MR imaging of brain maturation

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Abstract Magnetic resonance imaging (MRI) is the imaging tool of choice to evaluate brain maturation and especially brain myelination. Magnetic resonance imaging also provides functional insight through diffusion images and proton spectroscopy. In this review the MRI techniques are analyzed for both pre- and postnatal periods. The origin of MR signal changes is also detailed in order to understand normal myelination evolution and the consequences on brain maturation of the different pathologies encountered prior and after birth. Because MRI is “blind” in terms of signal on conventional sequences after 2 years of age, a particular attention is given to diffusion images and proton spectroscopy of the developing brain.

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Introduction

Numerous events are involved in brain maturation, some of which being detected by neuroimaging. Major changes in brain morphology are depicted by brain imaging during fetal period while changes in brain composition can be demonstrated in both pre- and postnatal periods. Metabolic changes are also part of brain maturation and are assessed by proton spectroscopy. Maturation of the brain begins in the second trimester and continues progressively to reach an adult-like pattern at approximately 2 years of age. Consequences of brain maturation are characterized by different windows of brain vulnerability and different diseases in infants and neonates compared to older children and adults. Although ultrasonography (US) and computer tomography (CT) can show the changes in brain morphology, these techniques are insensitive to myelination that is one of the most important events occurring during brain maturation. Magnetic resonance imaging (MRI) is currently the method of choice to evaluate brain maturation \[3,5,6,14,18,32-34,83,89,92\].

MRI techniques

The most important factor in obtaining high quality MR images is adequate sedation in young children, which can be obtained by sedation or general anesthesia. In neonates, sedation is generally not necessary because immobility can be obtained by tightly packing the baby.

Conventional sequences

Parameters of the MR sequences have to be adapted to the brain composition of young infants especially for T2 WI. Indeed the T1 values of brain structures are much higher than those seen in adults (Fig. 1), so that longer repetition time (TR) and echo-time (TE) of T2-weighted images are necessary to adequately evaluate brain maturation compared to older children and adult \[32,33\]. Heavily T2-weighted sequences are used in infants less than 12 months old. Fast spin-echo techniques are known to provide similar information on myelination in a shorter time than the conventional spin-echo sequences \[83\].

Fluid attenuated inversion recovery (FLAIR) sequences are considered highly efficient to look for regions of abnormal T2 prolongation. However, in young infants FLAIR images are not very helpful to evaluate normal brain maturation. Indeed, white matter appearance follows peculiar steps: in neonates the white matter is of low signal intensity as on T1 WI, then of high signal intensity in infants less than 6 months old. Three-dimensional GE T1 weighted sequence is also used in older infants allowing 1 mm contiguous slices, which can be reconstructed in any anatomic plane.

Inversion recovery sequences are also used for T1-weighted images and give excellent images of brain anatomy and maturation, and show accurately the differentiation between myelinated and unmyelinated white matter.

Diffusion images

Diffusion-weighted images (DWI) are used mostly to look for pathology such as hypoxic-ischemic changes. However, DWI is extremely useful to show brain maturation especially in the fetal, neonatal and infant period: myelination process in white matter tracts is detected before conventional T1 and T2 sequences \[17,18,29,33,82,89\]. The sequence used is an EPI sequence with b values (0, 500, and 1000) in order to obtain the apparent diffusion coefficient (ADC) map (Fig. 3).

Proton MR spectroscopy

Proton MR spectroscopy \(^{1}H\text{-MRS}) can also be used to assess brain maturation \[53,54,64,71,93\]. Monovoxel technique and PRESS sequences with short and long TE are used routinely at our institution. Parameters of the short echo sequence are characterized by a TR of 1500 ms, a TE of 30 ms, 128 acquisitions leading to an acquisition time of 2 min 52 s. Parameters of the long echo sequence are characterized by a TR of 1500 ms, a TE of 135 ms, 192 acquisitions with an acquisition time of 3 min 14 s. Peaks of N-acetylaspartate (NAA) and total creatine (tCr) are increasing along with brain maturation whereas choline-containing compounds (Cho) and myo-inositol (mi) peaks are decreasing.

Imaging techniques in utero

Although ultrasonography is currently still considered as the primary imaging method for routine examination of the fetal brain, MRI is highly accurate in illustrating the morphological changes of the developing brain as well as fetal brain abnormalities and thus constitutes a useful procedure when ultrasonography is inconclusive \[7,15,17,20,29,33-43,51,52,75,85,98\]. Magnetic resonance imaging indications are becoming more numerous during pregnancy because of the development in fast imaging techniques and of the safety of fetal MRI that has been highlighted since experimental studies did not show side effects for the embryo. As a consequence, brain abnormalities can be detected as early as possible during the pregnancy. Ultrasound is usually sufficient to ensure an accurate diagnosis of brain abnormality before week 18-20 so that in vivo MRI is usually performed during the second half of gestation (from 18th weeks onwards). Indeed, below 18-20 weeks, MRI limitations are essentially due to normal brain anatomy with underdeveloped cerebral parenchyma and large ventricles so that it is not possible to detect subtle changes in the white matter.

Preparation of the mother

Sedation of the mother is not always necessary along with the improvement of T2-weighted sequences that can be obtained in 30 s or less. However, T1-weighted images of good quality require longer sequences (from 1 to 3 mins),
Figure 1  T1 (A, C) and T2 (B, D) values of normal white and grey matter in neonates, on a 1 Tesla magnet. T1 values of the CNS in neonates are long so that longer TR and TE are needed to evaluate maturation in infants than in adults.

Figure 1  Les valeurs de T1 (A, C) et de T2 (B, D) du système nerveux central chez le nouveau-né étant plus longues, le TR et le TE doivent être allongés pour une évaluation optimale de la maturation chez l’enfant par rapport aux valeurs de l’adulte (résultats obtenus avec un aimant 1 Tesla).

