, cUS and MRI standardized scoring systems that consist of objective measurements, validated in a large group of extremely low gestational age infants and strongly predictive for long term outcome are missing. The population-based cUS and MRI data that we have acquired here in combination with the follow-up data that will be available soon, this data has the potential to build up the ground for such new developed scoring systems.

The ultimate future goal in neonatal neurology is the invention of effective neuroprotective treatment strategies. Brain imaging will play a crucial role to detect the optimal timing for treatment and monitor the treatment effects.

Personally, I hope that the differences in survival rates and outcome within Europe will diminish over time. To achieve that, open exchange between institutions, objective discussions, uniform definitions (including brain imaging) and data collection in networks will be necessary. We have to compare obstetric and neonatal treatments and long term outcome between centers and countries, not to compete, but to learn from each other and to find the best treatment in the best interest of our patients and their families.

8 SWEDISH SUMMARY

SVENSK SAMMANFATTNING

Ultraljudsundersökning (cUS) och magnetisk resonanstomografi (MRT) är de två oftast använda bildgivande tekniker för att undersöka förtidigt födda barns hjärnor. Med ultraljud kan man påvisa alla större förändringar i hjärnan (blödningar, infarkter, cystor, förstorade sidoventriklar) som associeras med allvarlig neurologisk utvecklingsstörning. Även mindre tydliga avvikelser, såsom hjärnatrofi och periventrikulära "flares", kan upptäckas med en cUs. Den kliniska betydelsen av dessa mindre avvikelser är dock inte helt klarlagd. Det saknas idag konsensus om hur man bäst mäter sidoventriklarnas volym med ultraljud. Mätning av sidoventriklarnas storlek är ofta nödvändigt för att kunna diagnostisera ventrikeldilation orsakad av blödning eller hjärnatrofi. MRT har visats effektivare än ultraljud för att upptäcka icke-cystiska skador i den vita hjärnsubstansen. Vidare har i en studie hävdats att MRT är överlägset cUS för att upptäcka skador på den vita hjärnsubstansen hos förtidigt födda barn samt för att förutse barnens framtida utveckling. I den studien utfördes cUS endast under barnens sex första levnadsveckor, och ingen cUS gjordes samtidigt med den MRT som genomfördes vid motsvarande fullgången tid.

Målsättningen med denna avhandling var att studera hur mindre förändringar hjärnan, upptäckta med ultraljud, påverkar barnens framtida neurologiska utveckling; att i en kohort extremt förtidigt födda barn (födda före v. 27 + 0) samla in och jämföra populationsbaserade ultraljuds- och MRT-data vid motsvarande fullgången tid; samt att bestämma vilka 2-dimensionella mätningar av sidoventriklarnas storlek på ultraljud som bäst överensstämmer med den totala volymen uppmätt med 3D MRT.

Studierna visar att i) det finns ett samband mellan tecken till hjärnatrofi på ultraljud och barnens neurologiska utveckling vid tre års ålder, ii) i Stockholms-kohorten av extremt förtidigt födda barn var förekomsten av avvikelser i hjärnan överraskande låg jämfört med publicerade resultat från andra regioner och länder, iii) att mätning av sidoventriklarnas framhorn och dess mittre del med cUS bäst korrelerar med den totala ventrikelvolymen mätt med 3D MRT, och slutligen iiii) att för de 40% av extremt förtidigt födda barnen där cUs inte visade några avvikelser i hjärnan MRT vid motsvarande fullgången tid inte tillförde någon eller endast marginellt kliniskt relevant information. Sammanfattningsvis understryker studierna cUS viktiga roll för att undersöka hjärnan hos förtidigt födda barn. MRT har fortsatt en viktig betydelse som kompletterande avbildande undersökning.

