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Radiological assessment of white matter injury in very preterm infants

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Abstract

Despite improvement of neonatal care, infants born very prematurely who survive the neonatal period are still at risk for neurodevelopmental disabilities. One of the main determinants for a poorer outcome seems to be damage to the cerebral white matter which frequently occurs during the perinatal period. This article summarizes the radiological assessment of white matter injury in very preterm infants, striving to aid clinicians who provide parents and caretakers with predictive information on the development of their preterm born infants. As the expertise of radiologists in assessing neonatal brain MRI may vary widely amongst centers, we also strive to provide radiologists with information on imaging findings of white matter injury.

Introduction

In infants born very prematurely (gestational age <32 weeks), germinal matrix and intraventricular hemorrhage, and white matter injury are frequently encountered,[1,2,3] while cerebellar injury is increasingly recognized.[4,5,6] These injuries are associated with later cognitive and motor impairment.[1,7,8,9,10,11,12,13]

White matter injury, also called periventricular leucomalacia (PVL) is one of the most frequently occurring forms of brain injury in infants born very prematurely.

Over the last years there has been a gradual change in incidence from cystic white matter injury to more diffuse white matter injury, where the majority of very preterm infants now show more subtle abnormalities of the developing white matter.[3,7,14,15]

Diffuse white matter injury is generally held responsible for the high incidences of cognitive and behavioural disorders in very preterm born infants.[1,2,8]

The two neuro-imaging modalities generally used in the neonatal period are cranial ultrasonography (CUS) and magnetic resonance imaging (MRI). CUS is safe, easily accessible, can be used on a serial basis and is reliable for detection of most forms of neonatal brain injury.[16] MRI is a safe and valuable tool to assess development and pathology of the very preterm infant's brain and gives detailed information on the exact location and extension of injury.[9,17,18,19,20] Advanced MR techniques such as diffusion tensor imaging (DTI) or volumetric analyses can detect axonal disturbances and volume loss resulting from diffuse white matter injury.

CT should only be used for specific limited indications in the neonate as it involves considerable radiation and generally will not provide more information than CUS and/or MRI.[16]

The aim of this article is to describe, in detail, the role and limitations of both widely accepted neonatal neuro-imaging modalities (CUS and MRI), with a specific focus on preterm white matter injury, the findings that can be encountered and the predictive significance of these findings.

White matter injury

The main pathogenic mechanisms for white matter injury in the very preterm neonate are ischemia and infection. These often coexist and may lead to focal or diffuse white matter injury and/or hemorrhages in the perinatal period due to the vulnerability of

Figure 1a. Cystic degeneration of white matter in the centrum semi-ovale (arrows) on axial T2-w MR image.

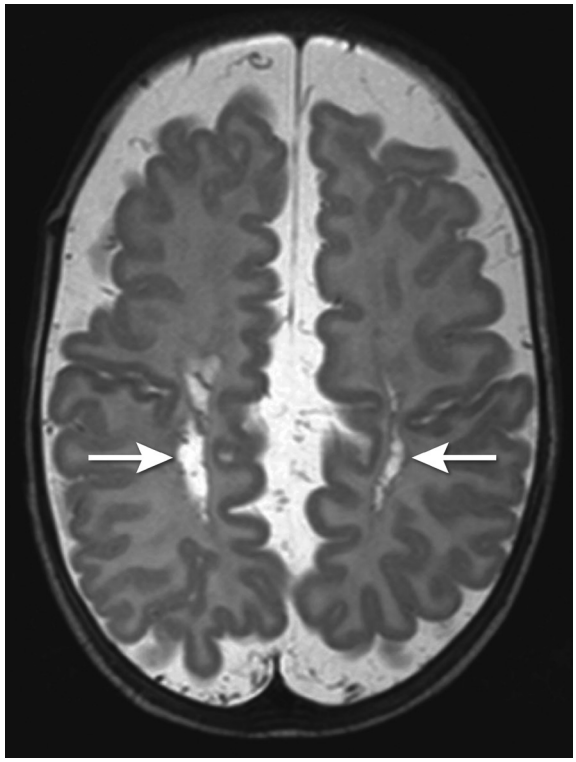


Figure 1b. Cystic periventricular leucomalacia (PVL) readily diagnosed (arrows) on a sagittal ultrasonography image.