Figure 2  White matter appearance on FLAIR images. Flair images at 7 days (A), 7 months (B), 14 months (C), 3 years (D). The white matter shows low signal in the neonate as on T1 WI, then is turning white in infants and the young child as the unmyelinated white matter on T2 WI, and then is reaching the mature aspect of low signal at 3-4 years of age.

Figure 2  Évolution de l’aspect de la substance blanche en imagerie FLAIR. Imagerie FLAIR à sept jours (A), sept mois (B), 14 mois (C), trois ans (D). La substance blanche est de basse intensité à la naissance tout comme en pondération T1, puis révèle une intensité élevée chez le nourrisson et l’enfant en bas âge, tout comme la substance blanche non myélinisée en pondération T2. Elle redevient finalement de faible intensité en approchant un niveau de maturation adulte vers 3-4 ans.

Figure 3  Diffusion (A), ADC map (B), T1 (C) and axial T2 WI (D) in a neonate 31 weeks old. The posterior limbs of the internal capsule display a bright signal on diffusion image and low signal on ADC map. The signal changes are not yet seen on T1 and T2 WI.

Figure 3  Image de diffusion (A), carte ADC (B), T1 (C) et T2 axial (D) chez un nouveau-né de 31 semaines. Le bras postérieur de la capsule interne révèle un hypersignal en imagerie de diffusion et un hyposignal sur la carte ADC. Une altération du signal n’est encore détectable ni en pondération T1 (C), ni en pondération T2 (D).
so that sedating the mother is sometimes necessary in order to obtain a complete evaluation of the brain including T1- and T2-weighted images as in the neonatal period. However, in breech presentation or transverse lie position, the fetal head move with the mother’s breathing. Fetal sedation is obtained by maternal premedication with flunitrazepam administered orally 15 mm to 1 h before the MR examination.

Image quality

Image quality can be deteriorated in utero by a low signal-to-noise ratio related to the coil used, and ultimately depend from the fetal position and the fetal movements. As opposed to the neonatal period, there is no coil devoted to the fetal brain itself. Images are obtained through a body coil alone or in combination with a surface coil. Consequently, high resolution MRI (e.g. 3D T1-weighted acquisition with 1 mm thickness sections) is not available in utero as opposed to the neonatal period. On the other hand, 3D T2-weighted sequence (TRUE FISP sequence) is available in utero allowing 1 mm thick contiguous sections, which are extremely helpful in evaluating the midline anatomy as well as the cortical sulcation.

Conventional sequences

Images are obtained routinely in sagittal, coronal and axial planes relative to the fetal head with both T1- and T2-weighted sequences.

Regarding T1 WI, gradient echo images (FLASH sequence i.e. Fast Low Angle Shot) are used in our experience because of excellent differentiation between the cortical ribbon, the white matter, and the ventricular walls as opposed to TSE images.

Regarding T2 WI, half-fourier single shot turbo spin-echo (HASTE) images are obtained routinely. HASTE images are available only with magnet of high gradient strength and are acquired much more quickly than TSE images: about 2 s for each slice, with a total of 30 s for 15 slices. Images obtained from HASTE sequence are true T2-weighted images with low susceptibility weighting and sequential slice capability. This last advantage improves the management of fetal movement. The low susceptibility is in one way an advantage giving a very high contrast of the layering of the developing brain; on the other way it is a disadvantage because of the difficulty in depicting old hemorrhage.

Other types of sequence can be run in particular conditions: angiographic images are obtained in our institution by a sequential 2D FLASH sequence, which allows a good compromise between vascular and tissue contrast; inversion recovery images allow a very good delineation of the cortical ribbon, of the extracerebral spaces and consequently of the lesions developed from the subarachnoid spaces.

Diffusion images

Diffusion images (echo-planar images) can also be performed [86,90] such as in the neonatal period to detect cytotoxic and/or vasogenic edema [18,19]. However, the acute response of the fetal brain is not as common as in the neonatal brain response [17,86]. On the other hand, the T2 diffusion (or B0) images are extremely useful especially in detecting old hemorrhage. Diffusion images also have the capacity to show premyelinating tracts. The sequence used in utero is similar to that of the postnatal period with 3 b values and ADC map.

Proton MR spectroscopy

A potential role of proton spectroscopy exists in utero. Although the feasibility of fetal brain spectroscopy has been already demonstrated [49,62,63], metabolic mapping of the fetal brain at different gestational ages from 18 to 40 weeks is still needed [43-45]. However, proton spectroscopy will possibly be highly efficient in demonstrating white matter metabolic changes such as in gliosis, which is currently not detectable on MR images. From a technical point of view proton spectroscopy is more difficult to perform in utero compared with the postnatal period because the coils used are not devoted to the brain (body phased array coils used in combination with spinal coils). Number of acquisitions is increased to get enough signals in the spectra leading to an acquisition time of 6 min 30 s for each sequence with short and long echo-time. Acquisition time is almost twice as long compared to the postnatal period.

MRI of brain maturation and origins of MR signal

Brain maturation is characterized by changes in brain morphology and in brain composition (Fig. 4).

Brain morphology

Changes in brain morphology include the increase in brain volume and weight, the changes in surface configuration, which are due to the developing sulcation, the changes in ventricular shape, and the decrease in volume of the subarachnoid spaces [15,28,34,35,38,40,50,69]. These changes are mostly seen during the fetal period and are well illustrated by fetal brain MRI (Fig. 5).

Brain weight is increasing dramatically during the fetal period and brain growth from mid-gestation through infancy is considered to reflect synaptogenesis, dendritic arborization and spine formation, axonal elongation and collateral formation, myelination, gliogenesis, neurotransmitter development, and vascular development.

The lateral cerebral ventricles are large in young fetuses (Fig. 4a,d) corresponding to the so-called “relative fetal hydrocephalus”, especially at the level of the atrium, which is also known as “colocephaly”. The ventricular size is quite constant throughout pregnancy from 14 to 40 weeks and the normal ventricular size at the atria level on the axial plane is known to be of 7.6 ± 0.6 mm from ultrasound (US) studies. The upper limit generally admitted is of 10 mm.