9 GERMAN SUMMARY

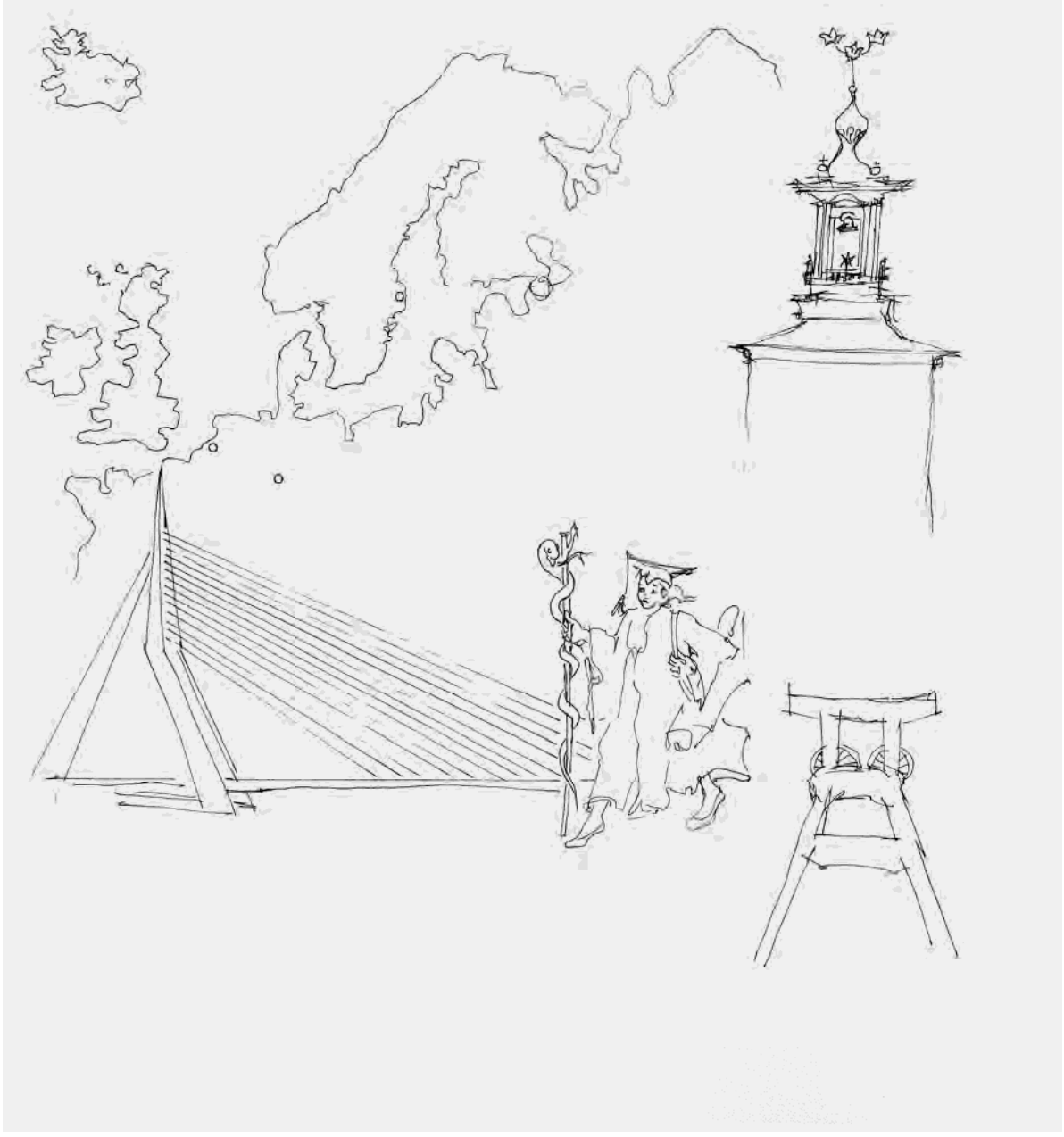
DEUTSCHE ZUSAMMENFASSUNG

Ultraschall (cUS) und Magnetresonanztomographie (MRT) des Gehirns sind die meist angewandten zerebralen Bildgebungsverfahren bei Frühgeborenen. Mittels cUS lassen sich alle wesentlichen zerebralen Schädigungen, die mit schweren Entwicklungsstörungen assoziiert sind (Hirnblutungen, Infarkte, Zysten, Dilatation der Seitenventrikel), zuverlässig bettseitig diagnostizieren. Jedoch kann man mittels cUS auch subtilere Auffälligkeiten wie Zeichen der Hirnatrophie und periventrikuläre Echogenitäts-erhöhungen erfassen, deren Bedeutung für das neurologische Outcome der Kinder noch unklar sind. Darüberhinaus ist cUS zwar das Standardverfahren, um eine Dilatation der Seitenventrikel nach einer Blutung oder bei Atrophie zu diagnostizieren, jedoch herrscht durchaus keine Einigkeit darüber, wie man eine solche Erweiterung am besten quantifiziert. Im Vergleich zur MRT hat cUS außerdem eine geringere Sensitivität, um nicht-zystiche Schädigungen der weißen Substanz, die heutzutage viel häufiger sind als die zystische Form, zu erfassen. Zusätzlich konnten 2 Studien zeigen, daß die MRT der cUs in der Fähigkeit, das Outcome Frühgeborener vorauszusagen, überlegen ist. Jedoch wurden in diesen Studien die cUS-Untersuchungen nur in den ersten 6 Lebenswochen und nicht parallel zur MRT am errechneten Geburtstermin (ET) durchgeführt. Es gibt bisher auch noch keine großen populations-basierten MRT Studien von extrem unreifen Frühgeborenen.
