

Normal Myelination

A Practical Pictorial Review

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KEYWORDS

• Myelin • Myelination • T1 • T2 • MR • Diffusion

KEY POINTS

- MR imaging is the best noninvasive modality to assess myelin maturation in the human brain.
- A combination of conventional T1-weighted and T2-weighted sequences is all that is required for basic assessment of myelination in the central nervous system (CNS).
- It is vital to have an understanding of the normal progression of myelination on MR imaging to enable the diagnosis of childhood diseases including leukodystrophies as well as hypomyelinating disorders, delayed myelination, and acquired demyelinating disease.

INTRODUCTION

Assessment of the progression of myelin and myelination has been revolutionized in the era of MR imaging. Earlier imaging modalities such as ultrasonography and computed tomography have no current role or ability to contribute to the assessment of myelin maturation or abnormalities of myelin. The degree of brain myelination can be used as a marker of maturation.

The authors discuss

1. Myelin function and structure
2. The MR imaging appearance of myelin
3. The normal progression of myelination on conventional MR imaging
4. Terminal zones of myelination

DISCUSSION

Myelin Function and Structure

To discuss normal myelination in the human brain, knowledge of the purpose and function of myelin

and its role in the human nervous system is needed.

Myelin is present in both the CNS and the peripheral nervous system. In the CNS, it is primarily found in white matter (although small amounts are also found in gray matter) and thus is responsible for its color.¹ Myelin acts as an electrical insulator for neurons.¹ Myelin plays a role in increasing the speed of an action potential by 10–100 times that of an unmyelinated axon¹ and also helps in speedy axonal transport.² Edgar and Garbern³ (2004) demonstrated that the absence of a major myelin protein (PLP/DM20) from the oligodendrocyte resulted in major impairments in axonal transport in a mouse model of hereditary spastic paraplegia. It has also been well established that axonal integrity depends on the myelinating cell body for support. Myelin also likely has a role in the regulation of both ion composition and fluid volume around the axon.⁴

Myelination is the formation of a myelin lipid bilayer around an axon.^{4,5} Myelination allows rapid transfer of information needed for cognitive

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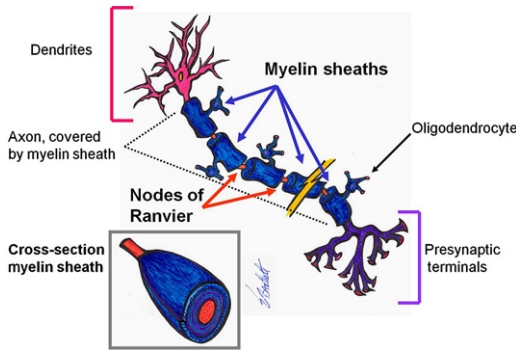


Fig. 1. Schematic of a neuron demonstrating the myelin sheaths wrapped around the axon and the separating nodes of Ranvier. (Courtesy of Dr E. Bartlett, Princess Margaret Cancer Centre, Joint Department of Medical imaging, University of Toronto, Toronto, Canada.)

functioning as well as emotional and behavioral functioning and decision making.⁵ Myelination begins during fetal life^{6,7} and continues after birth.

Myelin is a modified extension of an oligodendroglial cell process.^{6,8} An oligodendroglial cell is the key cell in myelination of the CNS and is the predominant type of neuroglia in white matter.⁹ Myelin sheaths are composed of multiple

segments of myelin, which are then wrapped around an axon.^{6,8} This sheath is instrumental in containing an electrical current around an axon and increasing the action potential of an axon because of the nodes of Ranvier, which are sodium channels in between the myelin sheaths that increase the traveling speed of an electric current down an axon (Fig. 1). Thus, myelin is thought to make impulses travel faster by increasing the speed of travel of a current. Myelin is also thought to be symbiotic with the axon.¹⁰ Myelin is metabolically active and involved in the turnover of its own components¹¹ and contains a large number of myelin-intrinsic enzymes.¹² Myelin also has a role in ion transport, which contributes to its own maintenance, and in the buffering of ions around the axon.^{11,12}

A single oligodendrocyte may be responsible for the production and maintenance of up to 40 fibers.⁹ Myelin has a high lipid content, having approximately 70% lipid and 20 to 30% protein.^{8,9,11} The main proteins that play a part in myelin structure are myelin basic protein (30%), proteolipid protein (50%), and cyclic nucleotide phosphodiesterase (4%).¹ Other proteins involved include myelin-associated glycol protein and myelin oligodendrocyte protein. Lipids that contribute to myelin ultrastructure include cholesterol, phospholipids, and glycosphingolipids.^{1,9}

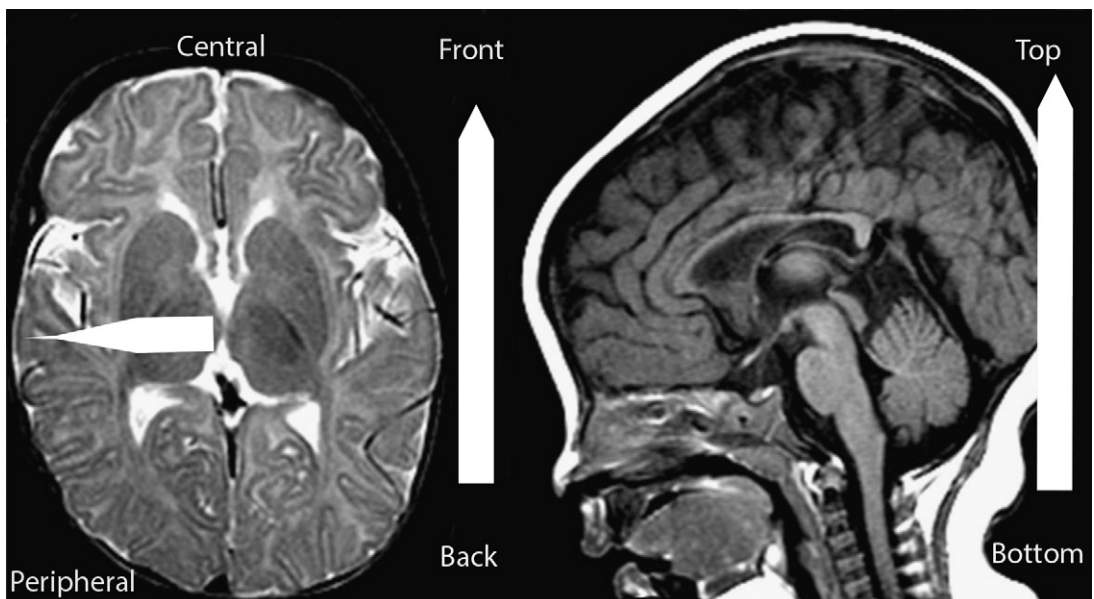
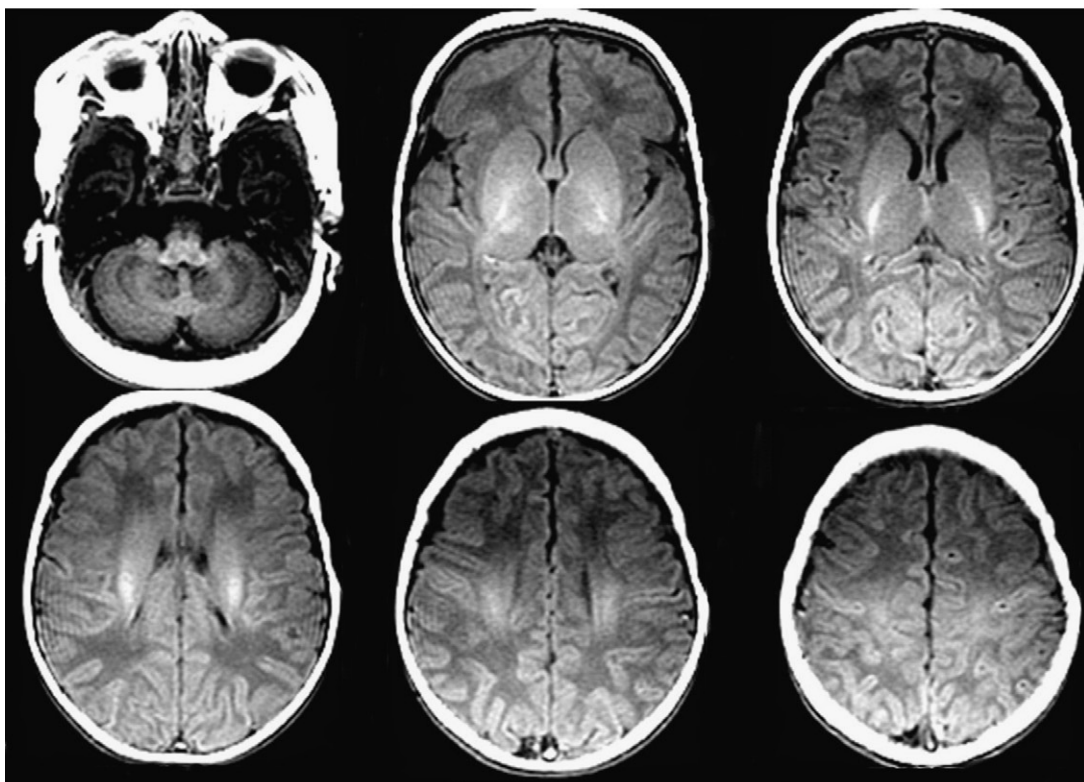