The subarachnoid spaces are also prominent in young foetuses (Figs. 4a,d and 5). Decrease in volume is seen from 30 weeks onwards. However, prominence of the subarachnoid spaces still persists in some fetuses at the parieto-occipital level; it can be associated with mild un-
or bi-lateral ventriculomegaly and these aspects are thought to reflect the vacuolization of the primary meninges which is known to occur from ventral to dorsal and posterior to anterior leading to posterior accumulation of cerebrospinal fluid (CSF) [39].

Sulcation is changing dramatically from 18 to 34 weeks, going from an agyric brain to a convoluted pattern (Fig. 5). The more significant sulci marking appear as follow — the parieto-occipital fissure is well shaped and already present at week 18 — the calcarine fissure is starting to fold at week 24 and shows its definite horizontal “Y” shape at week 30 — the central sulcus is seen at the surface of the brain at week 24, is reaching in depth half of the cerebral hemisphere at week 28-29 and shows its classical orientation and depth at week 34-35 — the callosomarginal fissure shows its definite shape at week 27-28 — the pre- and post-central sulci are identified at the surface of the brain at week 27 and are deep at week 35-35 — the first temporal sulcus is identified at week 28 — the superior frontal sulcus is deep at week 32. Gyration has almost its definitive shape by week 34-35. The sylvian fissure is the last to be achieved and is depending upon the development of the frontal and temporal operculum.

**Brain composition**

Changes in brain composition are characterized by changes in cellular density, increase in complex lipids content due to the evolving process of myelination, decrease in water content mostly in the white matter, developing fiber network both in the white matter and cortex, neurotransmitters and neurotransmitters-receptors interactions [1,2,5,6,10,11,13,21-27,30-32,46,47,55,59-61,66,67,70,73,84,87,88,91,94,96,97].

The effects on the MR signal are a shortening of T1 (bright signal on T1 WI) and a shortening of T2 (dark signal on T2 WI) (Fig. 4). Primary mechanisms responsible for these effects are the water content, the cellular density and the MR properties of lipids. The most rapid changes in myelination occur between mid-gestation and the second

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**Figure 4** Cerebral appearance on T1 WI (A, B, C) and T2 WI (D, E, F) at 22 weeks of gestation, 15 days and 5 years. Morphologic changes occur primarily in the fetal period while myelination although starting in utero is mainly developing in infants and children. In neonates brain contrast is reverse compared to the mature brain. Myelination is characterized in mature brain by bright signal on T1 WI and low signal on T2 WI. Note relatively large ventricles and subarachnoid spaces in young fetuses.

**Figure 4** Imagerie cérébrale en pondération T1 (A, B, C) et T2 (D, E, F) à 22 semaines de gestation, 15 jours et cinq ans. Les changements morphologiques se produisent essentiellement durant la période fœtale, alors que la myélinisation, bien que débutant in utero, a lieu principalement en période postnatale et durant l’enfance. Chez le nouveau-né le contraste du parenchyme cérébral est inversé par rapport au cerveau mature. La myélinisation est caractérisée par un hypersignal T1 et un hyposignal T2 dans le cerveau mature. À noter l’aspect larde de ventricules et des espaces sous-arachnoidiens chez le foetus jeune.
postnatal year. Two partially overlapping stages can be identified: a period of oligodendrocyte proliferation and differentiation, and a period of rapid myelin synthesis and deposition.

The high cellular density and the cellular packing observed in the cortex, the basal ganglia and the germinal matrix are responsible for a multilayered pattern of the cerebral hemisphere seen in utero (Fig. 6). The intense proliferation of astrocytes to guide neuronal migration and of oligodendrocytes before the onset of myelination (the so-called myelination gliosis) is depicted as an intermediate layer within the white matter (arrows in Fig. 6b). This layer of migrating cells is transient and is seen up to 30 weeks. From 30 weeks on, some residual nests of cells can persist and appear as periventricular nodules predominantly in the frontal areas that do not have to be mistaken with nodules of leukomalacia. The cells responsible for myelination are premyelinating oligodendrocytes (preoligodendrocytes), which are present before axonal ensheathment begins and emit processes for identifying target

Figure 5  Brain morphology from 23 to 38 weeks in the sagittal plane. 23 weeks (A), 27 weeks (B), 31 weeks (C), 34 weeks (D), 38 weeks (E).
Figure 5  Morphologie cérébrale entre 23 et 38 semaines de gestation dans le plan sagittal. Vingt-trois semaines (A), 27 semaines (B), 31 semaines (C), 34 semaines (D), 38 semaines (E).

Figure 6  Multilayered pattern of the cerebral hemisphere at 24 weeks. Coronal T1 WI (A), coronal (B) and axial (C) HASTE images. The cortex and the germinal matrix show bright signal on T1 and low signal intensity on T2 WI. Layers of low signal T2 and bright signal T1 are also seen within the white matter and correspond to migrating cells (arrow A,B). Also note that the basal ganglia show low signal on T2 WI and bright signal on T1 WI due to the high cellular density.
Figure 6  Aspect en multicouches des hémisphères cérébraux à 24 semaines. Pondération T1 dans le plan coronal (A), pondération HASTE dans le plan coronal (B) et axial (C). Le cortex et la matrice germinative sont hyperintenses T1 hypointenses T2. Les couches de cellules migrantes apparaissent aussi hyperintenses en T1 et hypointenses en T2 (flèches A,B). A noter aussi l’aspect hypo-intense T2 et hyperintense T1 des noyaux gris centraux en raison de leur haute densité cellulaire.
axons [47]. Preoligodendrocytes coincide with the high-risk period for periventricular leukomalacia (PVL) in highly premature neonates [51]. Absence of the intermediate layer prior 30 weeks on fetal MRI coincides with white matter damage whatever the cause of the damage [17,38,41]. Signal changes in the basal ganglia are more conspicuous at week 29-30 compared to the previous stages. However these conspicuous signal changes, especially on T1 WI are transient. Involvement of basal ganglia following asphyxia was considered to happen mostly in term infants. However with the increase of fetal MRI examinations, damage to the basal ganglia has been identified even in young fetuses (Fig. 7). Germinal matrix (also named ventricular zone, ependymal layer) is also highly cellular in young fetuses and appears as a thick layer on fetal MRI up to 29-30 weeks. Disruption or nodular appearance of the ventricular wall coincides with ependymal reactions to injury especially ventricular dilatation, infection or inflammation [88].

