PICTORIAL ESSAY

Myelination Clock: a Simplified Step-by-step Approach to Normal Myelination

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ABSTRACT

Myelination is an essential step in the functional maturation of the brain. Magnetic resonance imaging allows the degree of maturation of a child's brain to be assessed by estimation of the degree of myelination. Myelination follows an orderly and predictable sequence. Understanding the normal sequence and identifying an aberrant course can enable early detection of various leukodystrophies and hypomyelinating conditions. The purpose of this article was to describe a simple step-by-step approach that highlights important review areas and enables rapid and easy determination of the degree of myelination.

Key Words: *Magnetic resonance imaging; Myelin sheath; Nerve tissue protein; Neurons*

中文摘要

髓鞘的發展過程：觀察正常髓鞘形成的一個簡化步驟

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髓鞘化是大腦邁向成熟的重要步驟。MRI可以透過髓鞘形成的程度來評估兒童大腦的發展過程。髓鞘的形成是有序並可預測的一個過程。了解正常髓鞘化的過程以及辨識異常可及早發現各種腦白質營養不良和髓鞘過少的症狀。本文描述一個簡單的步驟來集中觀察一些重要區域，以及更快捷簡便地判定髓鞘化的程度。

INTRODUCTION

Myelination is the process by which a lipid bilayer forms around an axonal fibre. It is a key process in the maturation of the brain. Myelin is produced by oligodendroglial cells and contains approximately 70% lipid and 30% protein. The process of myelination is a continuous sequential process with an orderly and predictable course. Magnetic resonance imaging (MRI) is an important means to study the progression of myelination and determine the maturation of the brain.[1] Estimation of the degree of myelination is often the first step in paediatric neuroimaging. The normal appearance of the progressively myelinating infant brain is different from the adult brain and should not be mistaken for white matter abnormalities. The aim of this article was to provide a pictorial review of myelination progression

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as seen on T1-weighted (T1W) and T2-weighted (T2W) MRI. This article provides a simple step-by-step guide to facilitate detection of the degree of myelination by highlighting important review areas.

MAGNETIC RESONANCE IMAGING

MRI has the capability to demonstrate the continuous process of myelination at different ages of life. MRI sequences used to study myelination primarily include T1W and T2W images with additional utilisation of diffusion-weighted imaging and diffusion tensor imaging. Diffusion tensor imaging can demonstrate myelination progression over a longer period of development than conventional T1W and T2W images.[2] Conventional T1W and T2W images are used in routine clinical practice to determine degree of myelination.

T1 and T2 Signal Characteristics of Myelination

On T1W MRI scans, myelinated white matter appears hyperintense compared with grey matter. On T2W images it appears hypointense compared with grey matter. Hyperintensity on T1W images is a result of the high lipid content of myelin whereas T2 hypointensity is due to the hydrophobic nature of high lipid content myelin that results in reduced water content compared with grey matter.[1-4]

There are two important concepts to understand while studying myelination progression on MRI. Firstly, the myelination pattern demonstrated on MRI is an apparent myelination and not actual myelination. It is dependent on the field strength of scanning and the pulse sequences used. Hence the myelination pattern differs on T1W and T2W images at different stages. Second, myelination is not an all-or-none process. It is an ongoing process in which different structures are in different stages and degrees of myelination. Myelination nonetheless follows a predictable sequence in progression. By evaluating the differential progression of myelination on T1W and T2W images and the various sequential imaging milestones attained, the degree of brain maturation can be determined.[1,4,5]

Importance of Recognising Myelination on Imaging

A variety of factors can result in delayed myelination. Important causes include hypoxic ischaemic events, congenital and postnatal infections, congenital malformations, chromosomal abnormalities, and inborn errors of metabolism. Understanding the normal

pattern of myelination and identification of an aberrant course can result in early detection of the various leukodystrophies and hypomyelinating conditions. An unchanged pattern of deficient myelination on two successive MRI scans at least 6 months apart suggests hypomyelination.[6]

General Rules of Myelination

In general, and as outlined by Barkovich,[5] myelination progresses from caudal to cephalad, dorsal to ventral, and from central to periphery. Thus according to this rule, the brainstem myelinates before the cerebellum and basal ganglia; the basal ganglia and cerebellum before the cerebral hemisphere. Similarly, the dorsal part of the brainstem myelinates before ventral part, the occipital lobe myelinates before the frontal lobe, and the central corona radiata myelinates before the peripheral white matter of the lobes.

PATTERN RECOGNITION: MYELINATION CLOCK

The myelination clock is a simplified graphic display of myelination progression as seen on T1W and T2W MRI images (Figure 1). It is not a detailed representation of myelination but it details important milestones that help in rapid and easy determination of the stage of myelination (Figure 2).