Daher war das Ziel dieser PhD-Arbeit, 1. die Bedeutung von subtilen Veränderungen in der cUS wie Zeichen der Hirnatrophie, periventrikulärer Echogenitätserhöhungen für das neurologische Outcome zu untersuchen (Studie I), 2. populations-basierte cUS und MRT Daten von extrem unreifen Frühgeborenen (< 27 Schwangerschaftswochen) am ET zu akquirieren und zu vergleichen (Studie II und IV) , und 3. zu evaluieren, welches von 5 unterschiedlichen 2D cUS Abmessungen der Seitenventrikel am besten mit dem tatsächlichen, mit 3D-MRT gemessenen Seitenventrikelvolumen korreliert (Studie III).

In unseren Studien konnten wir zeigen, dass 1. sonographische Zeichen der Hirnatrophie, aber nicht periventrikuläre Echogenitätserhöhungen mit schlechterem neurologischen Outcome im Alter von 3 Jahren assoziiert sind, 2. die Inzidenz der mit MRT festgestelten Hirnschädigungen bei extrem unreifen Frühgeborenen aus der Stockholmer Region unerwartend niedrig war, 3. die Maße der Vorderhörner und des Ventrikelkörpers am besten mit dem tatsächlichen Ventrikelvolumen korrelierten, und 4. dass ca. 40% der extrem unreifen Frühgeborenen einen normalen cUs am ET hatten und bei diesen Kindern eine MRT am ET keine oder nur wenige klinisch relevante Zusatzinformationen bietet.

Zusammenfassend unterstreichen unsere Ergebnisse die Bedeutung der cUS in der täglichen zerebralen Diagnostik bei Frühgeborenen und illustrieren, wie die MRT als komplementär angewandtes Bildgebungsverfahren bei Frühgeborenen eingesetzt werden kann.

Acknowledgements



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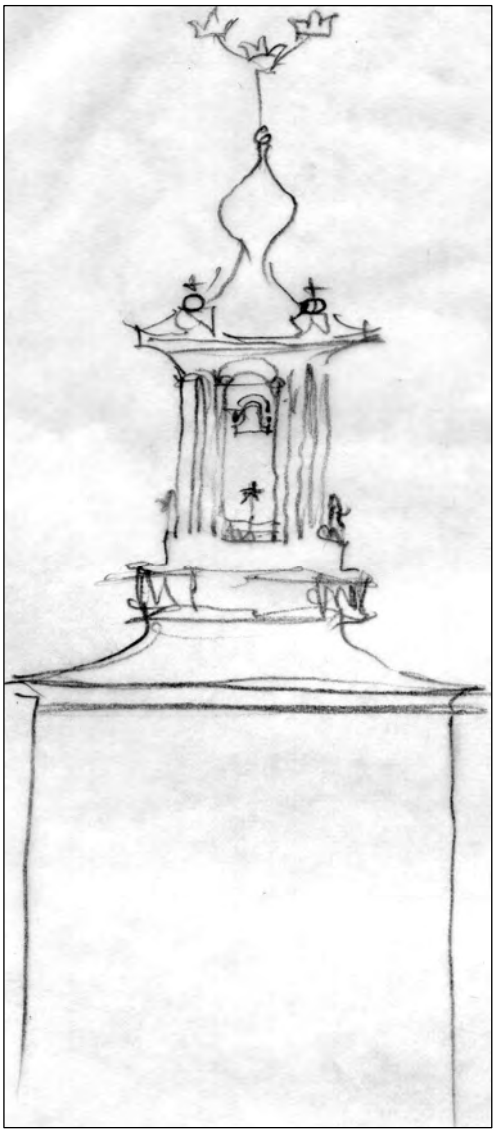

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