Imaging the preterm infant's brain

Leijser, L.M.

Chapter 13

General discussion and Future perspectives

General discussion

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

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

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

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

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

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

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

White matter

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Deep grey matter

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Future perspectives

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

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

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

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

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

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

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

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

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

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