Fig. 2. Myelination progresses in a predictable manner from bottom to top (caudocranial), back to front (posterior to anterior), and central to peripheral (deep to superficial).

A



B

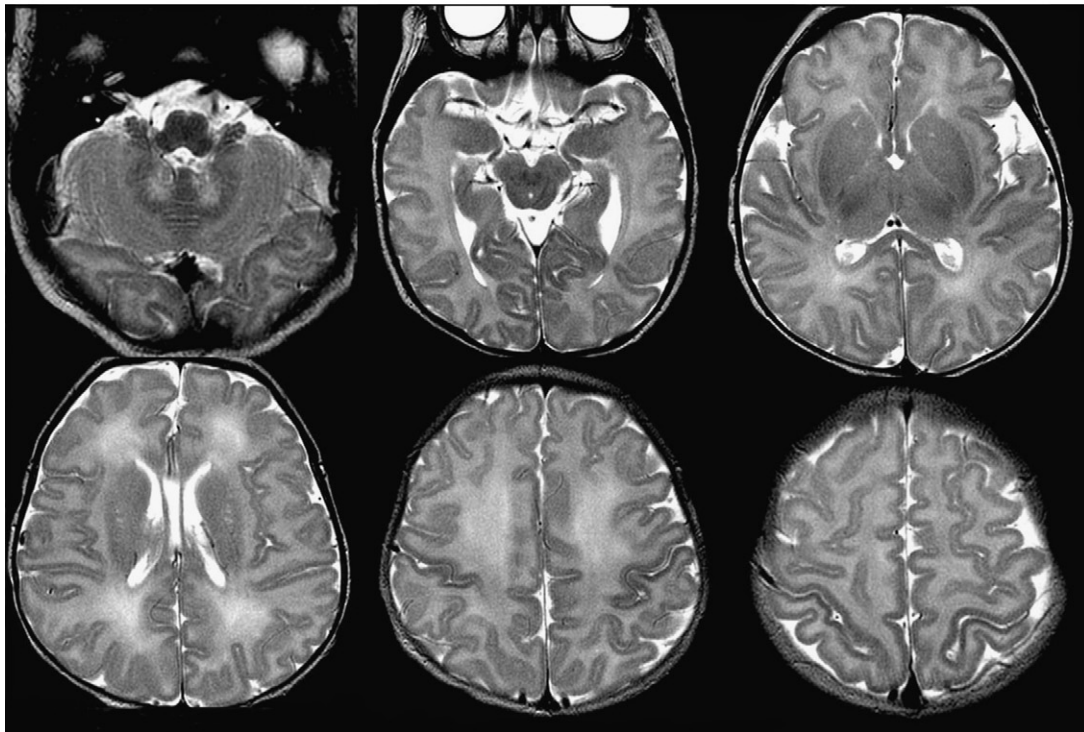


Fig. 3. Imaging of myelination. (A) Normal myelination for a term infant on T1. Structures myelinated at birth include the T1 dorsal brainstem, lateral thalami, posterior limbs of the internal capsule, central coronal radiata, and rolandic and perirolandic gyri. (B) Normal myelination for a term infant on T2. On T2, there is expected myelination in the dorsal brainstem, lateral thalami, posterior limbs of the internal capsule, and central corona radiata.

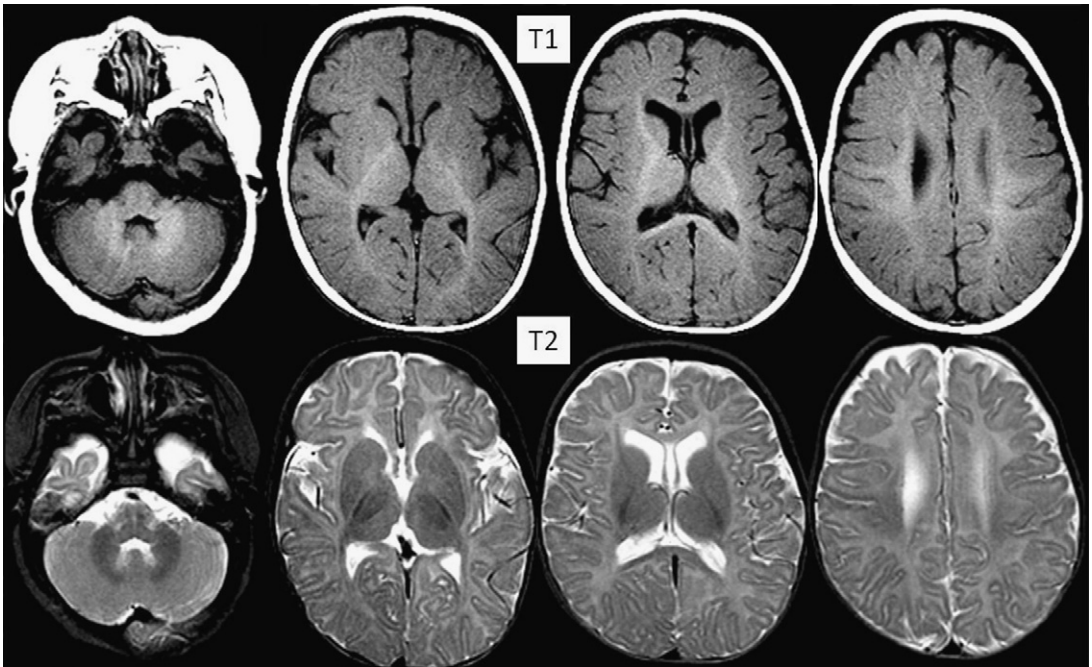


Fig. 4. Imaging of myelination. By 4 months, myelination on T1 in the anterior limbs of the internal capsule as well as thickening of those areas previously described especially central corona radiata and centrum semiovale should be seen. In addition, there should be evolving myelination in the splenium of the corpus callosum. Myelin is not yet well seen in the anterior limb of the internal capsule on T2.