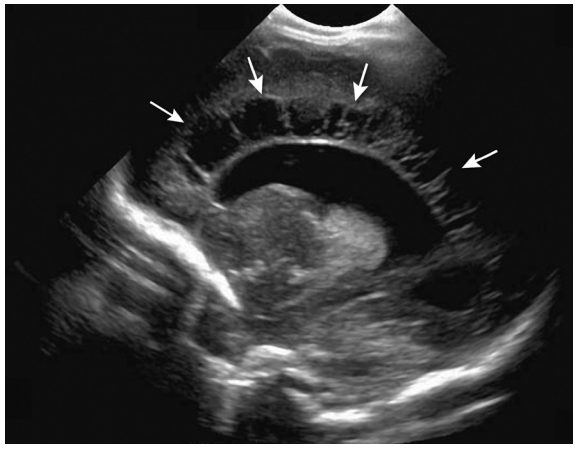
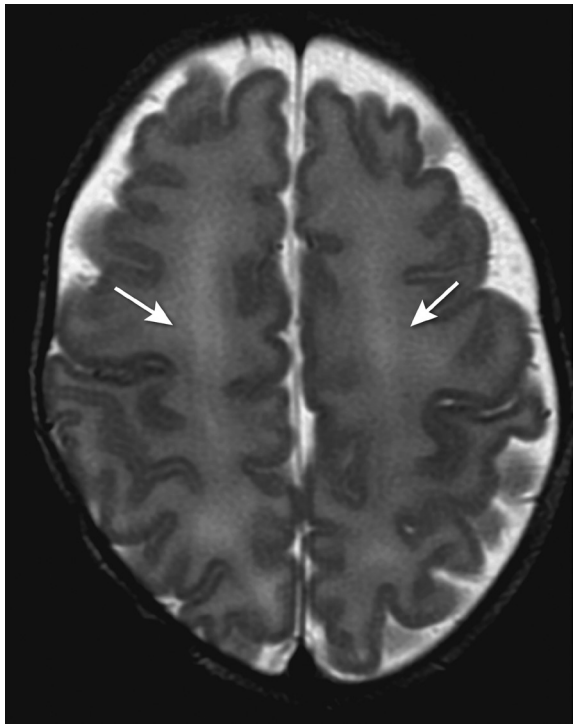


Figure 2. Diffuse white matter injury leading to hypomyelination and volume loss, resulting in widening of the pericerebral space. The arrows indicate the absence of myelination in the centrum semi-ovale in a very preterm infant imaged around term.



the developing white matter, immature vasculature and impaired cerebrovascular auto regulation of the immature brain.[2,21,22]

In focal white matter injury or cystic periventricular leucomalacia (Figure 1a and 1b) there is localized necrosis with loss of cellular elements that evolves over several weeks into macroscopic cystic lesions, readily visualized by both CUS and MRI. More commonly, the necrosis is microscopic in size and evolves into glial scars over several weeks. This more diffuse white matter injury accounts for the vast majority of cases.[2] The glial scars are characterized by astrogliosis and microgliosis. Damage to and significant decrease in premyelinating oligodendrocytes occurs.[2,21,23] Subsequently this leads to hypomyelination and cerebral white matter loss (Figure 2), resulting in decreased volumes of commissures, such as the corpus callosum.[24] The white matter injury will eventually also lead to grey matter loss and decreased volumes of the thalamus, basal ganglia, cerebral cortex, and cerebellum as early as term equivalent age, as a result of neuronal and axonal loss and abnormal connectivity.[2,7,23,25,26] Dif-

fuse non cystic white matter injury in itself is not readily depicted by neuro-imaging. The resulting volume loss can be identified by measuring the ventricular dilatation or by volumetric analysis of white and grey matter structures.[27,28] DTI studies have suggested axonal loss in the white matter of preterm infants at term equivalent age.[2,26,29,30,31,32,33]

Figure 3a. High echogenicity (arrows) of non physiological periventricular echo densities (PVE), as shown on a coronal ultrasonography image at the level of choroid plexus in the lateral ventricles in preterm infant with a gestational age of 31 weeks.

