Normal myelination: a practical pictorial review

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Learning objectives

The MRI techniques that have evolved for the assessment of cerebral myelination will be reviewed. This will be followed by a discussion of both general myelination patterns as well as age-related milestones in myelin development. Finally, we conclude with a brief review of normal variants and imaging pitfalls.
Background

Magnetic resonance imaging (MRI) has revolutionized our ability to evaluate myelination in young children.

Until the advent of cross-sectional imaging, the in vivo status of myelin development could only be evaluated through clinical history, neurologic exam, or by histology.

By the early 1980s, computed tomography allowed gross assessment of myelination through its depiction of white matter density in the pediatric brain.

However, it was not until the introduction of clinical MRI in the late 1980s that regional or tract-specific myelin maturation could be visualized.

Myelin assessment has since evolved to become a routine aspect of pediatric neuroimaging. By reviewing a combination of T1- and T2-weighted MRI series, radiologists and clinicians can quickly and reliably determine whether a child's myelin development is normal, delayed, or abnormal.

This capability has greatly enhanced our ability to detect childhood leukoencephalopathies and other disorders of myelin at younger ages, with the attendant benefit of allowing for earlier prognostication and/or treat-ment.

However, effectively detecting abnormalities of myelination is dependent on both proper imaging technique and an understanding of normal, age-related progression of this process.
Findings and procedure details

- **MR Sequences**

The core MRI techniques for myelin assessment in the infant are T1- and T2-weighted pulse sequences. These two forms of MRI contrast are complimentary in that T1-weighting provides information regarding the early stages of myelination, whereas T2-weighting provides insight into later stages of myelin maturation. Although T2-weighted FLAIR images are among the most commonly used pulse sequences in contemporary MRI of the brain, the white matter contrast created by these images has traditionally been considered substandard for myelin staging. However, T2-weighted FLAIR images demonstrate signal changes related to the completion of myelin maturation after myelin has already reached its adult appearance on T1- and T2-weighted images. Consequently, this pulse sequence may be of use in assessing the final stages of myelination in various regions of the brain.

A recently developed tool in the armamentarium for myelin evaluation is diffusion tensor imaging (DTI). This technique uses echo planar pulse sequences to exploit the anisotropic diffusion of water molecules in cerebral tissue and create images that reflect increasing axonal organization in the brain. As areas in the brain with increased axonal organization differentially restrict the movement of water molecules perpendicular to the axon bundles, the fractional anisotropy (FA) of water can be used as a surrogate measure for white matter organization.

Other advanced MRI techniques have been applied to gauging myelin maturation. These include MR spectroscopy, magnetization transfer, quantitative T2 measurement, functional connectivity mapping, and multiparametric mapping of myelin water fraction. Although none of these methods has yet seen widespread clinical use, they may provide important future contributions to clinical assessment of myelin development.

Finally, it should be stated that appropriate selection of MRI planes can improve one's ability to appreciate age-related changes in myelination. As myelination is mostly centered in the brainstem in neonates, the sagittal plane is particularly useful in that group. During the intermediate stages of myelination, the axial plane is preferred due to its ability to demonstrate major tracts within the brain, such as the corticospinal tracts and optic radiations with bilateral symmetry. In the terminal stages of myelination, coronal images are useful for clear depiction of subcortical U-fibers in the frontal lobes.

- **General Anatomic Patterns in Brain Myelination**

Myelination of the brain closely parallels pediatric neurologic functional maturity as measured through neurodevelopmental testing. Hence, anatomic brain regions
responsible for primitive functions myelinate earlier than anatomic sites corresponding to phylogenetically advanced function. Additionally, autopsy studies in infants have confirmed several general neuroanatomic rules regarding myelination.

- First, visual and auditory sensory regions myelinate, on the whole, faster than motor regions.

- Second, the proximal portions of a neuroanatomic subsystem myelinate sooner than the more distal components. For example, the optic tracts myelinate before the optic radiations. These proximal elements of a functional neuroanatomic unit also myelinate at a faster rate than their more distal counterparts.

- Third, projection tracts within the brain generally myelinate earlier than association tracts.

- Finally, the telencephalon begins myelination about the central sulcus region.

Myelination then concurrently extends peripherally toward the various poles of the brain, reaching them in the following order: occipital pole, frontal pole, temporal pole.

These neuro-histologic patterns have been distilled by various authors into simplified anatomic axioms of myelination:

1. Myelination proceeds from caudal to rostral
2. Myelination proceeds from posterior to anterior regions;
3. Myelination proceeds from central to peripheral locations.