T1-weighted Imaging

During the first 6 months of life, T1W images are considered ideal for studying brain myelination. Structures that show myelination on T1W images at birth are the medulla, dorsal part of pons, midbrain, posterior limb of internal capsule and perirolandic cortex (Figure 3). Important landmarks for myelination on T1 images include myelination of deep cerebellar white matter by 3 months, splenium by 4 months, and genu by 6 months. After 6 months of age, further distinction of myelination on T1W images is difficult and myelination is evaluated better on T2W imaging.[1,3,4]

T2-weighted Imaging

On T2W images at birth, the dentate nucleus hilus is hyperintense surrounded by a hypointense band (Figure 3). Loss of this hyperintensity is seen by 2 to 3 months (Figure 4).[1]

The dorsal part of the pons is myelinated at birth and appears hypointense compared with the ventral part that is unmyelinated and appears hyperintense resulting
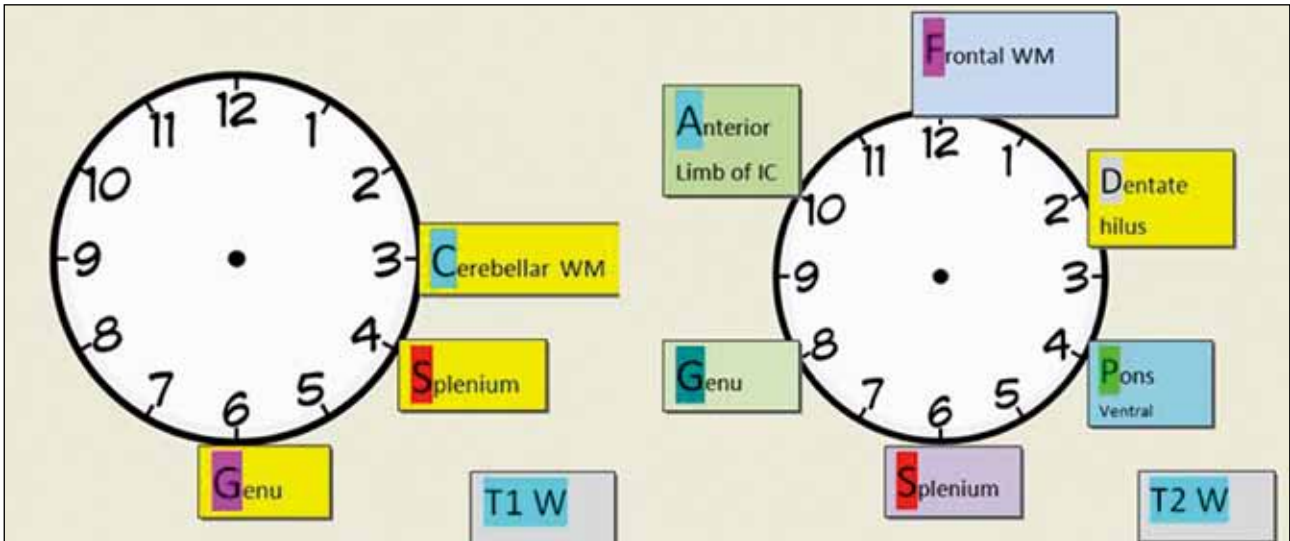
Figure 1. Myelination clock: graphical representation of myelination milestones at different ages on T1- and T2-weighted images. On T1-weighted images, important milestones are myelination of cerebellar white matter at 3 months, splenium of corpus callosum at 4 months, and genu at 6 months. On T2-weighted images, important milestones are myelination of dentate nucleus hilus at 2 to 3 months, ventral pons at 4 months, splenium at 6 months, genu at 8 months, anterior limb of internal capsule at 10-11 months, and frontal white matter at 12-13 months.
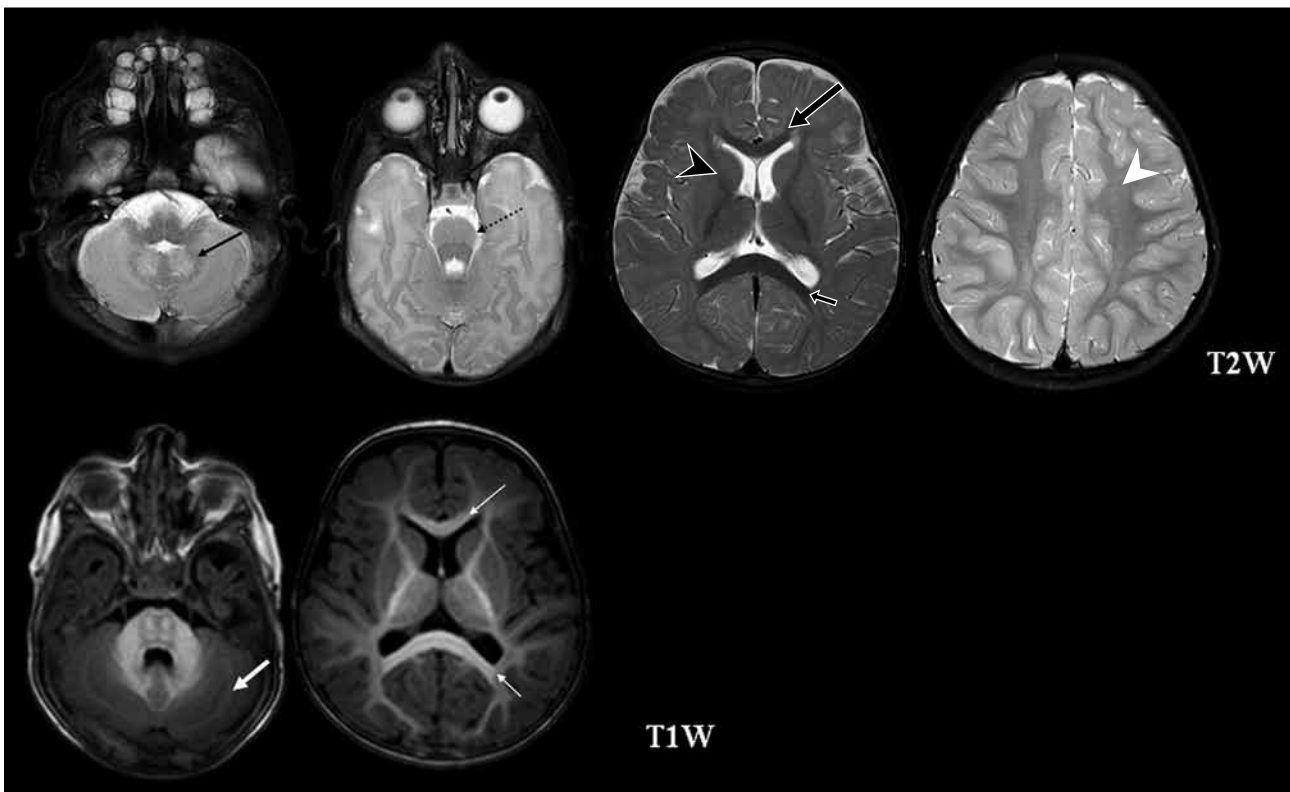
Figure 2. Myelination landmarks include myelination of the dentate nucleus hilus (thin black arrow) at 2-3 months, ventral pons (dotted arrow) at 4 months, splenium (thick long black arrow) at 6 months, genu (thick short black arrow) at 8 months, anterior limb of internal capsule (black