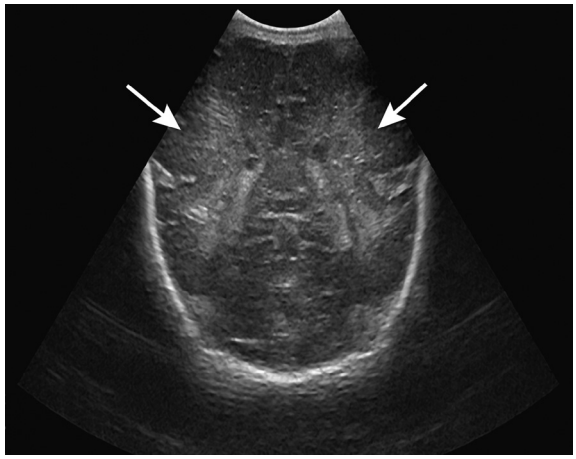
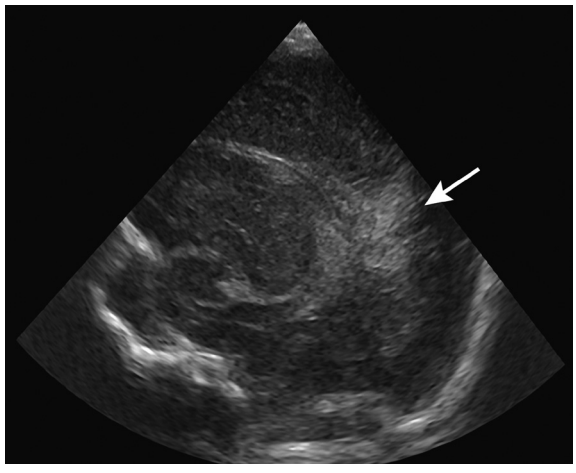


Figure 3b. Sagittal view in the same infant showing inhomogeneous PVE in the parietal white matter (arrow).



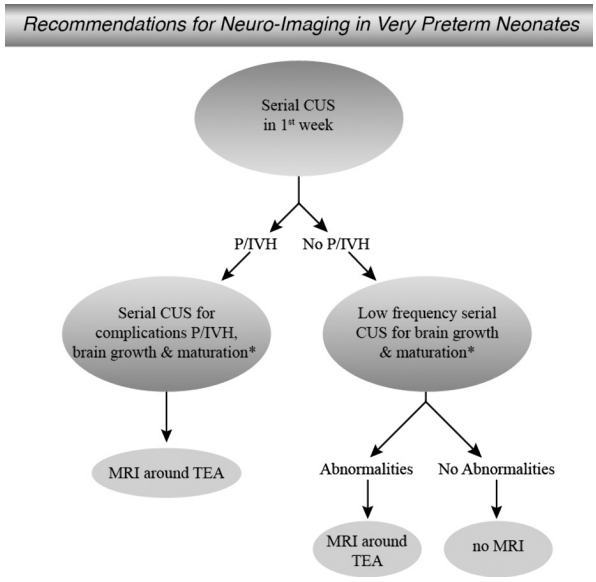
Imaging findings of white matter injury on CUS and MRI

Periventricular echo densities

On CUS, non-physiological periventricular echo densities (PVE) (Figures 3a and 3b) of the white matter are thought to reflect white matter injury. Their appearance is classified as homogeneous or inhomogeneous, and the echogenicity staged as grade one or two.[34] The more inhomogeneous and echogenic the PVE and the longer their duration, the more likely they present white matter injury. Presence of non-physiological PVE on CUS is predictive of abnormal white matter on MRI at term. However, absence of PVE does not predict normal white matter on MRI at term, but does predict a favorable outcome.[35] Presence of non-physiological PVE in itself is not associated with unfavorable short term outcomes.[35,36,37]

