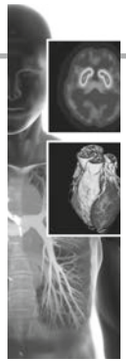

Radiological assessment of white matter injury in very preterm infants

Despite improvements in neonatal care, infants born very prematurely who survive the neonatal period are still at risk of 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 care takers with prognostic 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.

KEYWORDS: cranial ultrasonography ■ MRI ■ prognostication ■ very preterm infants ■ white matter injury

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

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

Over the last few 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 incidence of cognitive and behavioral disorders in very preterm born infants [1,2,8].

The two neuroimaging modalities generally used in the neonatal period are cranial ultrasonography (CUS) and MRI. CUS is safe, easily accessible, can be used on a serial basis and is reliable for the 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 [9,17–20]. 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 neuroimaging modalities (CUS and MRI), with a specific focus on preterm white matter injury, the findings that can be encountered and the prognostic 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 the developing white matter, immature vasculature and impaired cerebrovascular autoregulation of the immature brain [2,21,22].

In focal white matter injury or cystic periventricular leucomalacia (Figure 1), 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

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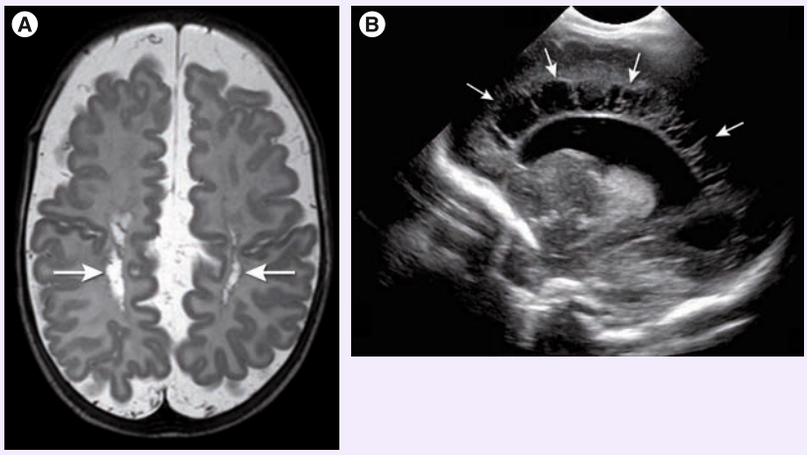

Figure 1. Focal white matter injury. (A) Cystic degeneration of white matter in the centrum semi-ovale (arrows) on axial T2-weighted magnetic resonance image. **(B)** Cystic periventricular leucomalacia readily diagnosed (arrows) on a sagittal ultrasonography image.

(Figure 2), resulting in decreased volumes of commissures, such as the corpus callosum [24]. The white matter injury will eventually also lead to gray 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]. Diffuse noncystic white matter injury in itself is not readily depicted by neuroimaging. The resulting volume loss can be identified by measuring the ventricular dilatation, or by volumetric analysis of white and gray matter structures [27,28]. DTI studies have suggested axonal loss in the white matter of preterm infants at term equivalent age [2,26,29–33].

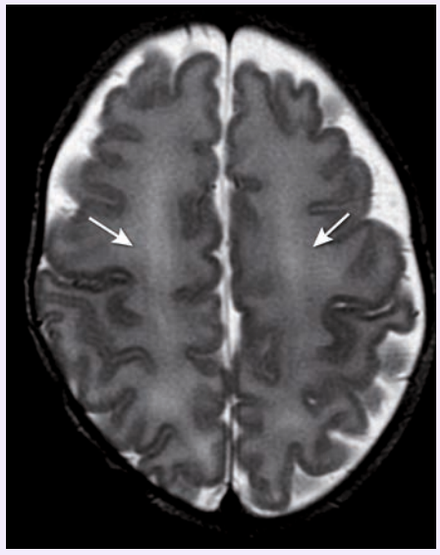

Figure 2. Diffuse white matter injury leading to hypomyelination and volume loss, resulting in widening of the pericerebral space. The arrows indicate the absence of myelination in the centrum semi-ovale in a very preterm infant imaged around term.

Imaging findings of white matter injury on CUS & MRI

■ Periventricular echodensities

On CUS, nonphysiological periventricular echodensities (PVE) (Figure 3) 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 it is that they present white matter injury. Presence of nonphysiological 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, but does predict a favorable outcome [35]. Presence of nonphysiological PVE in itself is not associated with unfavorable short-term outcomes [35–37].