arrowhead) at 10-11 months, and frontal white matter (white arrowhead) at 12-13 months on T2-weighted images. On T1-weighted images, landmarks include myelination of cerebellar white matter (thick white arrow) at 3 months, splenium (thin long white arrow) of corpus callosum at 4 months, and genu (thin short white arrow) at 6 months.
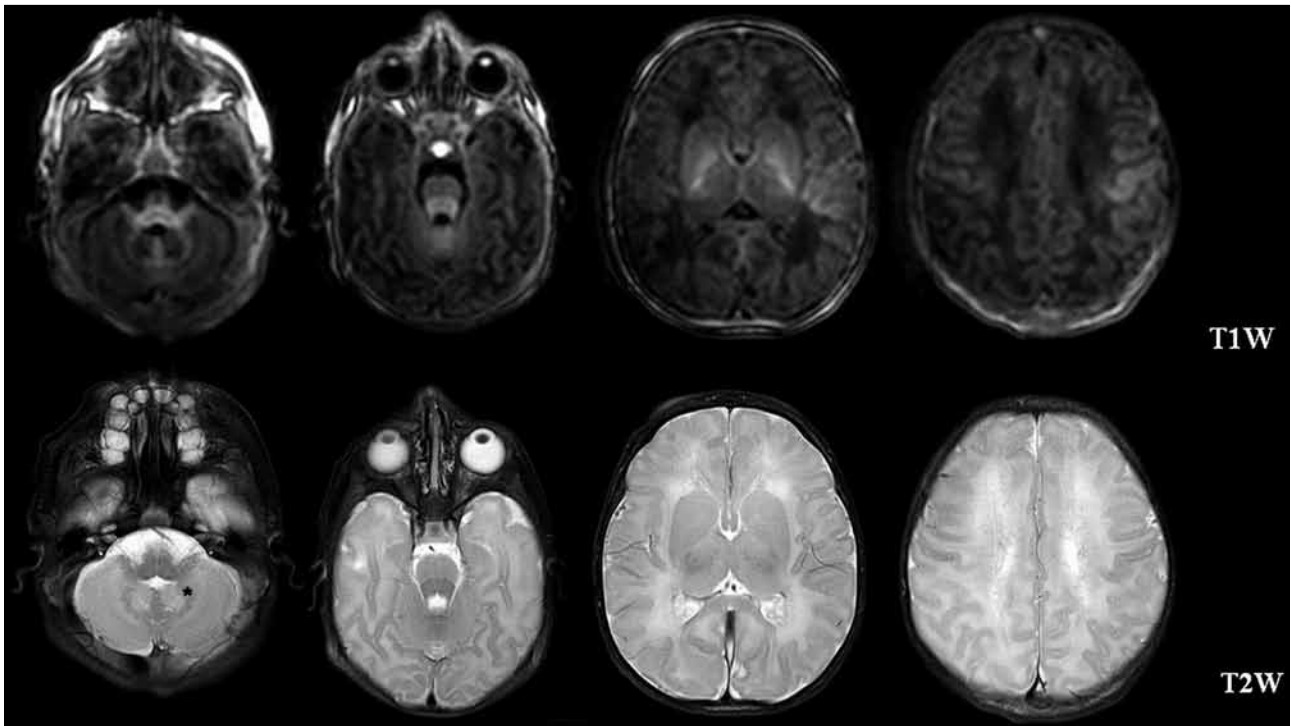
Figure 3. Myelination at birth in a term infant. On axial T1-weighted images, structures myelinated at birth include the dorsal brainstem, posterior limb of internal capsule, lateral thalamus, central centrum ovale, and perirolandic region. On T2-weighted images, dorsal brainstem, lateral thalamus, and perirolandic region appear hypointense. Note the hilus of dentate nucleus (*) is hyperintense surrounded by a dark band. The ventral brainstem is hyperintense compared with the hypointense myelinated dorsal brainstem.
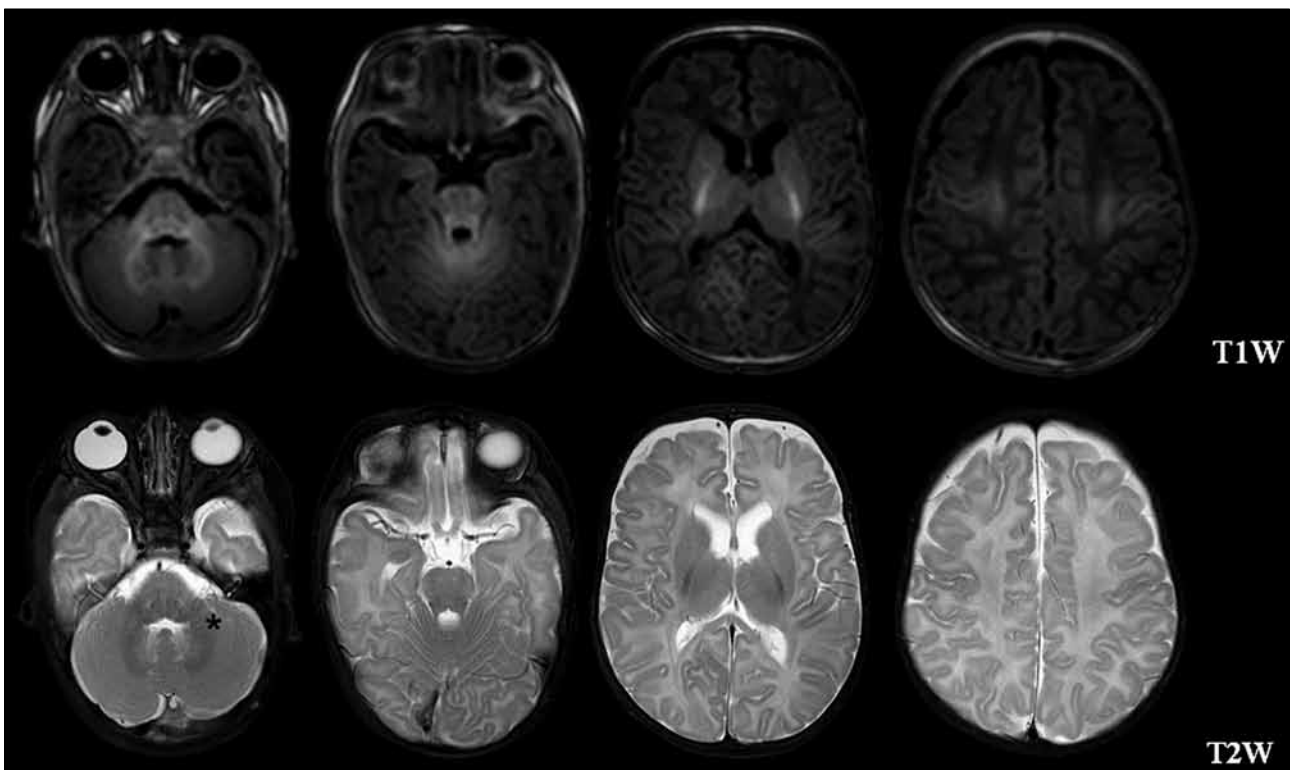