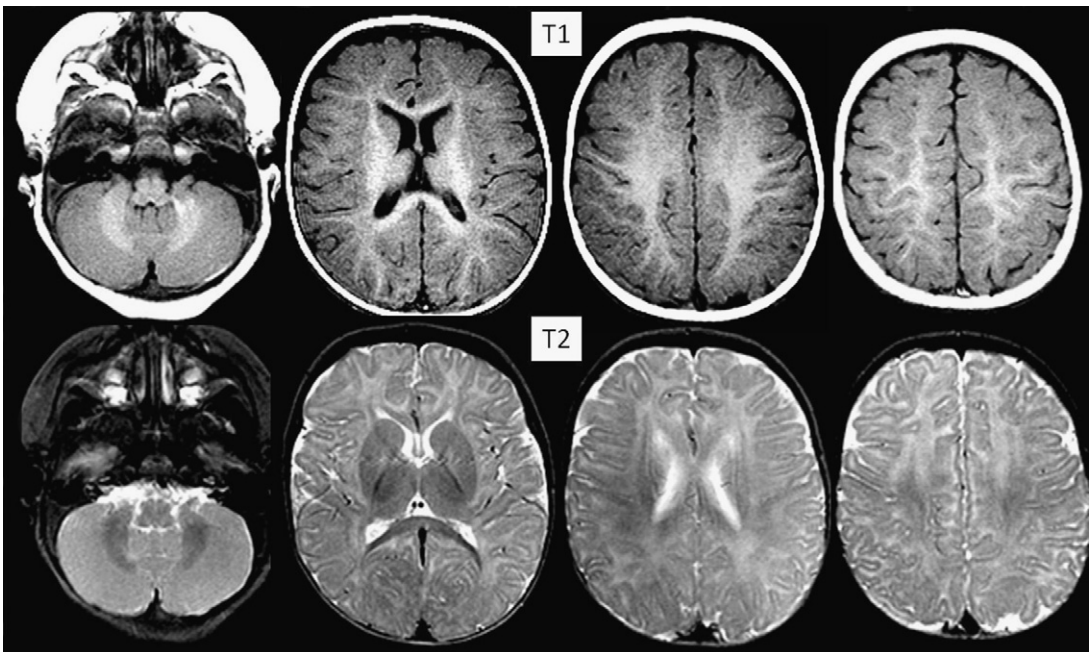


Fig. 5. Imaging of myelination. By 6 months, there is bulking up of myelin in the central white matter specifically in the centrum semiovale and corona radiata as well as the areas previously discussed. This bulking is most evident on T1 and lags on T2 where there is just a faint T2 hypointensity in the anterior limbs of the internal capsule as well as thickening of the myelin in the corpus callosum.

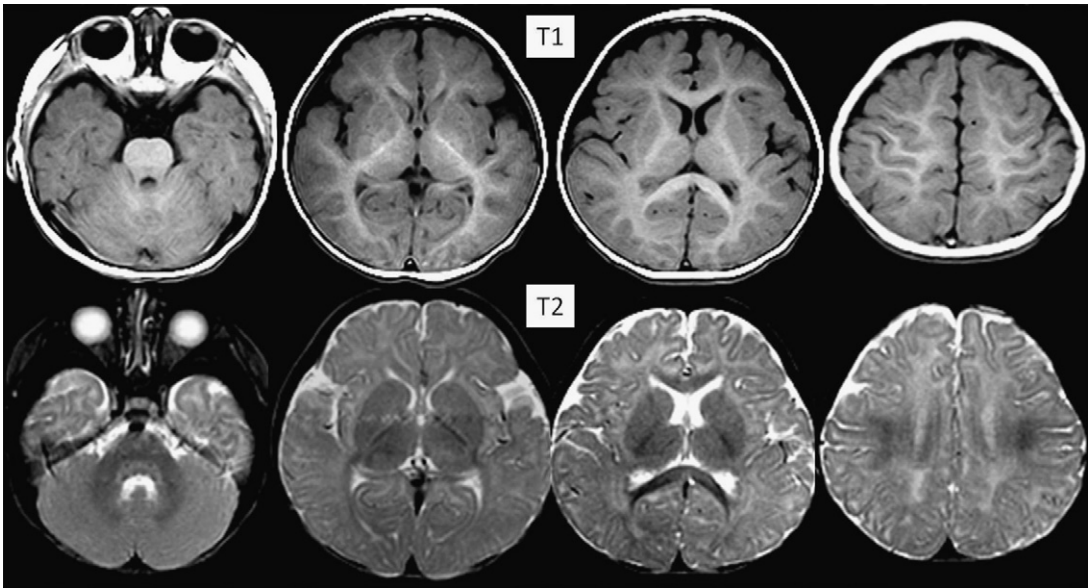


Fig. 6. Imaging of myelination. By 9 months, there is progressive darkening on T2 as well as further bulking up of the myelinated white matter on T1. Myelin should now be seen in the anterior limb of the internal capsule on T2.