In a retrospective study, inhomogeneous PVE showed no association with punctate white matter lesions (PWMLs) 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, the authors provided recommendations for performing serial CUS in all very preterm neonates during the perinatal period and a MRI at term equivalent age in some (Figure 4) [35].

■ 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 [39–41]. 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 [41–43]. It is now assumed that DEHSI represents a developmental

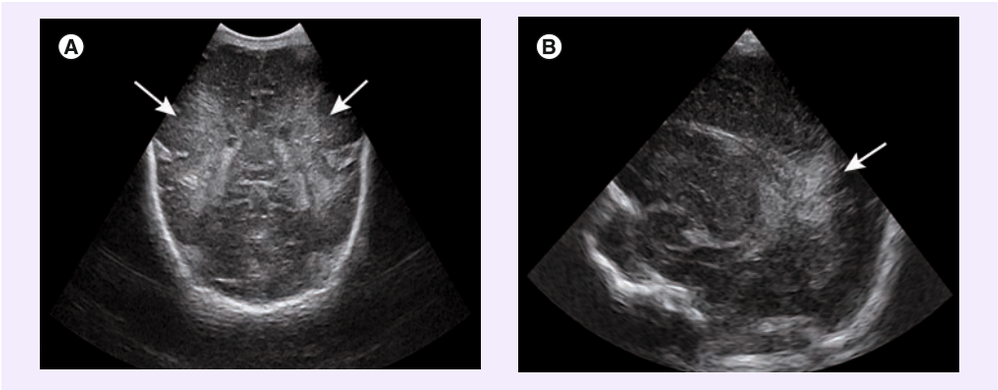

Figure 3. White matter injury on cranial ultrasonography. (A) High echogenicity (arrows) of nonphysiological periventricular echodensities, as shown on a coronal image at the level of choroid plexus in the lateral ventricles in a preterm infant with a gestational age of 31 weeks. **(B)** Sagittal view in the same infant showing inhomogeneous periventricular echodensities in the parietal white matter (arrow).

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 lesion

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

PWMLs 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 PWMLs 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 PWMLs 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 MRI for most preterm infants to investigate the extent of white matter injury [40]. These focal PWMLs are associated with a poorer neurodevelopmental outcome [41,46].

Neuroimaging modalities used to depict white matter injury

■ Cranial ultrasonography

Serial CUS is very reliable for the detection of peri- and intra-ventricular hemorrhage and its complications (posthemorrhagic 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

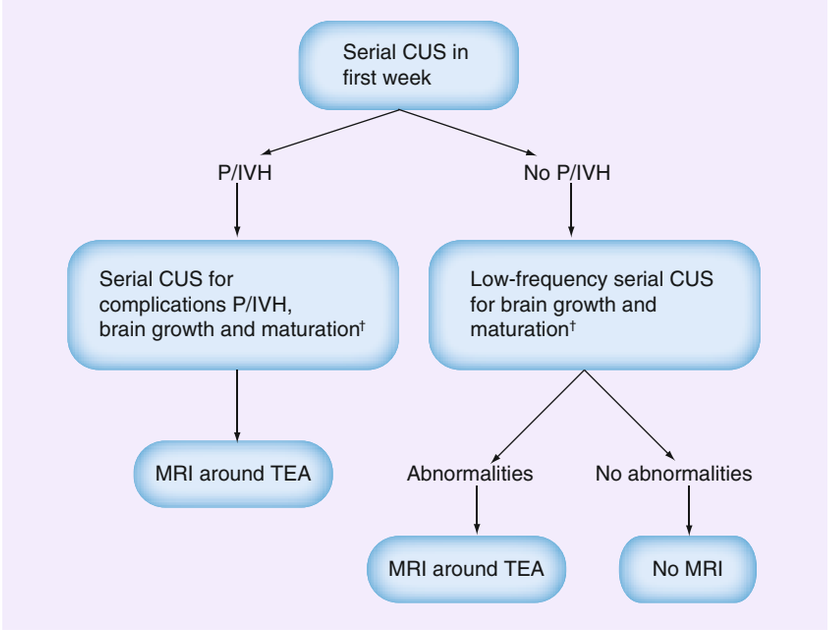

Figure 4. Recommendations for neuroimaging in very preterm neonates.
†Intensify if complications occur.
CUS: Cranial ultrasonography; P/IVH: Peri/intraventricular hemorrhage; TEA: Term equivalent age.