Myelin is a highly organized multilamellar structure formed by the plasma membrane of oligodendrocytes [47]. This membrane surrounds neuronal axons and facilitates electric impulse conduction. Biochemically, myelin contains small numbers of specific proteins and lipids, which are integrated into the membrane marked by a high degree of stability. Lipids constitute 70% of the dry weight of the myelin membrane. The major lipid components of CNS myelin include cholesterol, galactolipids and sphingomyelin. Phospholipid and cholesterol contents of myelin resemble other plasma membranes. Myelin differs in that it contains abundant quantities of galactolipids and plasmalogens, and a diverse group of glycerophospholipids. One third of the myelin lipids consist of two galactolipids, the galactocerebrosides and sulfatides. Proteo-lipid-protein (PLP) is a specific protein, which stabilizes the myelin membrane, although the mechanism remains unclear. PLP constitutes half of the protein in the mature myelin membrane [59]. Myelin basic protein (MBP) is also a specific protein, which interacts with the cytoplasm, faces of the sheath and facilitates the compaction of the myelin membrane. PLP and MBP are known as the major myelin proteins. Minor myelin proteins include the myelin associated glycoprotein (MAG) and the 2′3′-cyclic-nucleotide-3′-phosphohydrolase (CNPase). Galactocerebroside and sulfatides occupy the extracellular face of the membrane and are known from animal models to transduce developmental signals, to facilitate the protein trafficking and stabilize the membrane, and to be responsible for axon-myelin interaction [21,22]. When wrapping around an axon, the oligodendrocytic extension undergoes a process of compaction. Loss of cytoplasm from the compaction is responsible for loss of mobile protons and as a consequence loss of MR signal, especially on T2 WI. A single oligodendrocyte can be responsible of the myelination of several axons simultaneously (up to 50 nerve fibers). Consequently the destruction of a few oligodendrocytes can be responsible of extensive damage. On the other hand, oligodendrocytes are capable of proliferation, especially during maturation, which has probably implications in some reparative processes. Beside the intense proliferation of oligodendrocytes taking place before the onset of myelination, there is a period of greatly increased lipid synthesis in the oligodendrocytes. Lipids cause a decrease in T1 and T2, and an increase in the magnetization effect. Galactocerebroside is the major lipid responsible for the magnetization effect as demonstrated by Kucharczyk et al. [66].

Other factors are also of importance such as the hydrophilic properties of some constituents of myelin. Cholesterol, glycolipids and portions of the myelin proteins are hydrophilic and bond strongly with water molecules leading to a decrease in the amount of free water and shortening of T1 [5,6].

Although oligodendrocytes are the cells responsible for myelination, astrocytes also play an important role especially for homeostasis of the neuronal extracellular milieu. Astrocytes are also functionally coupled with oligodendrocytes through the astrocytic processes in contact with oligodendrocytes. Astrocytes are also involved in the metabolism of neurotransmitters glutamate and gamma-aminobutyric acid (GABA), in the detoxification of ammonia and in the glycogen pathway.

Interactions between neurons and oligodendrocytes are also needed to achieve proper myelination. Indeed sponta-

Figure 7 Basal ganglia damage following profound fetal asphyxia. MRI at 27 weeks: axial T2 (a) and T1 (b) WI. Bilateral necrosis of lentiform nucleus and thalamus.

Figure 7 Atteinte des noyaux gris centraux après asphyxie profonde. IRM à 27 semaines en séquence axiale T2 (A) et T1 (B). Nécrose bilatérale des noyaux gris et thalamus.
Figure 8  Illustration of general rules of myelination. Myelination is progressing at different speeds so that the onset of myelination prior or at birth is not necessarily associated with early myelination. Axial T1 (A, B) and T2 (C, D) WI respectively at 33 weeks (A), 35 weeks (B) and 4 months postnatal (C, D). The process of myelination is identified within the internal capsule at 33 weeks and the proximal portion of optic radiations at 35 weeks. Both white matter bundles are considered mature at 4 months of age.

Figure 8  Illustration des règles générales de la progression de la myélinisation. Étant donné que la myélinisation progresse à différentes vitesses, le fait que la myélinisation débute avant ou au moment de la naissance n’est pas synonyme d’une myélinisation précoce. T1 axial (A, B) et T2 axial (C, D) à 33 semaines (A), 35 semaines (B) et quatre mois après la naissance (C, D). La progression de la myélinisation est visible dans la capsule interne à 33 semaines de gestation et dans la partie proximale des radiations optiques à 35 semaines. Ces deux faisceaux de matière blanche sont considérés comme ayant atteint le stade de maturité à quatre mois d’âge postnatal.

Figure 9  Consequences of general rules of myelination. Anatomic distribution of brain damage is related to the mechanism underlying the disease responsible for cerebral damage. Term infant with a pyruvate carboxylase deficiency (A, B, C): axial T2 WI (A, C), parasagittal T1 WI (B). Term infant with birth asphyxia (D, E, F): axial T1 (D, E) and T2 (F) WI. In the case of inborn error of metabolism brain damage involves the white matter of the frontal and temporal poles as well as the anterior brainstem. On the other hand, birth asphyxia involves more mature areas as the cortex, basal ganglia and posterior brainstem.