Figure 4. Myelination at 2 months. On axial T1-weighted images, dorsal brainstem, posterior limb of internal capsule, central centrum ovale, and perirolandic region are hyperintense. On T2-weighted images, ventral brainstem is still hyperintense compared with the hypointense myelinated dorsal brainstem. The hyperintensity of the dentate nucleus (*), however, has been lost at 2 months and completely darkens at 3 months.

in differential signal characteristics. By 4 months of age, the ventral part of the pons becomes equally hypointense to the dorsal pons, resulting in loss of this in loss of this differential signal characteristic. This is an important landmark at 4 months (Figure 5).

At 6 months of age, the splenium of the corpus callosum shows diffuse myelination and appears hypointense compared with the genu that is still predominantly isointense. This results in differential signal characteristics between the splenium and the genu of the corpus callosum (Figure 6). By 8 months of age, the genu of the corpus callosum is completely myelinated and becomes hypointense and there is loss of this differential signal characteristic (Figure 7).

By 10 to 11 months of age, the anterior limb of the internal capsule appears completely myelinated on T2W images, showing similar hypointensity to the posterior limb (Figure 8).

By 12 months of age, ongoing myelination of the frontal white matter on T2W images is seen and is complete by 14 months. At this stage the temporal white matter remains hyperintense and this results in a differential signal characteristic between frontal and temporal white matter (Figure 9).

The temporal white matter myelination usually begins by 14 months and is completed by 16 months. The terminal U fibres are myelinated by 18 to 24 months. By 2 years of age, myelination is considered to be complete, except for the terminal zones of myelination; and the brain resembles that of an adult (Figure 10). At this stage it is again important to stress that these myelination landmarks are not all or none but a gradual steady process of ongoing myelination. For example, at 7 months of age, the genu shows mild T2 hypointensity compared with the completely myelinated dark splenium and this is due to ongoing myelination. At 8 months, the genu appears as hypointense as the splenium.

Terminal Zones: Peritrigonal White Matter and Subcortical White Matter

Areas of high signal intensity are commonly seen in the peritrigonal region, particularly posterior and superior to the ventricular trigones on T2W images. The underlying cause of this high signal intensity is a combination of the delayed myelination and large perivascular spaces. It
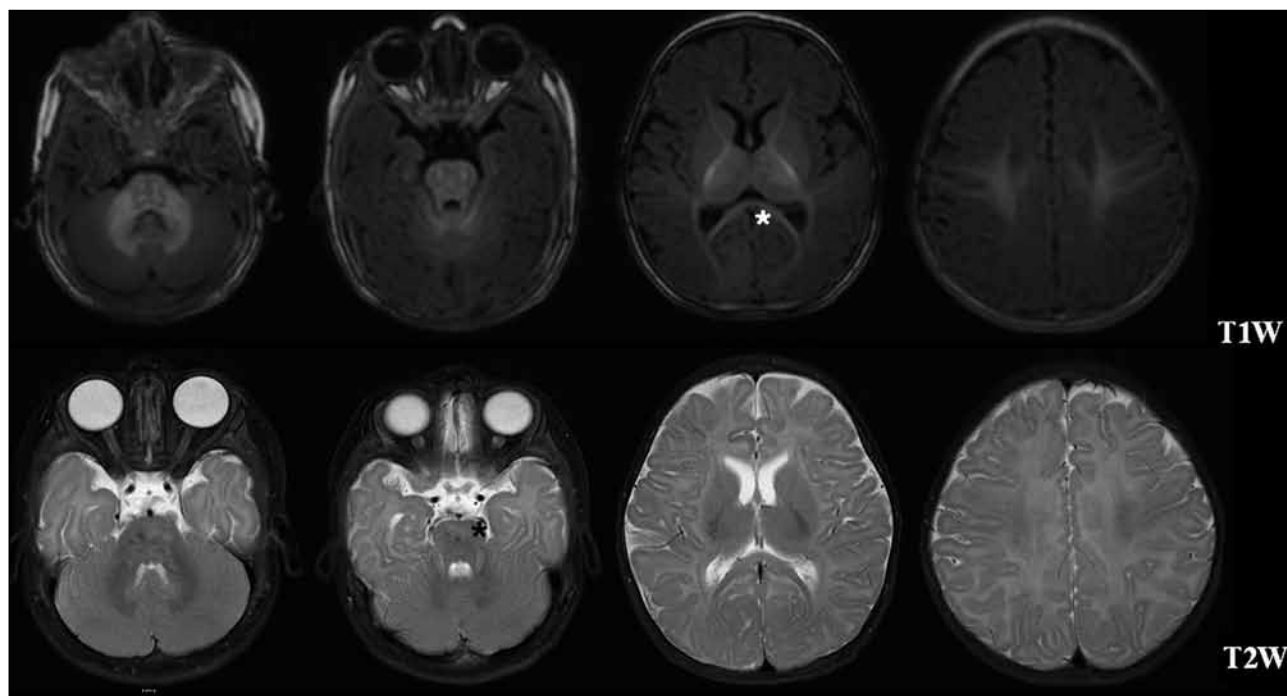