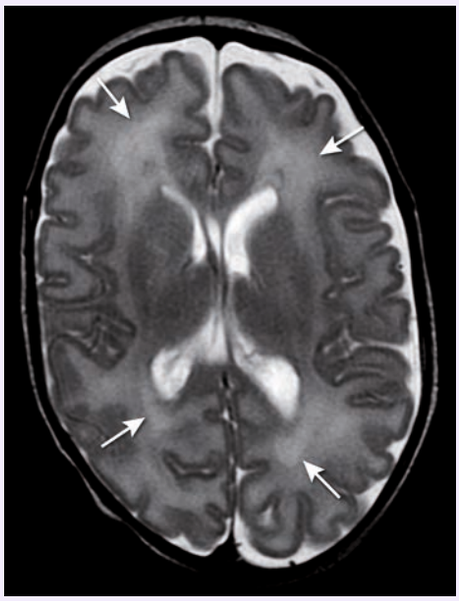

Figure 5. Periventricular diffuse excessive high signal intensity (arrows) is now thought to be a developmental phenomenon rather than white matter injury.

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 an unfavorable outcome [35].

Optimization of CUS to increase its accuracy and reliability has been extensively described by the authors' 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].

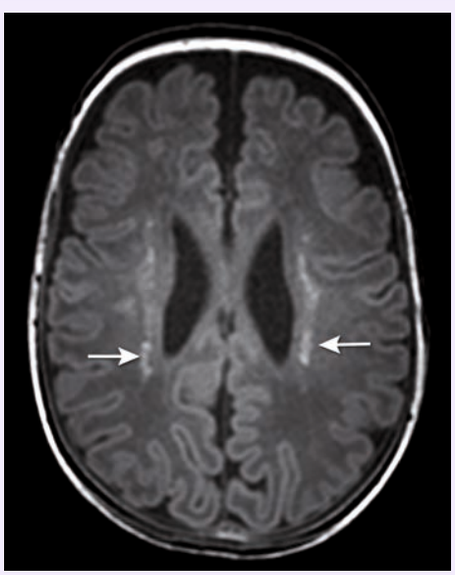

Figure 6. Punctate white matter lesions (arrows) located in the deep white matter around the lateral ventricles are thought to represent more focal white matter injury.

■ MRI

MRI is becoming more widely available and is 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 with 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].

At the Leiden University Medical Center, 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 (55 mg/kg), lay supine and are swaddled during the scanning procedure. Ear protection consists of neonatal earmuffs (Natus Minimuffs®; Natus Medical Inc., 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 192 × 152, flip angle 8°, TFE factor 128, slice thickness 1 mm), a T2-Turbo Spin Echo sequence (TR 6269 ms, TE 120 ms, FOV 180 mm, matrix size 336 × 234, TSE factor 18, slice thickness 2 mm), a T2* fast field echo sequence (TR 735 ms, TE 16 ms, FOV 230 mm, matrix size 256 × 163, flip angle 18°, slice thickness 4 mm) and a DWI sequence (SE-EPI in three directions, b-value of 1000 s/mm^2, TR 2406 ms, TE 64 ms, EPI

factor: 37, FOV: 180 mm, matrix size: 6 × 69, 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 MRI 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 be reliably evaluated on T1-w and T2-w sequences. The gray 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 prognostic 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 2 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 prognostication is less certain in infants with mild or moderate white matter lesions, which occurrs 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 prognostic 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 fiber orientation, integrity of cell membranes and degree of myelination. DTI can be used to assess cerebral development and connectivity by calculating diffusivity values [55,57].

The physical constant characterizing water molecule displacement is called the ADC or mean diffusivity. 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 organize and myelinate, the displacement of water molecules, as described by the FA value, is most restricted in the perpendicular direction and least restricted parallel to the myelinating fibers. The maturation of white matter is accompanied by an increase in anisotropic diffusion and thus in FA.