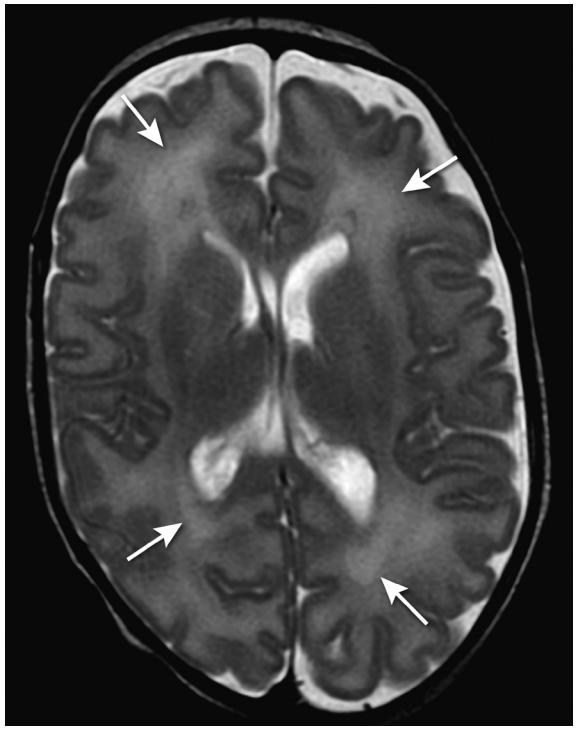
In a retrospective study, inhomogeneous PVE showed no association with punctate white matter lesions (PWML) on MRI.[38] The MRI or histological equivalent of inhomogeneous PVE remains unknown. The retrospective study by Leijser *et al*. showed that the performance of a MRI study before term equivalent age besides sequential CUS did not seem warranted in infants with mild to moderate abnormal white matter. Additional MRI only slightly increased the predictive value of CUS in severe white matter changes.[38] In our recent study on ultrasound detection of white matter injury and its practical implications we provided recommendations on performing serial CUS in all very preterm neonates during the perinatal period and a MRI at term equivalent age in some (Figure 4).[35]

Figure 4: Recommendations for neuro-imaging in very preterm neonates.



*Intensify if complications occur.
CUS = cranial ultrasonography,
P/IVH=peri/intraventricular hemorrhage,
TEA=term equivalent age.

Figure 5. Periventricular DEHSI (arrows) is now thought to be a developmental phenomenon rather than white matter injury.



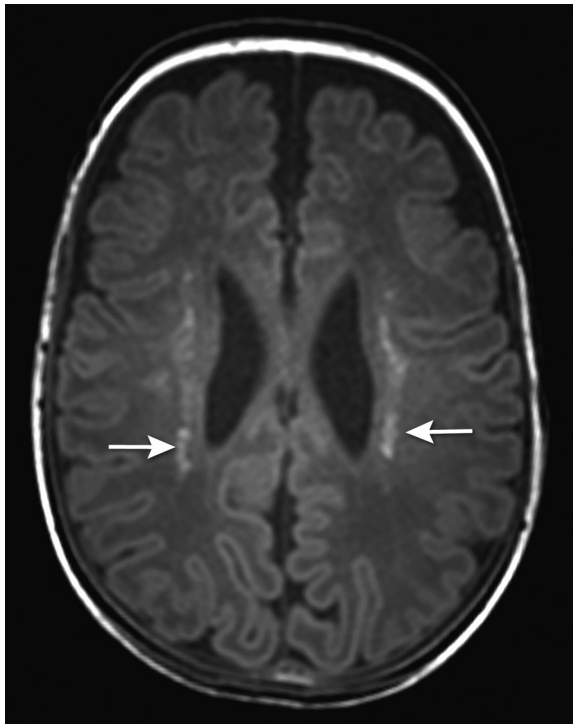
Diffuse excessive high signal intensity

Diffuse excessive high signal intensity (DEHSI) (Figure 5) on conventional T2-weighted (w) MRI has been described in the periventricular white matter in premature infants and is seen in the majority of these infants.[39,40,41] For a long time, it was thought to represent diffuse white matter injury on account of altered apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values compared with normal term born neonates.[31] However, this has recently been questioned by several authors.[41,42,43] It is now assumed that DEHSI represents a developmental phenomenon rather than white matter injury, because of its high incidence and the lack of association with short-term neurodevelopmental outcome.[41,44,45] So far, no histological equivalent of DEHSI has been found.