Although these general rules provide a useful construct for the practical review of pediatric MRI scans, one should understand that they are not inviolate. Important exceptions do exist within the normal developmental process. For example, the fact that the frontal poles myelinate before the temporal poles violates the posterior to anterior rule. Similarly, the more rostrally located perirolandic cortex myelinates before the more caudally located internal capsule anterior limb.

- **Contrast Specific Temporal Sequences of Myelination**

* T1-Weighted Images

- From birth through 12 months, T1-weighted images provide an excellent window into myelin development.

In the newborn, there is extensive brainstem myelination. Myelin-associated T1 signal hyperintensity is noted in the medulla, dorsal pons, brachium pontis, and both the inferior
and superior cerebellar peduncles. More superiorly, myelinated white matter is visible in the cerebral peduncles of the midbrain, the ventral lateral thalami, and the posterior limbs of the internal capsules. Additional T1 hyperintense myelin can be identified in the corticospinal tracts extending superiorly in the perirolandic centrum semiovale. The cortex along the central sulci is similarly T1 hyperintense. In the visual pathways, myelin is seen in the optic nerves, optic tracts, and optic radiations.

- By 2 to 3 months of age, myelination in the internal capsule has extended to involve the anterior limb. Between 2 and 3 months of age, T1 hyperintense myelin progresses peripherally from the deep cerebellar white matter to involve the entire cerebellum.

- At 4 months, the splenium of the corpus callosum has myelinated.

- Callosal myelination proceeds in an anterior to posterior direction to involve the genu by 6 months of age.

- Outside the central sulcus region, initiation of myelination in the subcortical white matter begins at # 3 months of age.

- Progression of T1 hyperintensity in the supratentorial white matter evolves peripherally from the perirolandic region to involve the subcortical U-fibers in the occipital pole by 7 months of age.

- On the other hand, T1 hyperintensity in the frontal and temporal lobes proceeds more slowly and does not reach the most anterior subcortical U-fibers in these lobes until #1 year.

- Despite the fact that there is still active, ongoing cerebral myelination, the brain at this stage has achieved a typical adult T1 contrast pattern. Consequently, T1-weighted images are of little use for myelin assessment beyond the first year.

* T2-Weighted Images

- In the newborn, myelination, as demonstrated by low T2 signal, is anatomically less extensive than the signal changes contemporaneously demonstrated by T1 images.

- Sites of myelination include the medulla, dorsal pons, superior and inferior cerebellar peduncles, midbrain, and ventral lateral thalamus.

- The cortex surrounding the central sulcus also demonstrates low signal at the time of birth or shortly thereafter.

- By 2 months, low T2-signal myelin has extended to involve the brachium pontis, posterior limb of the internal capsule, and the perirolandic component of the centrum semiovale.
- Also, at about this time, myelin becomes visible in the optic tracts. Progressive myelination of the visual system leads to low T2 signal in the optic radiations and subcortical white matter about the calcarine fissure by 4 months of age.

- T2-signal changes in the corpus callosum lag 1 to 2 months behind the T1-signal changes at this site.

- Notably, at 6 months, while the entire corpus callosum is hyperintense on T1, the T2-signal changes are just beginning in the splenium. The genu of the corpus callosum will not demonstrate T2 hypointensity until 8 months.

- Concurrent with these callosal signal changes, the anterior limb of the internal capsule achieves T2 hypointensity by 8 months.

- Within the posterior fossa, the ventral pons demonstrates T2 hypointense myelin by 6 months and the deep cerebellar white matter becomes hypointense by 12 months. The entire posterior fossa white matter is T2 hypointense by 18 months.

- With respect to the hemispheric white matter, signal changes commence in the central occipital white matter by 7 months, with progressive involvement of the central frontal white matter by 11 months and the central temporal white matter by 12 months.

- As this process is completing, peripheral extension of T2 hyperintensity into the subcortical U-fibers is beginning with early involvement of the occipital lobes around the 1-year mark. Occipital subcortical white matter signal changes should be complete by 15 months.

- However, the anterior aspect of the frontal and temporal lobes will not achieve a similar state of myelination until around 24 months.

* T2-Weighted FLAIR Images

- Assessing myelination on the basis of T2-weighted FLAIR imaging is controversial with some authors advocating this pulse sequence, and other authors considering it to be of minimal utility.

- Regardless of one's opinion on the matter, familiarity with the appearance of myelination on FLAIR images is important as this pulse sequence is frequently encountered in clinical imaging.