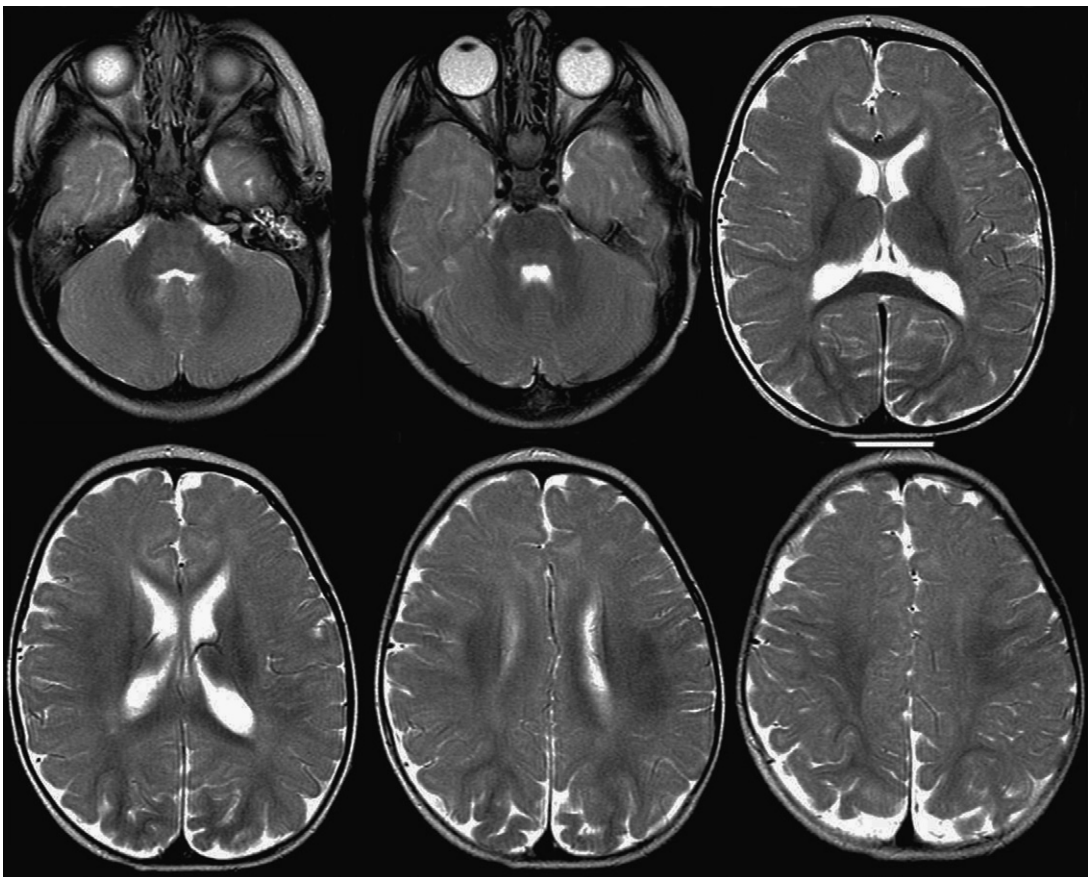


Fig. 7. Imaging of myelination. By 12 months, myelination on T1 is complete and there has been further myelination in the centrum semiovale and coronal radiata as well as the corpus callosum and internal capsule on T2. There is still a fairly large amount of unmyelinated white matter, in particular in the frontal and temporal lobes.

Electron microscopy has demonstrated that myelin is composed of multiple sheaths wrapped around the axon and that the sheaths are made up of a “protein-lipid-protein-lipid-protein” structure. Compaction of these sheaths or processes gives rise to apposition of extracellular and cytoplasmic surfaces, which represents alternating extracellular and intracellular spaces.¹² The lipid bilayer is composed of phospholipids, glycolipids, and cholesterol. Most of the glycolipids (sulfatide and cerebroside) and cholesterol are in the outer layer and exposed to the extracellular space, whereas the phospholipids (plasmalogen) are in the inner layer and are hydrophobic.⁶ The formation of compact myelin is required for the growth and maturation of the axon.¹⁰

The MR Imaging Appearance of Myelin

There is no technique that has been developed to view the myelin lipid bilayer directly with imaging. Myelin is assessed qualitatively. The commonly used MR techniques include conventional anatomic imaging, that is, T1-weighted and T2-weighted sequences as well as MR spectroscopy and diffusion tensor imaging (DTI). Other techniques that have been used include magnetization transfer imaging and T2 relaxation separation.¹ In clinical practice, conventional anatomic imaging is the mainstay because it can be easily performed. Quantification of myelin can be achieved in multicomponent relaxation (MCR) analysis.⁵ MCR is a volume-weighted summation of distinct

A

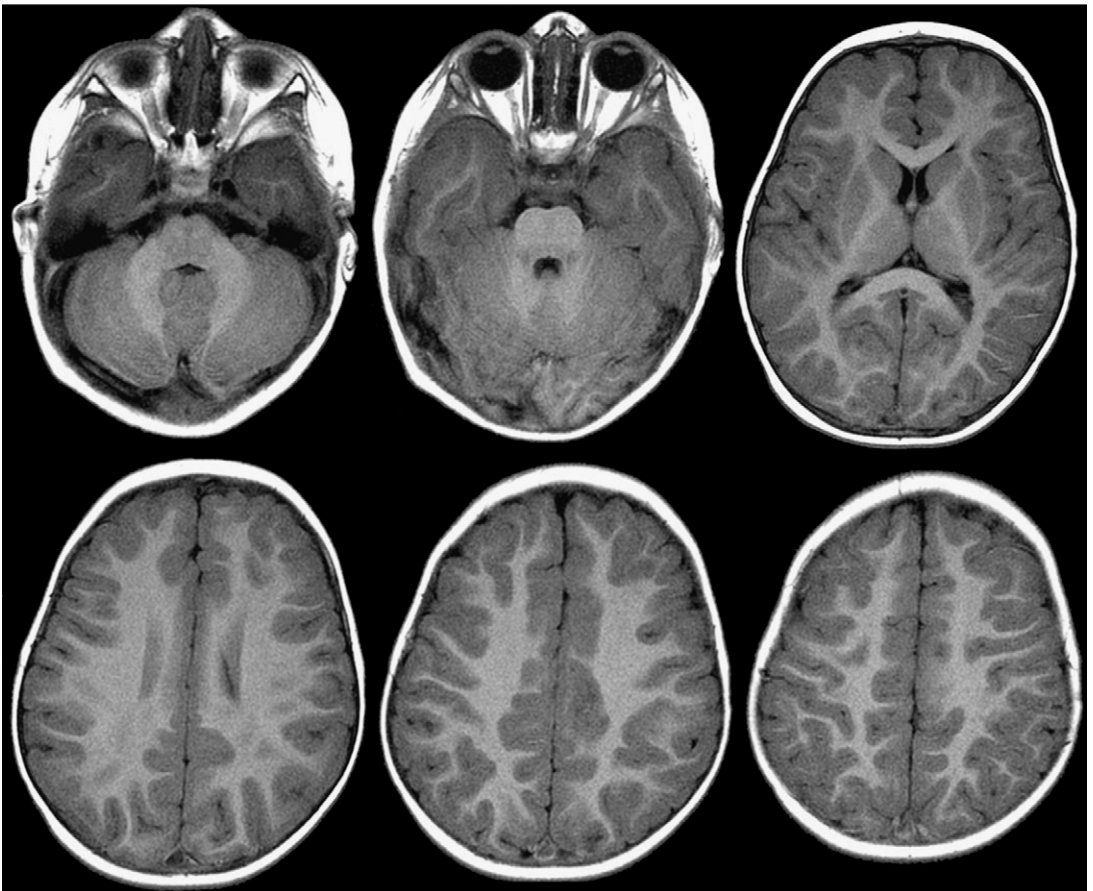


Fig. 8. Imaging of myelination. (A) On T1, at 18 months, myelin is complete and similar in appearance to that of 12 months. There is further thickening and “bulking up” of the central and deep white matter.

microanatomic water compartments. This analysis has revealed 2 water subdomains, namely, a slow relaxing species with free intracellular and extracellular water and a faster relaxing species of molecules from the water trapped between the lipid bilayer sheath.^{5,6}