Punctate white matter lesions

Focal small punctate white matter lesions (PWML) (Figure 6) have been described as small areas with high signal intensity on T1-w MRI images and a less pronounced low signal intensity on T2-w MRI images.[46,47] These lesions can be differentiated from small

Figure 6. PWML (arrows) located in the deep white matter around the lateral ventricles are thought to represent more focal white matter injury.



hemorrhages by using gradient echo MRI techniques, which are susceptible to hemorrhages and blood break down products such as hemosiderin.[48]

PWML are thought to represent more focal white matter injury. There is no known histological correlate and the pathogenesis is not completely understood, although they may be the MR equivalent of astrogliosis.[40] Some PWML are hemorrhagic. If so, these lesions probably occur due to increased pressure in the medullary veins draining towards the ventricles, and represent small hemorrhagic venous infarctions.[48] In the acute phase, some of these lesions show diffusion restriction on diffusion weighted imaging (DWI) sequences compatible with small venous infarcts. In the perinatal period when these lesions occur, they can easily be missed on CUS.

Since PWML occur during the perinatal period and tend to fade and decrease in number over time, it is likely that the exact incidence of these lesions is underestimated at term equivalent age, the preferred age of MR imaging for most preterm infants to investigate the extent of white matter injury.[40] These focal PWML are associated with a poorer neurodevelopmental outcome.[41,46]

Neuro-imaging modalities used to depict white matter injury

Cranial Ultrasonography (CUS)

Serial CUS is very reliable for the detection of peri- and intraventricular hemorrhage and its complications (post-hemorrhagic ventricular dilatation and periventricular hemorrhagic infarction).[3,49] In addition, it is used to evaluate ventricular size, and the status of the basal ganglia and the white matter in very preterm neonates during the perinatal period.[16] Recent studies have shown that ultrasonography can reliably detect severe (cystic) white matter injury, but it is less reliable for the detection of mild or moderate white matter abnormalities.[50,51] Moreover, it has been shown that PVE of the white matter on ultrasonography can predict abnormal white matter on MRI at term equivalent age, but absence of PVE did not predict absence of white matter changes. Germinal matrix and intraventricular hemorrhages, on the other hand, were predictive of abnormal white matter on MRI and together with abnormal ventricular size or shape, were reasonably predictive of unfavorable outcome.[35]

Optimization of CUS to increase its accuracy and reliability, has been extensively described by our group.[16,49,52] However, even while using optimal protocols and a modern ultrasound system operated by an experienced ultrasonographist, CUS seems to underestimate diffuse white matter injury. As 25 - 50% of very preterm infants with diffuse white matter injury develop cognitive problems,[2] this may prompt the use of MRI around term equivalent age in these infants.[35]

Magnetic resonance imaging

MRI is becoming more widely available and increasingly important for neonatal brain imaging. It is safe and reliable, but poses challenges regarding patient preparation, safety and sequence optimization in neonates.[19] Compared to ultrasonography, it has the disadvantage of the necessity to transport the neonate from the neonatal intensive care unit to the radiology department. The development of MRI compatible incubators has largely overcome this disadvantage as patient preparation can now be performed in the neonatal intensive care unit and after transportation, the entire incubator can be placed into the MR scanner.[9]