Figure 5. Myelination at 4 months. On axial T1-weighted images at 4 months, the cerebellar white matter and splenium of corpus callosum are now hyperintense. Note the differential contrast between the myelinated splenium (white *) and unmyelinated genu. On T2-weighted images, the ventral brain stem (black *) is now myelinated and isointense to the dorsal brainstem, resulting in loss of differential contrast in the brainstem.
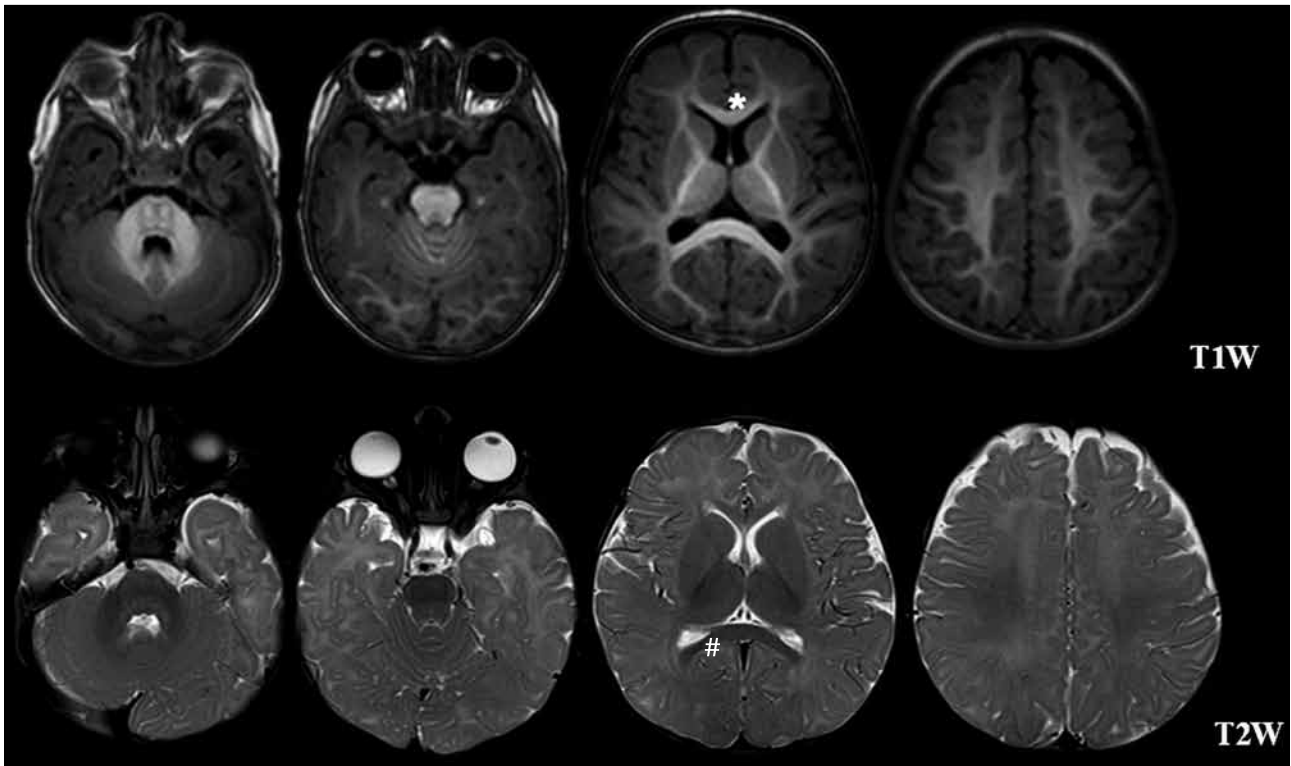
Figure 6. Myelination at 6 months. On axial T1-weighted images at 6 months, genu (white *) is now myelinated and equal in signal intensity to the splenium. On T2-weighted images, splenium (#) is now myelinated compared with the unmyelinated genu, resulting in differential contrast in signal intensity.
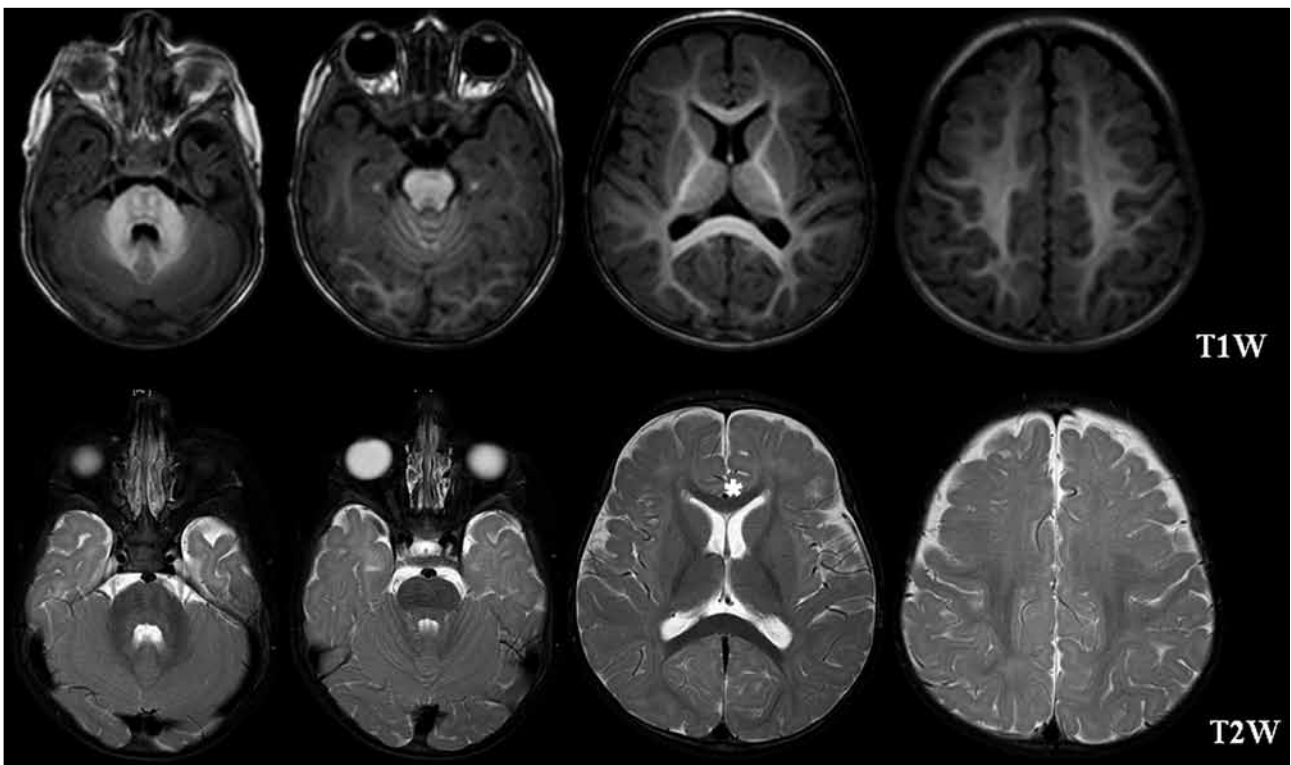

