Imaging the preterm infant's brain

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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.