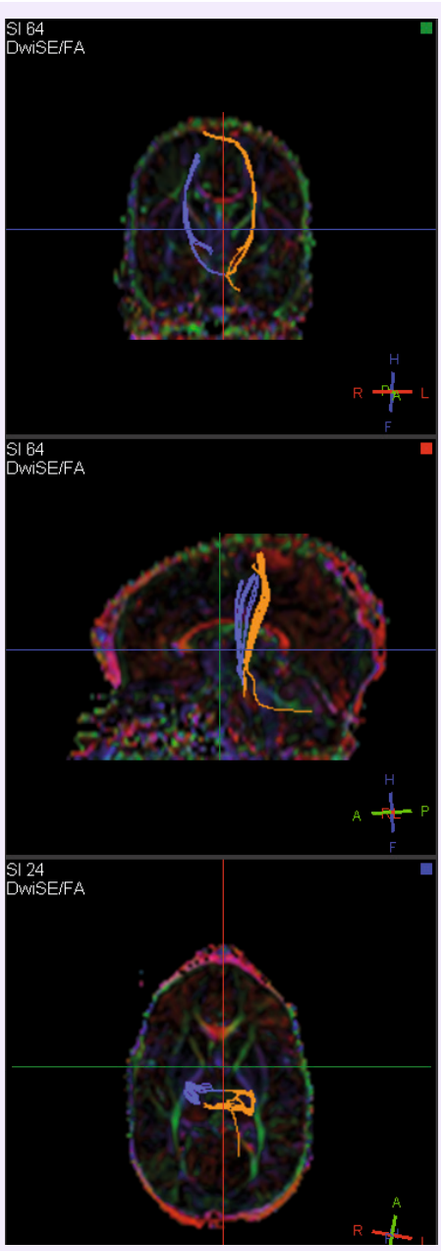

Figure 7. Fibers passing through the posterior limb of the internal capsule in a preterm infant imaged at a postmenstrual age of 40 weeks.

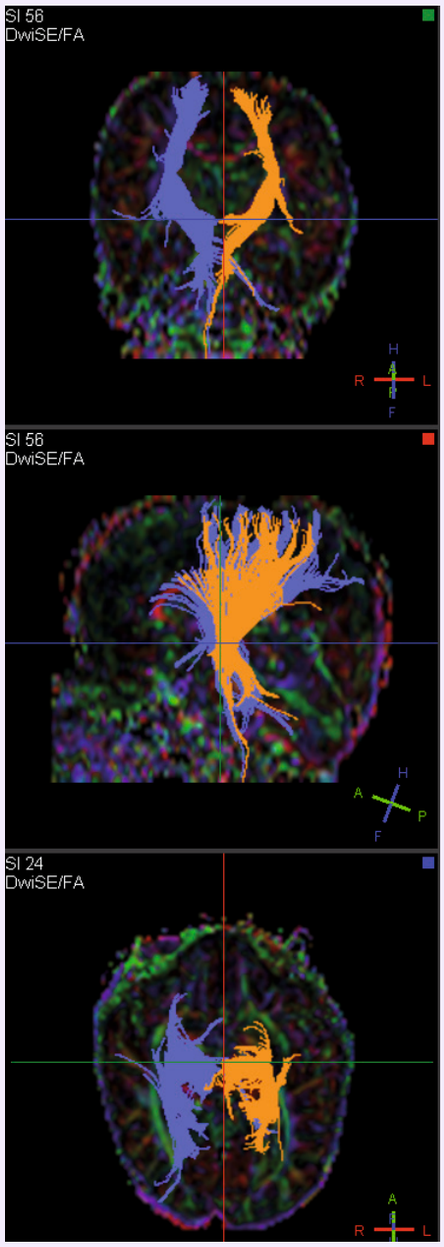

Figure 8. Preterm infant imaged at a postmenstrual age of 62 weeks showing an increase in length and number of fibers passing through the posterior limb of the internal capsule as a result of brain maturation and development.

Fiber tractography offers insight into developing white matter by visualization of the white matter tracts (Figures 7 & 8) [55,59–63].

Diffusion parameters at term equivalent age have only scarcely been 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 2 years of age [64,65]. DTI values at term equivalent age may help further prognostication of neurodevelopmental outcome at 2 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 gray 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 to 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 data sets [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 18–24 months [69].

Conclusion

Long-term clinical follow-up remains necessary to further evaluate the prognostic values of certain neuroimaging 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].

Future perspective

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

prognosticate 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 noninvasive 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 [77–79]. 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].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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, gray matter and commissures.

Imaging findings of white matter injury on cranial ultrasonography & 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 diffuse excessive high-signal intensity represents a developmental phenomenon rather than white matter injury, as there is no association between diffuse excessive high signal intensity and short-term neurodevelopmental outcome.

Advanced MRI techniques

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

Future perspective

- Long-term follow-up is necessary to further evaluate the prognostic value of MRI findings at term equivalent age, especially for 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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