In our hospital, all neonatal MRI examinations are performed using a 3T MRI system (Philips Medical Systems, Best, the Netherlands) according to a standard protocol for imaging the newborn infant's brain.[19] The infants are sedated using chloral hydrate (55mg/kg), lay supine and are swaddled during the scanning procedure. Ear protection consists of neonatal earmuffs (Natus Mini Muffs; Natus Medical Inc., San Carlos, CA, USA) covered by a headphone. All MRI examinations include a 3D T1-Turbo Field Echo

sequence (TR 9.7 ms, TE 4.6 ms, FOV 180 mm, matrix size 192x152, flip angle 8º, TFE factor 128, slice thickness 1 mm), a T2-Turbo Spin Echo sequence (TR 6269 ms, TE 120 ms, FOV 180 mm, matrix size 336x234, TSE factor 18, slice thickness 2 mm), a T2* Fast Field Echo sequence (TR 735 ms, TE 16 ms, FOV 230 mm, matrix size 256x163, flip angle 18º, slice thickness 4 mm) and a DWI sequence (SE-EPI in 3 directions, *b*-value of 1000 s/mm^2, TR 2406 ms, TE 64 ms, EPI factor 37, FOV 180 mm, matrix size 96x69, slice thickness 4 mm).

Frequently used MRI techniques

Most MRI sequences are performed to assess the development or injury of the brain in preterm infants. Specifically myelination can be assessed on T1-w and T2-w sequences. MRI can easily detect germinal matrix/intraventricular hemorrhages, periventricular hemorrhagic infarctions, cystic white matter lesions and PWML using T1-w, T2-w, T2*-w gradient echo and/or DWI sequences. White matter volume loss, resulting in increased pericerebral spaces, ventricular dilatation and thinning of the corpus callosum, can reliably be evaluated on T1-w and T2-w sequences. The grey matter volume loss, resulting from white matter injury can be recognized as a less complicated gyral pattern and lower volumes of the basal ganglia and/or thalami.

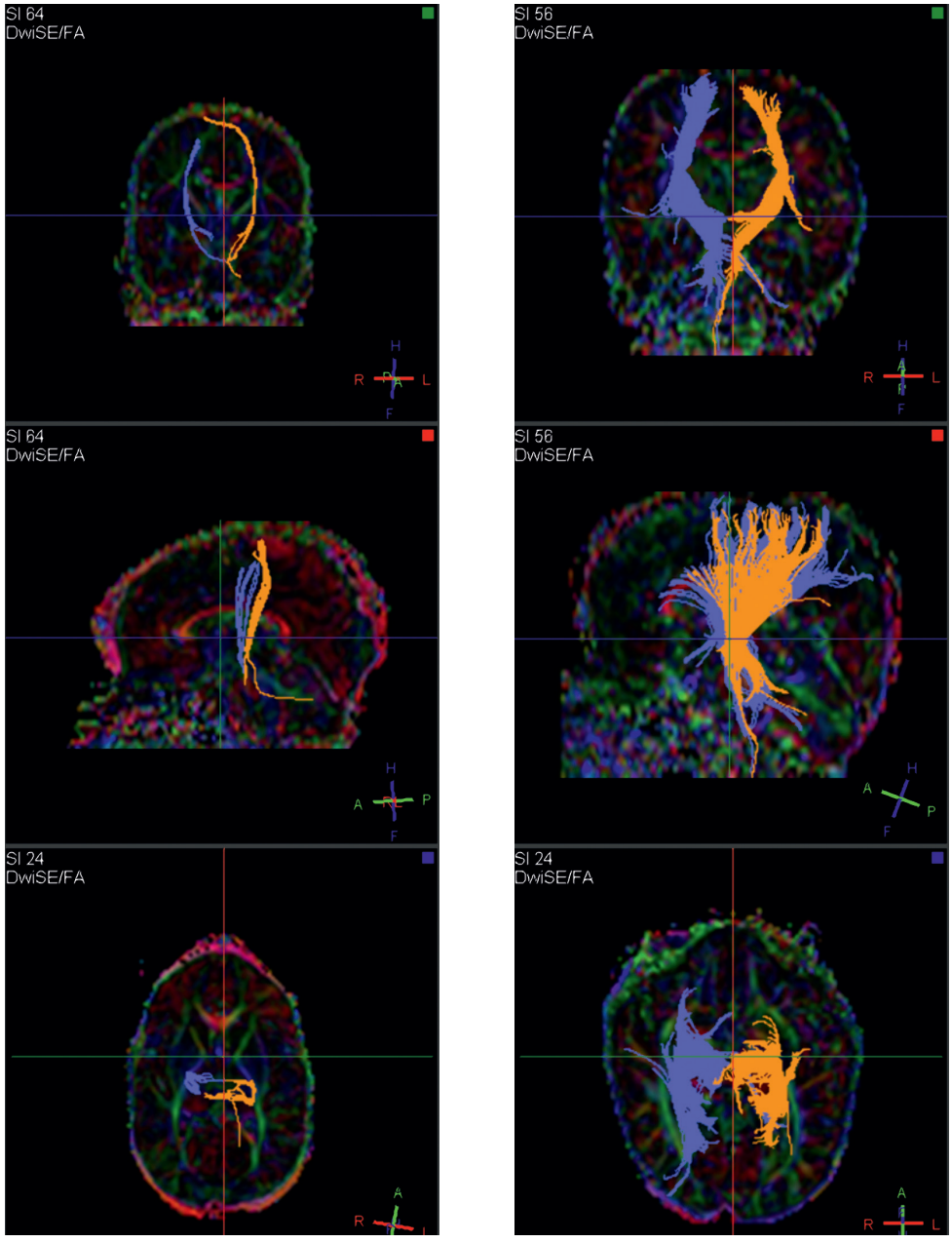
MRI obtained at term equivalent age in preterm infants has predictive significance, as parenchymal lesions such as hemorrhages, changes consistent with white matter injury, infarctions, hypomyelination and reduction of white matter volumes have been shown to be predictive of cognitive and motor delay and cerebral palsy at two years of age.[41,44,53] The combination of these different parenchymal lesions adds up to predict an adverse outcome in most preterm infants with severe white matter lesions, but prognosis is less certain in infants with mild or moderate white matter lesions, which occurs in the majority.[54]