Currently, standard MR imaging techniques do not specifically have the ability to quantitate myelin. Instead, these techniques study a combination of the following: changes in axonal size and density, changes in membrane structure including lipid and protein content, and water and macromolecule content.⁵ DTI is not a reliable indicator of the total amount of myelin, but it can give some information on changes in myelin.¹

As reviewed by Barkovich⁶ there are 2 distinct populations of water molecules that play a direct role in the signal characteristics of myelin on MR imaging. These populations are water located within the myelin sheath and that located outside the myelin sheath. On conventional imaging, mature myelin is hyperintense to the gray matter cortex on T1 and hypointense to the gray matter cortex on T2. However, on T1, this increase in signal is most likely because of increasing glycolipids, predominantly galactocerebroside¹³ and cholesterol,^{6,14} within the myelin membranes.^{6,15} The T2 hypointensity is thought most likely due to the reduced water content as more myelin is laid down^{7,16} with greater maturation of the myelin

B

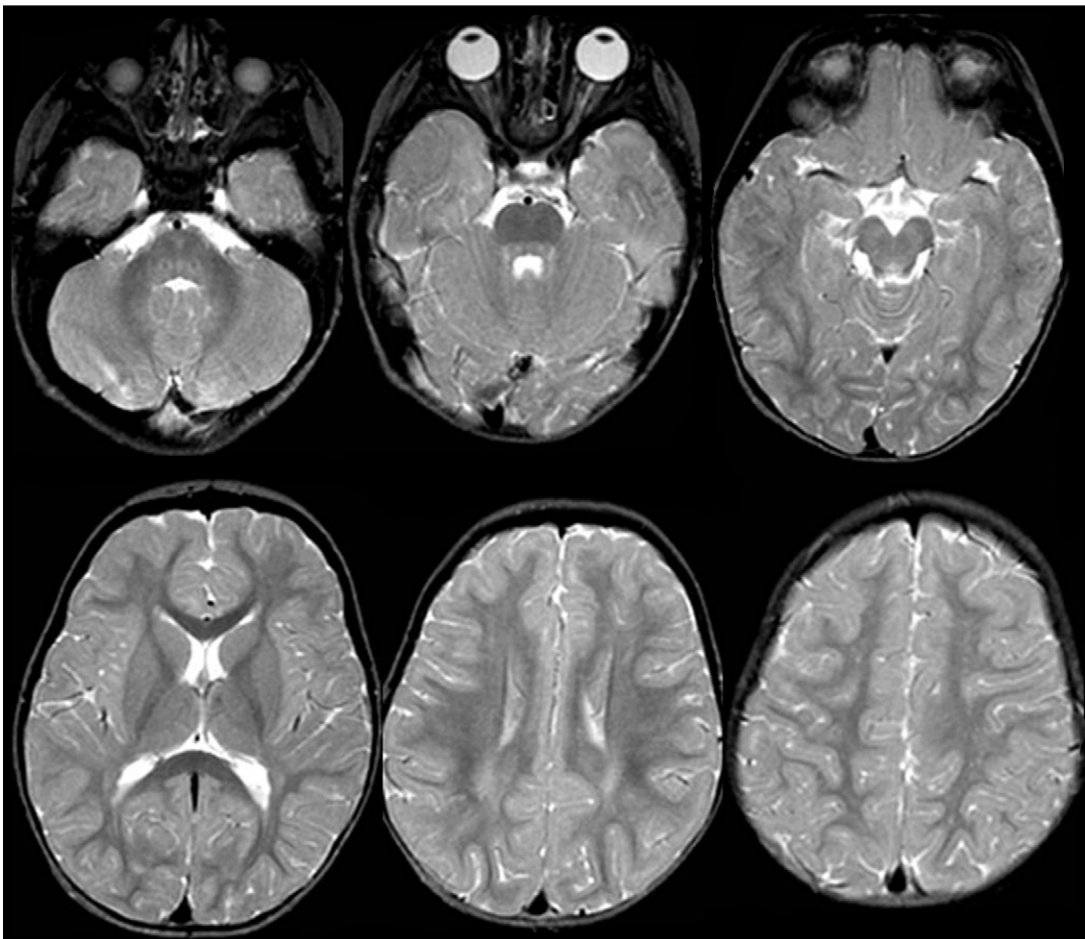


Fig. 8. (B) By 18 months, on T2, there is almost complete myelination except for the inferior frontal and temporal lobes as well as the terminal zones of myelination in the peritrigonal regions.

sheath, and tightening of the myelin spiral around the axon.^{6,15}

The Normal Progression of Myelination

The general rule of progression of normal myelination as outlined by Barkovich⁸ is that myelination begins in the fifth fetal month and continues throughout life. Myelination commences with the cranial nerves, which makes sense because we need these to rely on for survival. Generally, myelination progresses from bottom to top (caudocranial), back to front (posterior to anterior), and central to peripheral (deep to superficial) (Fig. 2).^{17,18} It therefore makes sense that the

brainstem and cerebellum myelinate before the cerebrum and that the basal ganglia and thalami commence myelination before the white matter. In addition, the posterior limb of the internal capsule myelinates before the anterior limb, splenium before the genu, and the central corona radiata before the subcortical regions.¹⁹

Counsell and colleagues²⁰ described myelination in the very preterm infant and confirmed myelination in the cerebellar vermis, vestibular nuclei, cerebellar peduncles, dentate nucleus, medial longitudinal fasciculus, medial geniculate bodies, subthalamic nuclei, inferior olivary nuclei, ventrolateral nuclei of the thalamus, medial and lateral lemnisci and inferior colliculi, as well as gracile