Figure 7. Myelination at 8 months. On axial T2-weighted images, further progression of myelination occurs with myelination of the genu (*) of corpus callosum. The genu is now equal in signal intensity to the splenium. Myelination is complete on T1-weighted images.
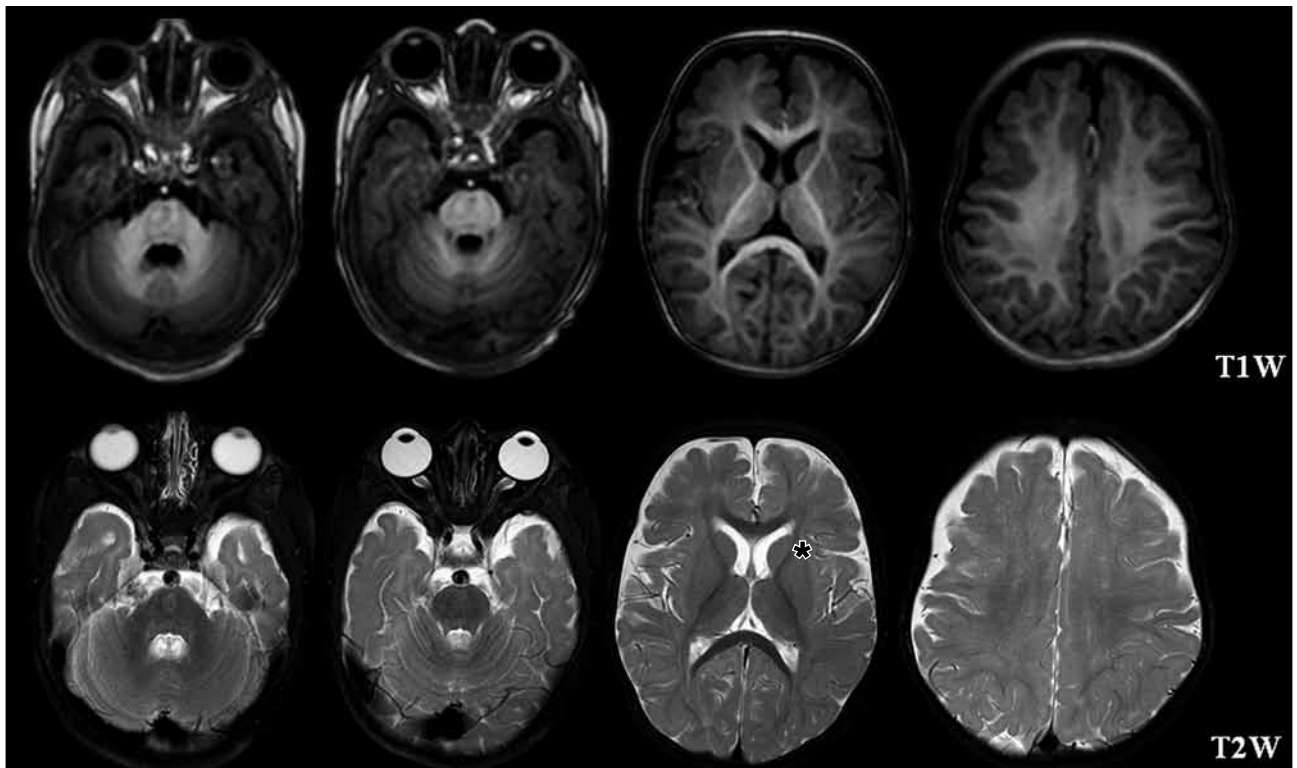
Figure 8. Myelination at 10 months. On axial T2-weighted images, myelination of the anterior limb of internal capsule (*) is seen, which is now equal in signal intensity to the posterior