Figure 9  Conséquences des règles générales de la myélinisation. La distribution anatomique des lésions cérébrales résulte du mécanisme pathologique de destruction du parenchyme cérébral sous-jacent. Nouveau-né à terme avec déficience en pyruvate-décarboxylase (A, B, C) : axial T2 (A, C), parasagittal T1 (B). Nouveau-né à terme avec asphyxie néonatale (D, E, F) : axial T1 (D, E) et axial T2 (F). Dans le cas d’une erreur de métabolisme congénitale, les lésions cérébrales se retrouvent principalement dans la substance blanche frontale et temporopolaire ainsi que dans la partie antérieure du tronc cérébral. Dans le cas d’une asphyxie périnatale, ce sont les régions à la maturation plus avancée comme le cortex, les noyaux gris centraux et la partie postérieure du tronc cérébral qui sont les plus touchées.
Figure 10  Cerebral appearance in the term neonate on T1 and T2 WI. Sagittal (A) and axial (C, E) T2 WI. Sagittal (B) and axial (D, F) T1 WI. The anterior brainstem at the level of the pons is not yet fully myelinated and appears of low signal intensity on T1 WI (B), of bright signal on T2 WI (A) compared to the remaining areas of the brainstem. Myelination is more advanced in the calcarine area (D) and central area (F). Myelination is also more advanced in the posterior limb of the internal capsule compared to the optic radiations: a conspicuous bright signal is seen in the posterior limb on T1 WI (D) while myelination is not yet fully detected on T2 WI (C). Note that the white matter underlying the central sulcus is myelinated and displays a low signal on T2 WI (E).

Figure 10  Imagerie cérébrale d’un nouveau-né à terme en pondération T2 dans le plan sagittal (A) et axial (C, E), ainsi qu’en pondération T1 dans le plan sagittal (B) et axial (D, F). La partie antérieure du tronc cérébral au niveau du pons n’est pas encore complètement myélinisée. La myélinisation est plus avancée au niveau cortical de la région calcarine (D) ou de la région centrale (F). La myélinisation est également plus avancée dans le bras postérieur de la capsule interne comparé aux radiations optiques : un hypersignal intense est visible dans le bras postérieur en pondération T1 (D) alors que la myélinisation n’est que partiellement visible en pondération T2 (C). À noter que la substance blanche en dessous du sillon central est déjà myélinisée et démontre un hyposignal en pondération T2 (E).

Figure 11  Cerebral appearance at 2 months of age. T2 (A, B) and T1 (C, D) WI. The anterior brainstem at the level of the pons is now considered mature. The posterior limb of the internal capsule is fully myelinated with its low signal on T2 WI (B). Myelination is identified in the optic radiations (B) but is not as advanced as in the posterior limb of the internal capsules.

Figure 11  Imagerie cérébrale d’un enfant âgé de deux mois. Images en pondération T2 (A, B) et T1 (C, D). La partie ventrale du tronc cérébral au niveau du pons a atteint son niveau de maturation définitif. Le bras postérieur de la capsule interne est actuellement myélinisé et démontre un hyposignal en pondération T2 (B). La myélinisation est identifiable dans les radiations optiques (B), mais pas aussi avancée que dans le bras postérieur de la capsule interne.
Figure 12  Cerebral appearance at 4 months of age. Axial T2 (A, B, C) and T1 (F) WI. Coronal T1 WI (D, E). The entire internal capsule is myelinated with low signal intensity in the anterior limb on T2 WI (A, B) and high signal on T1 WI (E). The optic radiations are also now well identified (A, D). Maturation is also seen within the splenium of the corpus callosum (B). Myelination within the centrum semi-oval has reached the pre- and post-central areas (C, F).

Figure 12  Imagerie cérébrale d’un enfant âgé de quatre mois. Images axiales en pondération T2 (A-D) et T1 (H). Images coronales T1 (E-G). La totalité de la capsule interne est actuellement myélinisée avec un hyposignal du bras antérieur en pondération T2 (A, B) et un hypersignal T1 (E). Les radiations optiques sont également bien identifiables (A, D). Une maturation avancée est visible dans le splénium du corps calleux (B). La myélinisation a atteint les régions pré- et post-centrales (C, F).

Figure 13  Cerebral appearance at 7 months of age. Axial T2 (A, B) and T1 (C) WI. Myelination has reached the anterior part of the corpus callosum (A). Although almost the entire centrum semi-oval is bright on T1 WI, myelination is not yet achieved on T2 WI (B) and the subcortical white matter, the periventricular frontal and parietal white matter are still bright on T2 WI.

Figure 13  Imagerie cérébrale d’un enfant âgé de sept mois. Images axiales en pondération T2 (A-B) et en pondération T1 (C). La myélinisation a atteint la partie antérieure du corps calleux (A). Bien que presque la totalité du centre semi-ovale révèle un hypersignal en pondération T1, la myélinisation n’est cependant pas encore achevée sur les images en pondération T2 (B), et la substance blanche tant sous-corticale que périventriculaire frontale ou pariétale est toujours encore hyperintense en pondération T2.
Figure 14 Cerebral appearance at 19 months of age. Axial T2 (A, B) and T1 (C) WI. The subcortical white matter is now displaying a mature appearance with low signal intensity on T2 WI.

Figure 14 Imagerie cérébrale d’un enfant âgé de 19 mois. Images axiales en pondération T2 (A, B) et en pondération T1 (C). La substance blanche sous-corticale révèle à présent un niveau de maturation définitif avec une hypo-intensité généralisée sur les images en pondération T2.

Figure 15 Cerebral appearance on diffusion images of b = 1000 (row A) and ADC maps (row B) at 23 weeks. The brainstem is bright on DWI in the anterior and posterior areas because diffusion is sensitive to myelination and high cell density. The cortex, the migrant cells and the germinal zone are also bright on diffusion with low ADC. The germinal matrix and the intermediate layer of migrating cells are however not easily distinguishable from one another. Also note the identification of anterior and posterior parts of the corpus callosum.