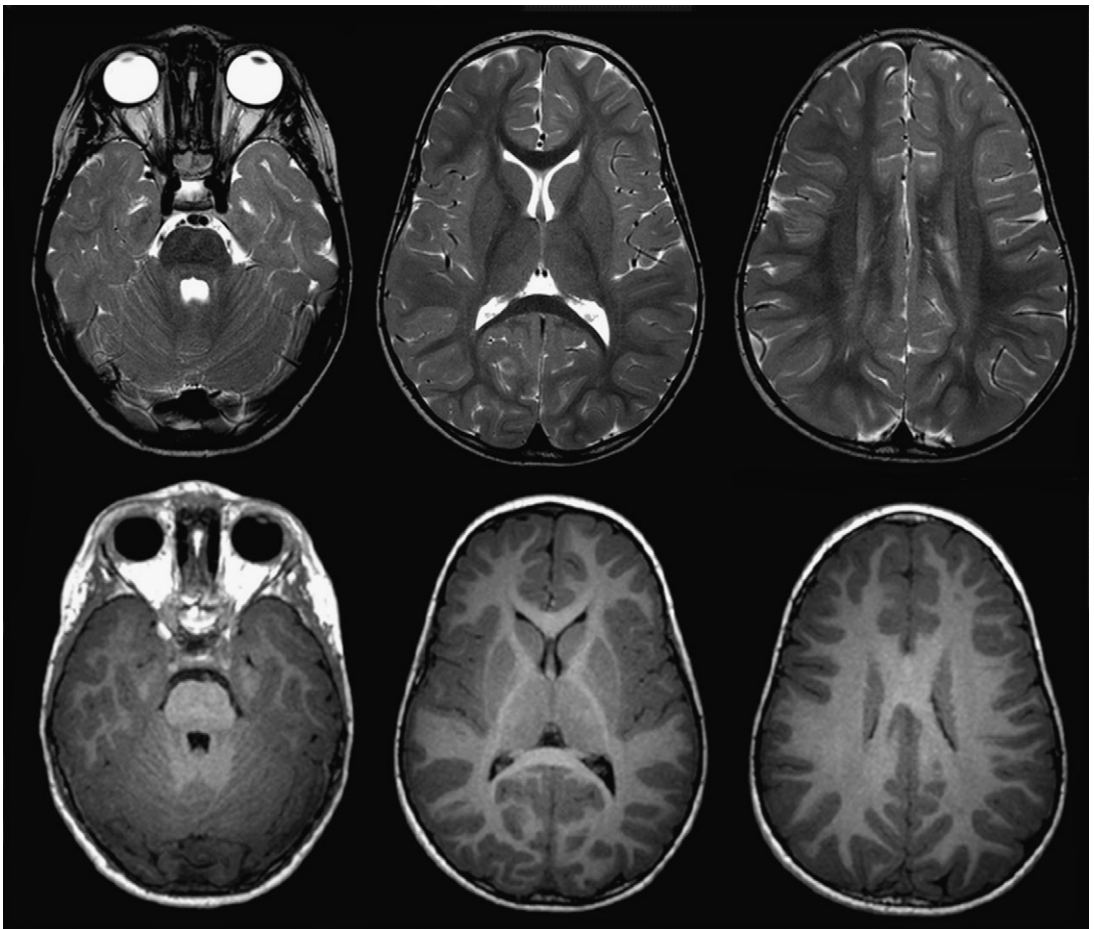


Fig. 9. Imaging of myelination. By 2 years, myelination is complete on T1 and T2 with some residual T2 hyperintensity parallel to the lateral ventricles as well as to the inferior frontal and temporal lobes.

and cuneate nuclei and fasciculi. The investigators did not find any new myelin sites between 28 and 36 weeks, after which there were again new myelin sites at the posterior limb of internal capsule, corona radiata, and the corticospinal tracts of the precentral and postcentral gyrus.

Histologic studies demonstrate myelination at birth in the brainstem, cerebellar white matter, and posterior limb of the internal capsule with extension to the thalamus and basal ganglia.²¹

Bird and colleagues¹⁹ (1989) reviewed 60 patients on MR imaging and found that there was wide variation in the rate, onset, and appearance of changes associated with myelination. The investigators studied marker sites for certain ages in determining normal myelin. For example, at birth (term), there was mature myelination in the posterior limb of the internal capsule, the cerebellar

peduncles, and the corona radiata around the central sulcus. The slowest areas to myelinate were the central white matter of the supratentorial lobes.¹⁹ The investigators again consistently confirmed progression of myelination in the posterior limb before the anterior limb, splenium before genu, and central corona radiata before poles in all subjects. This posterior to anterior sequence has been seen in autopsy subjects.²²

Paus and colleagues²³ (2001) described 3 developmental patterns seen with respect to gray–white matter differentiation in the first 12–24 months of life. These patterns are the infantile pattern for less than 6 months with a reversal of the normal adult pattern, the isointense pattern (8–12 months) in which there is poor differentiation between gray and white matter, and the early adult pattern (greater than 12 months) in which gray matter

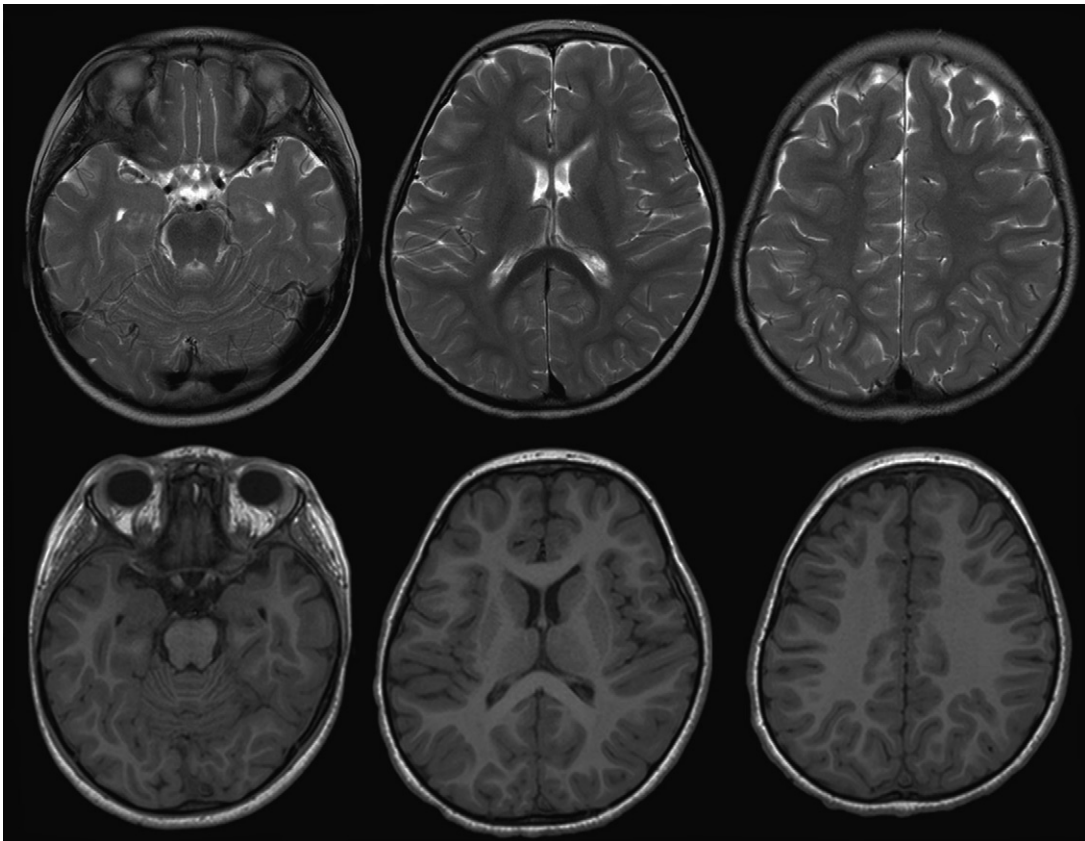


Fig. 10. Imaging of myelination. By 3 years of age, myelin should be complete and adultlike in appearance on both T1-weighted and T2-weighted sequences.

signal is greater than that of white matter on T2 and less than that of white matter on T1. This change is thought to be related to changes in relaxation times with rapid shortening in the first 12 months because of a rapid decrease in the water content of gray and white matter.²³

Welker and Patton (2011)¹⁵ recently published a table of age-specific progression of myelination on MR imaging with reference to T1, T2, Fluid-attenuated inversion recovery (FLAIR), and DTI sequences (Figs. 3–11). The reader is referred to this article for further detail.