Advanced MRI techniques

DTI has been proposed as an additional tool in the assessment of white matter injury in preterm infants and may provide more adequate diagnostic and predictive information in relation to neurological outcome than other MR techniques.[55,56] DTI describes the diffusion of water molecules in tissues and reflects the direction of the underlying microstructure. In DTI, diffusion is measured in at least six diffusional directions, while in DWI, diffusion is measured in only three perpendicular directions. Contrast is based on the Brownian motion of water molecules, which is influenced by various factors including fibre orientation, integrity of the cell membranes and the degree of myelination. DTI can be used to assess cerebral development and connectivity by calculating diffusivity values.[55,57]

Figure 7. (left) Fibers passing through the posterior limb of the internal capsule in a preterm infant imaged at a postmenstrual age of 40 weeks.

Figure 8. (right) Preterm infant imaged at a postmenstrual age of 62 weeks shows an increase in length and number of fibers passing through the posterior limb of the internal capsule as a result of brain maturation and development.



The physical constant characterizing water molecule displacement is called the apparent diffusion coefficient (ADC) or mean diffusivity (MD). In very preterm infants the ADC of the white matter is high due to the high water content of the immature brain. When the brain further matures the ADC will decrease.[55] ADC values may be abnormal in infants with brain injury or abnormal brain development.[58]

While the axons in the developing brain organise and myelinate the displacement of water molecules, as described by the fractional anisotropy (FA) value, is most restricted in the perpendicular direction and least restricted parallel to the myelinating fibres. The maturation of white matter is accompanied by an increase in anisotropic diffusion and thus in FA.

Fibre tractography offers insight into developing white matter by visualisation of the white matter tracts (Figure 7 and 8).[55,59,60,61,62,63]

Diffusion parameters at term equivalent age have only been scarcely studied in relation to neurodevelopmental outcome and have shown an association between lower FA values in the posterior limb of the internal capsule and higher ADC values in the splenium of the corpus callosum at term, and motor delay around two years of age.[64,65] DTI values at term equivalent age may help further prediction of neurodevelopmental outcome at two years. In combination with clinical parameters and white matter injury seen on T1-w and T2-w MRI, specificity further increases.