Figure 15 Imagerie cérébrale de diffusion b = 1000 (rang A) avec carte ADC (rang B) d’un foetus âgé de 23 semaines. Les parties antérieure et postérieure du tronc cérébral sont hyperintenses, car les images de diffusion sont sensibles à la myélinisation et à la densité cellulaire. Le cortex, les cellules migratrices et la matrice germinative sont également hyperintenses en diffusion avec des valeurs d’ADC basses. Il n’est cependant pas aisé de différencier de manière certaine la matrice germinative de la zone intermédiaire de cellules migrantes. À noter également l’identification de la partie antérieure et postérieure du corps calleux.
neous neuronal activity plays a major role in the initiation of myelination and induces the onset of myelination process by oligodendrocytes [25].

Cellular and biochemical processes of brain maturation are complex and any failure in synthesis of specific proteins or lipids will produce myelination disorders. Absence of the specific proteins will produce an unstable myelin. Absence of the PLP gene is currently known to produce the Pelizaeus-Marzbacher disease (and its connatal form, the Seitelberger disease) with absence of myelination. Absence of the specific MBP is part of the 18p− syndrome. Enzymatic defects in lipid synthesis, glycogen synthesis and others will produce the so-called leucodystrophies or metabolic diseases [55]. Inability of astrocytes to realize their functions is known as the Alexander’s disease due to a mutation in the glial fibrillary acidic protein (GFAP) gene [1], GFAP being a marker of astrocytes.

Changes of MR signal from the myelination process are apparent first on T1 WI and then on T2 WI: this is probably due to the fact that T1 and T2 WI express different mechanisms. Signal changes from brain myelination are detected early in utero and are seen in the posterior brainstem at 20 weeks, in the posterior limb of the internal capsule from 33 weeks on (Fig. 8a), in the optic tracts (Fig. 8b) and in the white matter underlying the central area from 35 weeks onwards.

General sequences of central nervous system myelination (CNS)

General rules of brain myelination are well known from histological studies [16,50,56–58,66,69]. CNS myelination is progressing in predictable sequences from caudal (spinal cord and brainstem) to rostral (telencephalon). It begins at 12-13 weeks in the spinal cord and continues well after birth (at least into the third decade) in the intracortical fibers of the cerebral cortex. In the cortex myelination spreads in a concentric fashion whereas in the subcortical white matter myelination follows functionally defined bundles. Sensory pathways are myelinating before motor pathways. Associative areas are the last to be myelinated. In a given cortical-subcortical functional unit the cortex is generally myelinated first. Myelination of different parts of the brain develops at different times, at different speeds, and at a variable speed for a given structure: indeed the rate of myelination in a particular pathway may change across time, such that the onset of myelination prior or at birth is not necessarily associated with early myelination. As an example the process of myelination is identified on T1 WI in the posterior limb of the internal capsule and in the proximal area of the optic radiations respectively at 33 and 35 weeks of gestation and both white matter bundles will
Figure 17  Diffusion (row A) and ADC maps (row B) at 33 weeks. The migrating cells are barely visible compared to the previous stages. The process of myelination is identified in the white matter located below the central area (arrows).

Figure 17  Imagerie cérébrale de diffusion (rang A) avec carte ADC (rang B) d’un foetus âgé de 33 semaines. Les cellules migratrices ne sont presque plus identifiables comparées aux stades de développement précédents. La progression de la myélinisation est visible dans la substance blanche en dessous de la région centrale (flèches).

Figure 18  Diffusion (row A) and ADC maps (row B) in the neonate. ADC is lower in the posterior fossa compared to cerebral hemispheres. Process of myelination is identified in the corticospinal tracts as bright signal on DWI and low signal on ADC within the pons, the central area and the posterior part of the internal capsules. This process is also seen in the optic radiations and in the splenium of the corpus callosum. Unmyelinated white matter shows low signal on DWI and high signal on ADC.

Figure 18  Imagerie cérébrale de diffusion (rang A) et carte ADC (rang B) chez un nouveau-né à terme. Les valeurs d’ADC dans la fosse postérieure sont inférieures aux valeurs retrouvées dans les hémisphères cérébraux. On retrouve la myélinisation des faisceaux corticospinaux au niveau du pont, de l’aire centrale, du bras postérieur de la capsule interne. À noter aussi que la myélinisation est identifiée au niveau des radiations optiques et du splénium du corps calleux. Les faisceaux de substance blanche qui ne sont pas encore dans le processus de myélinisation apparaissent hypo-intenses en diffusion et hyperintenses en ADC.
be considered as mature at 4 months postnatal (Fig. 8). In telencephalic sites myelination progresses from the central sulcus outward toward all poles; occipital pole myelinates before the frontal pole, which in turn myelinates before the temporal pole. As a consequence, a disease that is leading to impeachment of normal myelination (such as an inborn error of metabolism manifesting prior or at birth) will display brain damage in unmyelinated areas at the level of frontal and temporal poles as well as in the anterior brainstem (Fig. 9a,b,c). On the other hand, a disease known to affect preferentially mature areas such as birth asphyxia will give brain lesions predominantly of the central area, basal ganglia and posterior brainstem (Fig. 9d,e,f). At birth large areas of the cortex are already myelinated whereas the subcortical white matter is not. Primary areas of the cortex (central area, calcarine area, auditory area of the medial temporal lobe) show low signal intensity on T2 WI. Cortical and subcortical myelinations are not necessarily interrelated.

Biochemical sequences closely follow the anatomic sequences. Sphingomyelin is followed simultaneously by cerebrosides, MBP, PLP and non-hydroxy-sulphatide, followed by hydroxy-sulfatide. Biochemical sequences are identical in the different sites of myelination but occur at different times. This probably contributes to the regional variability of many inborn disorders of CNS white matter [56-58].