The corpus callosum also undergoes a fairly uniform pattern of thickening and myelination. The splenium myelinates first by approximately

3 months followed by the body at 4 to 5 months and the genu by 5 to 6 months. There are changes in both the shape and signal intensity throughout development. These changes occur mainly in the first year of life.²⁴ As a neonate, the corpus callosum is thin in its entirety with thickening first seen in the genu (by 2–3 months) followed by the splenium, which demonstrates rapid thickening at about 5–6 months reaching the size of the genu by the end of the seventh month.²⁴ The corpus callosum enlarges gradually over 12 months (Figs. 12 and 13).²⁴ With respect to myelination on T1, the splenium of the corpus callosum demonstrates increased signal intensity by 4 months, and the genu by 6 months.¹⁷ Thus

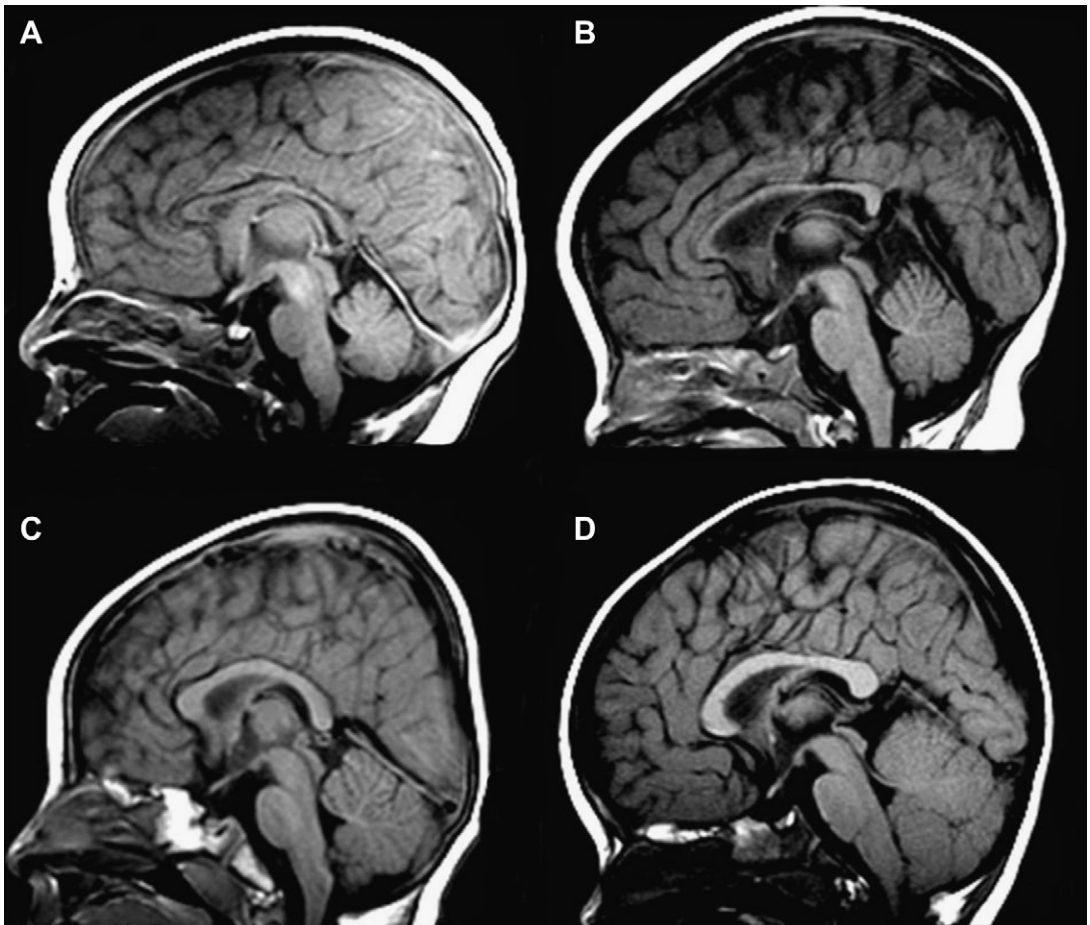


Fig. 11. Imaging of myelination. Sagittal T1-weighted sequences demonstrating normal development of the corpus callosum. (A) term, (B) 4 months, (C) 6 months, and (D) 16 months.

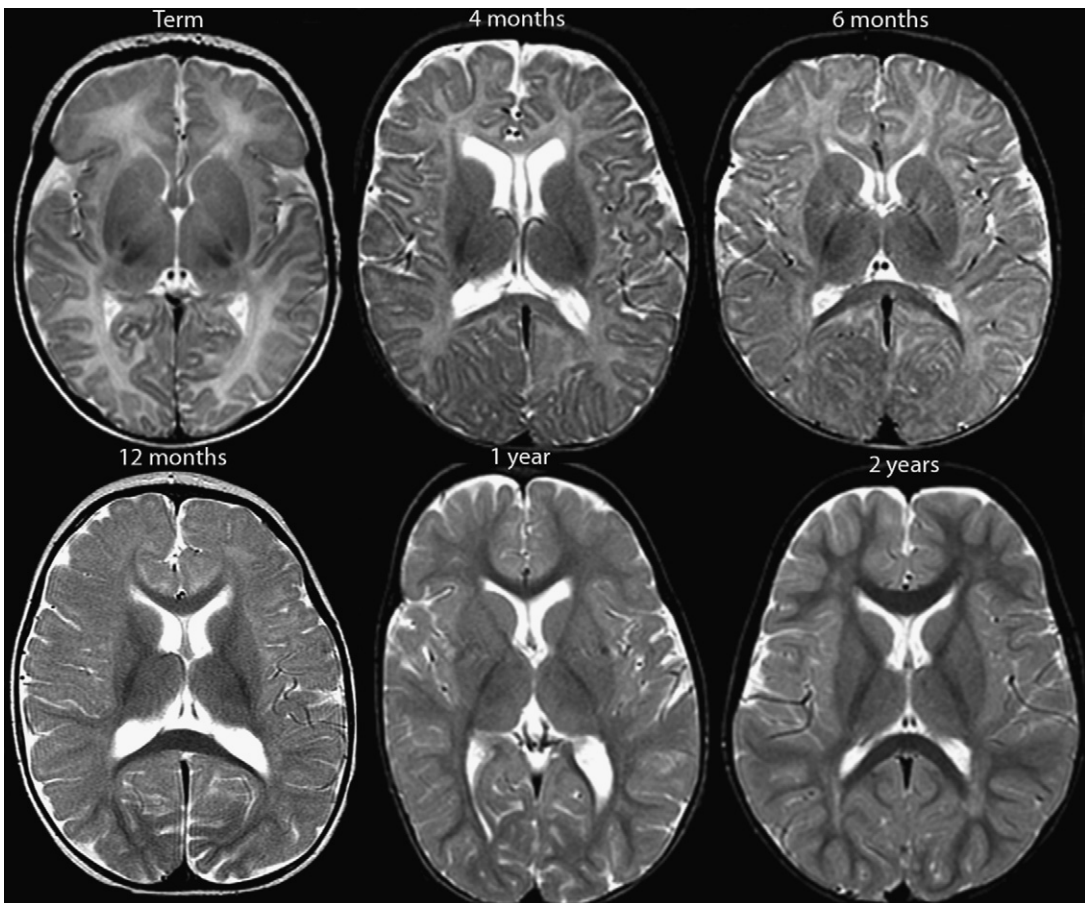


Fig. 12. Summary slide of progression of normal myelination. Progression of normal myelination on MR imaging from birth (term) to 2 years of age on a T2-weighted sequence.

the splenium myelinates before the genu.¹⁹ By 8 to 9 months, the corpus callosum appears identical to that of an adult.^{24,25}

Terminal Zones of Myelination

The last associative area to mature on MR imaging is the peritrigonal zone, which is the region posterosuperior to the trigones of the lateral ventricles.²⁶ This region maintains a persistent T2 hyperintensity, but not brighter than the gray matter on T2-weighted sequences (Fig. 14). Parazzini and colleagues,²⁶ also described terminal zones of myelin maturation on T2 in the frontotemporal subcortical regions. The investigators determined that these areas can exhibit subcortical T2 hyperintensity until 36 to 40 months (see Fig. 14).