- At birth, areas of low T2 signal are noted in the deep white matter of the occipital, frontal, and temporal lobes. As previously discussed, this is the result of a large amount of free water in these regions with consequent FLAIR signal suppression.
- By 1 month of age, this low FLAIR signal will have converted to high signal in the occipital lobe.

- By 2 months of age, this same deep white matter signal conversion will be complete in the frontal and temporal lobes.

- On FLAIR imaging, familiar myelination landmarks generally lag behind conventional T2-weighted images, with the posterior limb of the internal capsule and brachium pontis first demonstrating low T2 signal # 3 months. Low myelin-related signal in the dorsal pons is not seen on FLAIR images until # 4 months of age, a site that appears myelinated at birth on both T1- and T2-weighted images.

- Visualization of myelin in the supratentorial motor and visual systems is similarly delayed, with the perirlandic centrum semiovale demonstrating myelin by # 5 months and the optic radiations demonstrating myelin by # 6 months.

- Of interest, there is minimal, if any, delay in myelin-related signal changes in the corpus callosum with respect to T2-weighted images.

- Authors describe callosal myelination to be complete on FLAIR between 5 and 7 months, which minimally lags behind reported callosal myelination on FSE T2-weighted images.

- However, this FLAIR signal change may slightly precede the time of callosal myelination as reported by conventional spin echo T2-weighted images.

- Similarly, the appearance of myelin in the anterior limb of the internal capsule at 8 months on FLAIR imaging is contemporary with similar signal changes reported on conventional spin echo T2-weighted images, but apparently lags behind those seen on FSE T2 pulse sequences.

- In the second year, the deep white matter completes its triphasic FLAIR signal progression by reverting again to low signal as myelin matures. This occurs first in the deep occipital white matter at 12 months, followed by the deep frontal white matter at # 14 months, and the deep temporal white matter at # 22 to 25 months.

- Low FLAIR signal in the peripheral white matter of the cerebral hemispheres occurs later than the deep white matter changes at each respective location. Subcortical low FLAIR signal is present in the occipital lobes at 14 months and in the frontal lobes at 20 months.

- On T2-weighted FLAIR sequences, white matter in the subcortical U-fibers of the temporal lobes commonly remains hyperintense beyond 24 months.

* Diffusion Tensor Imaging
- In contrast to T1- and T2-weighted imaging, the majority of the major white matter tracts in the brain are visible at birth on FA maps.

- However, while the central portions of these tracts demonstrate increased anisotropy, the peripheral portions of these tracts have relatively low FA that is difficult to distinguish from gray matter.

- Structures that are well seen at birth include the superior and inferior cerebellar peduncles, as well as the brachium pontis.

- In the brainstem, a composite dorsal tract that includes the medial longitudinal fasciculus, medial lemniscus, and reticular formation is evident. Visible components of the motor system include the corticospinal tracts, cerebral peduncles, internal capsules, and corona radiata. Within the limbic system, the cingulum and fornix are discernible. In addition, several association tracts demonstrate increased anisotropy, including the corpus callosum, anterior commissure, and uncinate fascicules.

- By the fourth month, the peripheral portions of the previously demonstrated tracts demonstrate increasing anisotropy. Increased FA is also visible in subcortical U-fibers. Newly visible white matter tracts include the inferior frontal occipital fasciculus and the inferior longitudinal fasciculus. The forceps minor and forceps major can now be identified. However, the forceps major demonstrates an immature inverted V shape at 4 months that will convert to an inverted U shape by 6 months.

- At 1 year of age, the superior longitudinal fasciculus becomes the last major white matter tract to become conspicuous. White matter landmarks unique to DTI, the so-called crossing areas, demonstrate increased FA at this time. The term "crossing areas" refers to the four white matter locations where the forceps minor and forceps major meet with the internal capsules along the lateral aspect of the corpus callosum.

- Prior to 12 months, these are low anisotropy structures.

- Beyond the first year, there is gradual, progressive increase in FA as well as tract thickness throughout the brain.

- However, unlike T1- and T2-weighted images that have a relatively mature appearance by 2 years, color-encoded directional FA maps do not achieve a mature appearance until about 4 years of age.

- Despite the adult-like appearance of FA maps, quantitative analysis demonstrates gradual increasing anisotropy throughout the white matter throughout the first decade of life.

• **MR Spectroscopy**
- During brain maturation the metabolic peaks are age-dependant 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.

- 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.

- 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, and probably reflects high density of glial cells that multiply and differentiate before myelination 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. 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. However, no significant increase pre- and postnatally has been demonstrated in other studies.