**Postnatal MRI timetables**

Magnetic resonance imaging will illustrate identical anatomic sequences as histology, but with a time delay compared to histological studies [32,81]. However the postnatal timetables as seen by MRI can be summarized as follow – at birth (Fig. 10) the medulla and the mesencephalon display a bright signal on T1 WI and a low signal on T2 WI, whereas the anterior part of the pons is not yet myelinated completely. The white matter underlying the central area also shows a bright signal on T1 WI and a low signal on T2 WI. Cerebellum and the brainstem are now of low signal intensity compared to the previous stage.

- At 2 months of age (Fig. 11) the posterior limb of the internal capsules display a bright signal on T1 WI, but is not yet myelinated on T2 WI.
- At 4 months of age (Fig. 12) the entire internal capsule (anterior and posterior limbs) is now of low signal intensity on T2 WI as well as the periventricular optic radia-
Myelination of the white matter within the centrum semi-oval has reached the pre and post-central areas. Splenium of the corpus callosum also shows low signal intensity on T2 WI whereas the anterior part is not yet myelinated.

- At 7–8 months of age (Fig. 13) the entire corpus callosum appears of low signal on T2 WI because myelination has reached the genu. Although the white matter of the cerebral hemispheres shows a bright signal on T1 WI, it is not myelinated on T2 WI.
- At 18–24 months (Fig. 14) a mature pattern of the white matter is seen and the subcortical “U” fibers also show low signal intensity on T2 WI.

Although the mature pattern is reached at 18-24 months depending on the magnet used, the myelination of the brain is known to go on far beyond that age, at least until 20 years [89].

**Diffusion-weighted images and brain maturation**

Diffusion WI is sensitive to changes in cell density and myelination and show signal changes before T1 and T2 sequences.

In young fetuses below 25 weeks of gestation diffusion images show the multilayered pattern of the cerebral mantle as described on conventional T1 and T2 images. On diffusion images the cortical ribbon appears of bright signal and the sub cortical white matter of low signal (Fig. 15). However, the germinal matrix and the intermediate layer of migrating cells are not easily distinguishable from one to another and appear as a large band of bright signal between the ventricles and the sub cortical white matter. On ADC map, the signal is reversed compared to DW image b 1000, with the cortical ribbon of low signal, the subcortical layer of bright signal and the periventricular area (made of the intermediate layer and the germinal zone) appear as a large band of low signal. The layer of migrating cells is thick at the level of the centrum semi-oval. The germinal matrix at the level of the caudate nucleus is thick and of very low signal on ADC map. The basal ganglia also show a bright signal on diffusion-weighted images and a low signal on ADC map more conspicuous than the signal changes on conventional T1- and T2-weighted images. The brainstem appears bright on diffusion images and of low signal on ADC map in both anterior and posterior areas of the pons whereas signal changes from maturation are only seen in the posterior part of the brainstem on T1- and T2-weighted images. Crossing fibers of the corpus callosum are also identified as bright signal on diffusion and low ADC.

Along with increasing gestational age up to 29-30 weeks, the multilayered pattern is clearly identified compared to earlier stage (Fig. 16). The intermediate layer of migrating...
cells is well seen as bright signal on DW images and low signal on ADC map whereas the periventricular and subcortical white matter are respectively on DW images and ADC map of low and bright signal. At the level of the centrum semi-oval the signal changes from migrating cells on DW images and ADC map are less conspicuous than in earlier stage providing a homogeneous aspect of the white matter. The anterior part of the corpus callosum is well identified and appears of bright signal on DWI images and of low signal on ADC images, compared to conventional images. The basal ganglia are also well identified and delineated from the germinal matrix.

From 30-31 weeks on, the multilayered pattern is less conspicuous and the migrating cells are barely visible. Process of maturation within the posterior limb of the internal capsule is seen at 30-31 weeks as a slight bright signal on DW images and a low signal on ADC map whereas signal changes are not yet identified on T1- and T2-weighted images. Myelination process is depicted around 33 weeks within the white matter underlying the central area as a bright signal on DW images and a low signal on ADC map with no apparent signal changes on T1 and T2 WI (Fig. 17).

ADC values have been calculated in the fetal brain with a low ADC value in the basal ganglia compared to the frontal and parietal white matter supposedly related to a higher cellular density in the basal ganglia with less interstitial water than in the unmyelinated white matter [86].

Postnatal reports have shown a tendency in decrease of ADC within the anterior and posterior brainstem predominantly in the posterior areas [72] as well as in the cerebellar white matter [80]. Significant correlations have been also seen postnatally in the corticospinal tracts [77] within the white matter underlying the central-rolandic area (Fig. 18). Decrease of ADC is associated with increase of fraction anisotropy in white matter and central gray matter (lentiform nuclei, thalamus) until 12 years of age [76,78,79, 89] and largely during the first 2 years of life (Figs. 19-21).

The mechanisms responsible for the decrease in ADC values are complex and unclear: animal studies [4] showed that the changes during development are mainly caused by changes in the diffusivity of the cellular compartment including an increased concentration of macromolecules and a greater membrane surface-to-cell volume ratio caused by proliferation of processes and organelles with an additional possible factor related to change in cell membrane permeability. Others authors suggested that isotropic diffusion reflects the brain water content especially the extracellular water concentration [4,72] whereas anisotropic diffusion may reflect the premyelinating state [95]. Diffusion is in fact multi-modal with fast and slow components. The majority of water molecules belong to the fast component. The slow component in myelinated white matter is higher than in gray matter, and is thought to be related to water molecules trapped within the lipid layers of myelin [8,65].

Figure 21 Diffusion (row A) and ADC maps (row B) at 6 years of age. The subcortical white matter is now of low ADC compared to the previous stage.

Figure 21 Imagerie de diffusion (rang A) et carte d’ADC (rang B) d’un enfant âgé de six ans. La substance blanche sous-corticale démontre à présent des valeurs basses sur les cartes ADC comparées au stade de développement précédant.
MRS of brain maturation and origin of metabolic peaks

During brain maturation the metabolic peaks are age-dependent with time-courses of metabolic changes and pronounced regional variations. Therefore, in pathologic cases with focal lesion, a comparison with contralateral side is necessary whereas in diffuse disease intensities of the different metabolic peaks have to be compared with normative values.