With respect to idiopathic developmental delay, Maricich and colleagues²⁷ studied 93 children and found no definite evidence for correlation between idiopathic developmental delay and delay in myelination on T2-weighted imaging.

SUMMARY

MR imaging is to date the best modality for noninvasive assessment of myelin and myelination in the pediatric brain. To allow diagnosis of disorders with permanent hypomyelination or delayed myelin deposition, the normal progression of myelination should be known. For this reason, a pictorial review and discussion of normal MR imaging progression of myelination has been performed. In addition, normal progression of the development of the corpus callosum as well as recognition of the normal terminal zones of myelination is vital in understanding imaging of the pediatric brain.

ACKNOWLEDGMENTS

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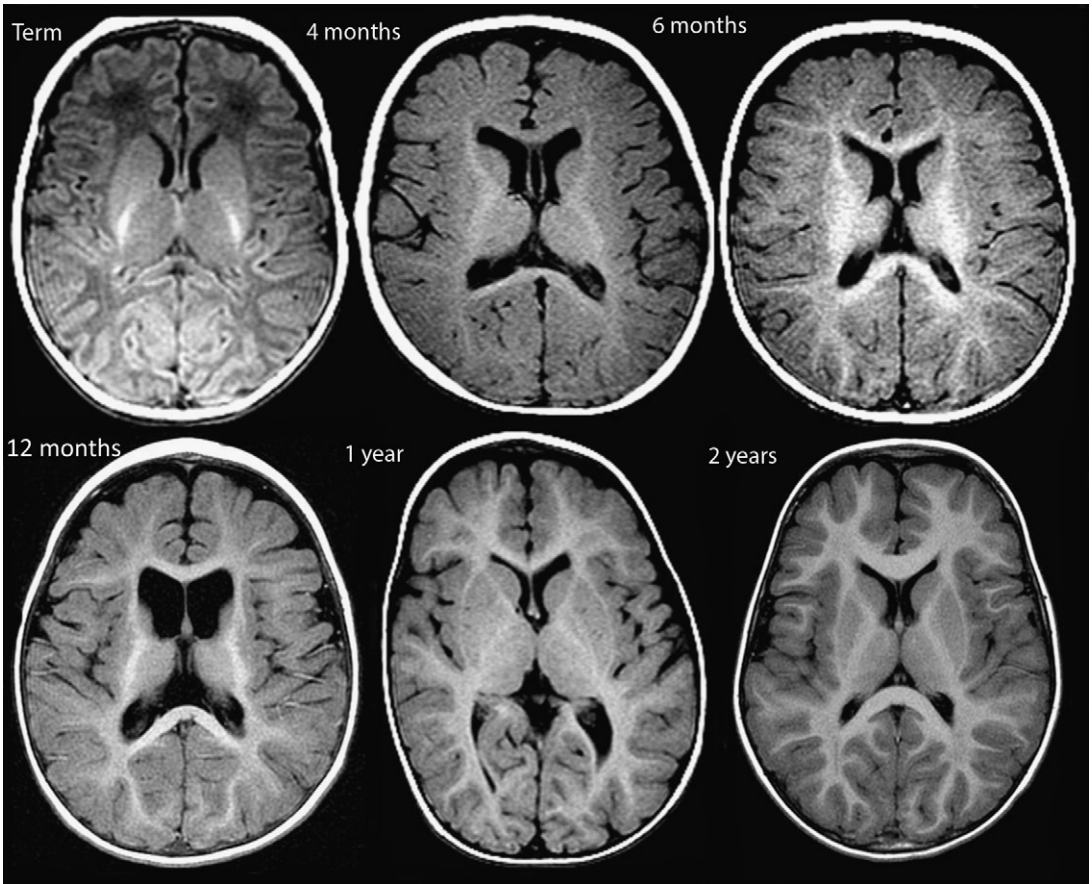


Fig. 13. Summary slide of progression of normal myelination. Progression of normal myelination on MR imaging from birth (term) to 2 years of age on a T1-weighted sequence.

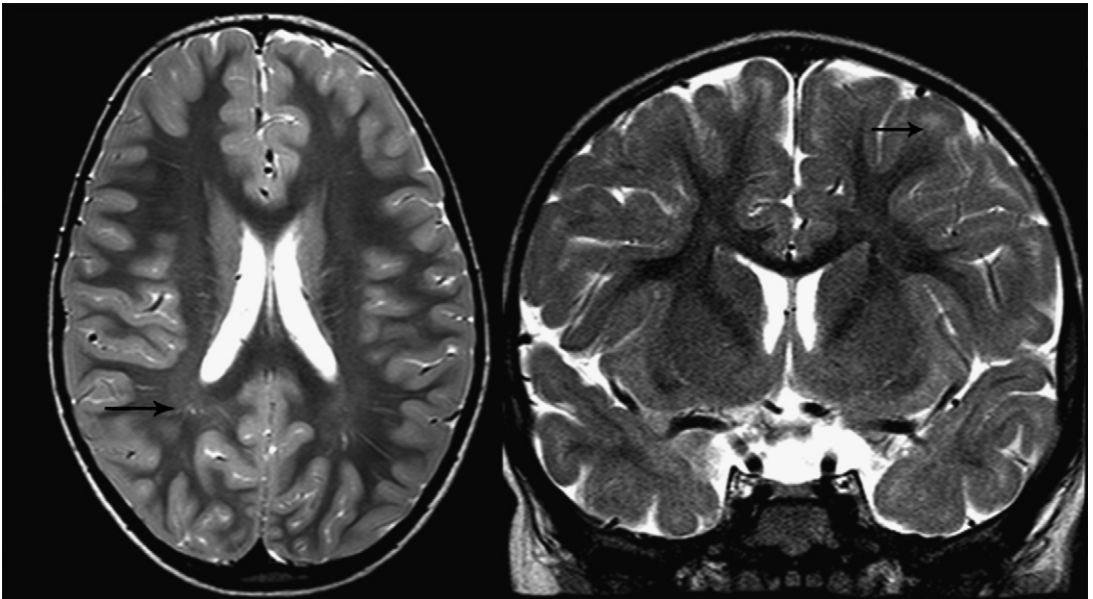


Fig. 14. Axial and coronal T2-weighted sequences demonstrate normal terminal zones of myelination (*black arrows*). These zones are classically located in the posterior periventricular region as well as the frontotemporal subcortical regions.

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