- Increase of Glx has also been demonstrated. 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.

- 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. 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.

- 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. 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. Taurine peak intensity increases during infancy and decreases in childhood. 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 membranes. 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.

- 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.

- **Normal Variants and Pitfalls**

* TERMINAL ZONES*

- A point of confusion that frequently arises in reviewing the T2-weighted conventional images and T2-weighted FLAIR images in the brains of children and young adults are the
presence of small, bilaterally symmetric foci of high signal occurring in the white matter
dorsolateral to the atria of the lateral ventricles.

- These most commonly represent so-called terminal zones of incompletely myelinated
brain.

These small areas of signal hyperintensity are considered to be a normal developmental
variant and at times are even identifiable in the young adult population.

- Although early histo-pathologic studies have documented unmyelinated brain in these
regions, more recent literature has suggested that prominent perivascular spaces may
also be contributing to this signal hyperintensity.

- When these periatral hyperintensities are seen in a young child, it is important
to differentiate normal terminal zones from pathologic periventricular leukomalacia
associated with prematurity.

- The two conditions can be distinguished from each other by looking for small bands
of low signal, normally myelinated brain separating the high signal regions from the
ventricles. This finding will be present with terminal zones of myelination, but will be
absent in periventricular leukomalacia where the high signal intensity will commonly
extend all the way to the ventricular ependyma.

- Another helpful clue is that terminal zones have a triangular appearance in the coronal
plane with the tip of the triangle oriented superiorly.

- Finally, periventricular leukomalacia typically occurs more inferolaterally along the atria,
near the optic radiations.

- In addition to the periventricular regions, persistent unmyelinated areas of white matter
are occasionally seen in the anterior frontal lobes and anterior temporal lobes beyond
2 years of age.

- Consequently, when bilaterally symmetric white matter T2 signal hyperintensities are
identified in the frontotemporal regions in young children, consideration should be given
to this developmental variant.

- Generally, these sites of terminal myelination will convert to a normal myelinated
appearance by the age of 40 months.

* MYELINATION IN THE PRETERM INFANT

- Frequently, brain imaging is performed on children that have a history of premature
birth, and the question arises as to whether assessment of myelination should be based
on the child's birth age or an age adjusted to account for prematurity.
- Although some authors advocate using the adjusted age, others argue that rapid acceleration of brain growth during the first 2 postnatal months due to endogenous steroid secretion eliminates the need for such an adjustment after 2 months of age.

- Finally, it should be noted that research has been performed on normal myelination in fetuses and very preterm infants. This literature can be used to guide myelination assessment for infants imaged at less than 40 weeks gestational age.
Fig. 1: Normal myelination : Neonate vs Mature

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**Fig. 2:** Normal myelination: 4 months

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Fig. 3: Normal myelination : 3 years

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Fig. 4: Age Specific Progression of Myelination on MRI

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Fig. 5: Diffusion tensor imaging with 26 diffusion directions. Directionally encoded fractional anisotropy (FA) maps from four different aged children: 9 months (A), 15 months (B), 2 years (C), and 3 years (D). Green indicates those white matter (WM) tracts oriented anterior to posterior. Red indicates WM tracts oriented in a transverse direction. Blue indicates WM tracts oriented in the superoinferior direction. Notice increasing FA in the so-called anterior crossing area between the genu of the corpus callosum and the anterior limb of the internal capsule (arrows) with age progression as indicated by increasing color in this region. The thickness of corpus callosum is seen to gradually progress with age.

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**Fig. 6:** 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.

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Conclusion

- In the young infant, brain myelination is a crucial component of neurologic development that correlates with increasing sensory, motor, and cognitive ability.

- Consequently, a directed evaluation of myelination should be conducted on each pediatric brain MRI.

- Both supratentorial and infratentorial white matter should be scrutinized for signal changes of myelination and compared against age-appropriate milestones.

- At the present time, T1- and T2-weighted images continue to provide the most important information regarding cerebral myelination.

- T1-weighted images are most useful during the first year.

- As T1-weighted images approach a mature appearance, T2-weighted images become superior for continued surveillance of ongoing myelination.

- As our understanding of the later stages of myelination increases, particularly beyond the first two years of life, other techniques, such as FLAIR and DTI, are gaining increasing clinical relevance.

- Additionally, quantitative MRI techniques for evaluation of myelin may become clinically useful in the near future.

- As knowledge of normal myelination advances, our ability to both recognize and address conditions of abnormal myelination is enhanced.
References