Brain maturation is characterized by increase of NAA and Creatine and a concomitant decrease of Choline, Myo-Inositol and lipids [64] (Figs. 22-24).

Although elevated lactate levels have been demonstrated and considered a normal finding in preterm babies, we did not find any Lactate during normal in utero maturation [43–45].

Inositol is a precursor molecule for inositol lipid synthesis and is considered as an osmolyte, and above all as an astrocyte marker. Inositol is the predominant peak from 22 to 28 weeks (Fig. 23), and probably reflects high density of glial cells that multiply and differentiate before myelino genesis starts in many locations of the brain.

The choline peak includes free choline, glycerophosphorylcholine, and phosphorylcholine. It represents high levels of substrate needed for the formation of cells membranes with gradual reduction as soon as incorporation of lipids has taken place.

NAA is considered as a neuronal marker and is also expressed in oligo-type2 astrocyte progenitors, immature oligodendrocytes, and mature oligodendrocytes. Therefore, NAA also reflects oligodendrocyte proliferation and differentiation [12]. As neuronal cell density in cortex decreases with dendritic maturation, the increase in NAA with age may reflect a contribution from nonneuronal origins.

Creatine reflects energy metabolism and has been shown to increase postnatally and before and around term [64]. However, no significant increase pre- and postnatally has been demonstrated in other studies [68].

Increase of Glx has also been demonstrated [64]. However, no significant changes could be seen in utero studies. Glx peak becomes clearly identified at 24 weeks and demarcates gradually from NAA moiety with progressing gestational age [45].

Regional variations are pronounced at all ages between gray and white matter, and also within different areas of gray and white matter. Highest choline, creatine, and NAA peak intensities occur in the thalamus, followed by basal ganglia, and then other regions in preterm and term infants [9]. This probably reflects the high cellular density in these areas and the more mature status compared to white matter. Concentration of NAA is higher in gray matter than in white matter probably because NAA is expressed in mitochondria located in the cellular soma and not in axons or prolongations of oligodendrocytes. Creatine is higher in gray matter than in white matter. Indeed no creatine is found in mature oligodendrocytes [12]. Choline is slightly lower in gray matter than in white matter. The reason is unclear and one could say that gray matter contains less membranes of myelin.

In term of white matter, NAA, Choline peak intensities are higher in the parietooccipital area than in frontal white matter [48]. The parietal area is myelinated before the frontal area so that the adult pattern is reached first in the parietooccipital region.

Posterior fossa has a peculiar metabolic pattern. The developing cerebellum shows a rapid NAA increase from infant to childhood, a rapid increase in Creatine and Glx from fetus, infant and childhood (Fig. 24). Taurine peak intensity increases during infancy and decreases in childhood [54]. Cerebellum has the highest concentration of Cr that is possibly related to the high creatine kinase activity. However, the more likely explanation is the high activity of guanidinoacetate N-methyltransferase, which permits synthesis of creatine.

Cerebellum is also characterized by high content of Glx, choline, inositol/Gly compared to cerebral hemisphere. High inositol content can be explained by the glomerular synaptic arrangements in the cerebellar cortex with partial encapsulation by astrocytic processes.

Glycine is an inhibitor aminoacid that predominates in the spinal cord and brainstem. High choline content is more difficult to explain, and is probably due to more mem-
branes. High Glx is also difficult to interpret. However cerebellum is rich in Glu receptors and GABA receptors within the cortex and the axons.

Regional variations are also seen in the posterior fossa. The lower concentrations are in the vermis whereas highest concentrations are in the pons [74].

In summary peak intensities of metabolites are age-dependant and display regional variations. The mechanisms responsible for the metabolic changes are however not yet understood and explained.

Figure 23  In utero spectra with short and long echo-time obtained at 29 weeks (a, b), 33 weeks (c,d), 39 weeks (e, f). Postnatal spectra obtained at 7 months (g, h), 18 months (i, j) and 5 years (k, l). Short echo-time spectra are in the left panel and long echo-time in the right panel.

Figure 24  Short echo-time spectra in a 5-year-old boy, in the supratentorial white matter and the cerebellar hemisphere. Cerebellar hemisphere shows an elevated Glutamine-Glutamate peak (Glx), Choline peak (Cho), Creatine peak (Cr) and Inositol peak compared to the spectrum taken from the supratentorial white matter.

Figure 24  Spectroscopie en écho court d’un enfant âgé de cinq ans, au niveau de la substance blanche supratentorielle et dans l’hémisphère cérébelleux. L’hémisphère cérébelleux a une concentration plus élevée du massif glutamine-glutamate (Glx) ainsi que de la choline (Cho), de la créatine (Cr) et de l’inositol comparé au spectre de la substance blanche sus-tentorielle.

Concluding remarks

Magnetic resonance imaging gives normal milestones of brain maturation especially of brain myelination. MRI detects simple anatomical structures, which appear at determined periods, thereby providing an easy and reliable approach to the morphological evaluation of the brain development and maturation. Potential benefits of prenatal MRI are thence the recognition of disorders of the brain development as early as possible by the detection of abnor-
nal contrasts. MRI is also used as follow-up imaging tool in the prediction of outcome especially in birth asphyxia or in neonates at risk of brain damage (i.e. neonate of very low birth weight and very premature). MRI also provides the illustration of the windows of vulnerability of both the grey and white matter. Indeed aside the anatomic and biochemical sequences of brain myelination, brain maturation also include the maturation of neurotransmitters. Glutamate is one of the neurotransmitters and is known to be responsible for the selective vulnerability of the neurons (of the basal ganglia and deep layers of the cortex) to hypoxia beyond 34 weeks and for the selective vulnerability of the white matter before 32 weeks.

References