Over the last decade, numerous MRI techniques have been proposed to measure brain volumes in the very preterm infant as a measure of brain development and injury. Segmentation techniques for grey matter, unmyelinated and myelinated white matter, and cerebrospinal fluid have been developed.[28,66] However, in daily clinical practice, their use is not feasible and the relation with neurodevelopmental outcome has not been studied extensively. Linear measurements have been developed and validated in the preterm infants' brain and can be applied manually to 2D and 3D datasets.[67]

The utility of MR spectroscopy for risk-stratifying preterm infants in relation to long term adverse outcome is not well established. There are difficulties concerning the use of this technique, such as age related differences in metabolites, as measured by MR spectroscopy in the perinatal and early childhood period.[68] MR spectroscopy has not been found to be a good predictor of outcome in preterm infants at the age of 18 to 24 months.[69]

Future perspectives

Development of brain functions and the structural-functional correlates of brain injury remain difficult to evaluate in preterm infants. MRI at term equivalent age better depicts diffuse white matter injury in very preterm infants than ultrasonography. Combined grading of white matter injury and advanced (quantitative) MRI techniques, such as DTI, help to predict adverse neurodevelopmental outcome.[54] However, most very preterm infants show mild to moderate diffuse white matter injury, and in this group, prediction of outcome remains uncertain. Whole brain statistical methods developed for neonatal DTI analysis, such as optimized tract-based spatial statistics[70] and atlas-based analysis,[71] might have the potential to detect mild to moderate white matter injury related to the neurological outcome. Another quantitative MR technique to evaluate brain development and possibly brain injury in preterm infants is magnetization transfer imaging, which can be used to evaluate myelination.[72] Magnetization transfer is a MR imaging phenomenon based on the interaction between immobile protons in macromolecules and free water protons of tissue. A magnetization transfer ratio is obtained by calculating the percentage difference between two images, one with and one without an off-resonance radio frequency pulse.[73] Magnetization transfer ratio provides a reproducible measurement sensitive to myelination and thus an index to brain maturation.[74]

Functional resting state MRI may be a new non invasive technique to assist evaluating early life brain function and its recovery from injury.[75,76] This technique is based on data analysis applied to functional MRI, revealing patterns of interconnections between neural networks. Resting state networks have been identified in preterm infants.[77,78,79] Additional research is necessary to determine the clinical utility of resting state functional connectivity analyses and the potential for the method to reveal the anatomical substrate for cognitive deficits in preterm infants who do not appear to have abnormalities on other imaging techniques.[68]

Conclusion

Long term clinical follow up remains necessary to further evaluate the predictive values of certain neuro-imaging findings and quantitative values around term equivalent age, especially for cognitive neurodevelopmental outcome in very preterm neonates.

Advanced techniques, such as DTI, magnetization transfer imaging, functional

resting state MRI and volumetric methods are still under active investigation. Serial MRI and the application of these newer analysis techniques will provide insights into the trajectories of brain development and the impact of injury on the development.[9]

Executive summary

White matter injury

- White matter injury occurs frequently in very preterm neonates.
- White matter injury seems to be one of the main determinants for a poorer neurodevelopmental outcome in very preterm infants.
- White matter injury results in hypomyelination, underdevelopment of white matter tracts, grey matter and commissures.

Imaging findings of white matter injury on CUS and MRI

- Diffuse white matter injury is a common finding on MRI in preterm infants but is not reliably detected by ultrasonography.
- It is now assumed that DEHSI represents a developmental phenomenon rather than white matter injury, as there is no association with short-term neurodevelopmental outcome.

Advanced MRI techniques

- DTI quantifies development and injury to the white matter.
- Abnormal DTI values around term equivalent age in preterm infants predict psychomotor delay.

Future perspectives

- Long term follow up is necessary to further evaluate the predictive value of MRI findings at term equivalent age for especially cognitive neurodevelopmental outcome.
- Serial MRI and the application of newer analysis techniques will provide further insights into the trajectories of the developing and injured brain in the very preterm infant.

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