limb. Note the hyperintense frontal and temporal white matter. Myelination is complete on T1-weighted images.
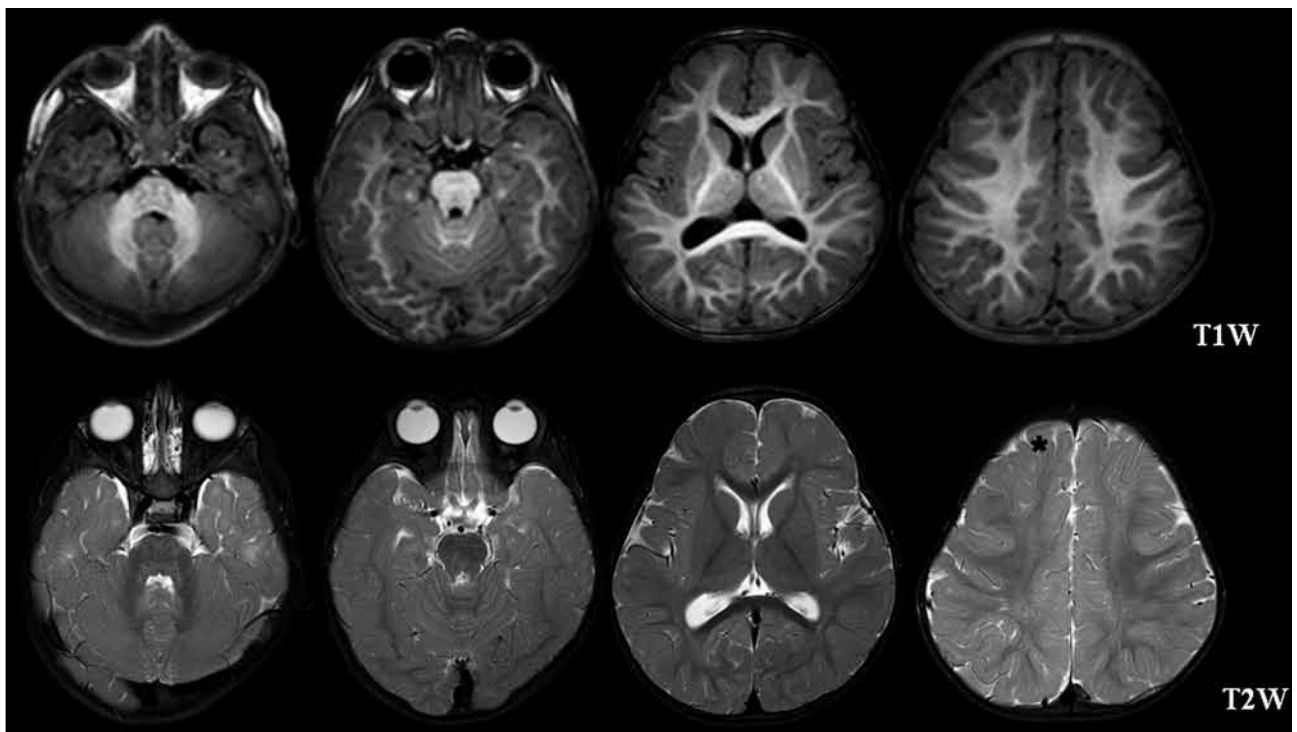

Figure 9. Myelination at 1 year. On axial T2-weighted images, progression of myelination is seen in the frontal white matter (*) and is complete by 14 months. Note the hyperintense temporal white matter, resulting in differential contrast in signal intensity in frontal and temporal white matter. Myelination is complete on T1-weighted images.
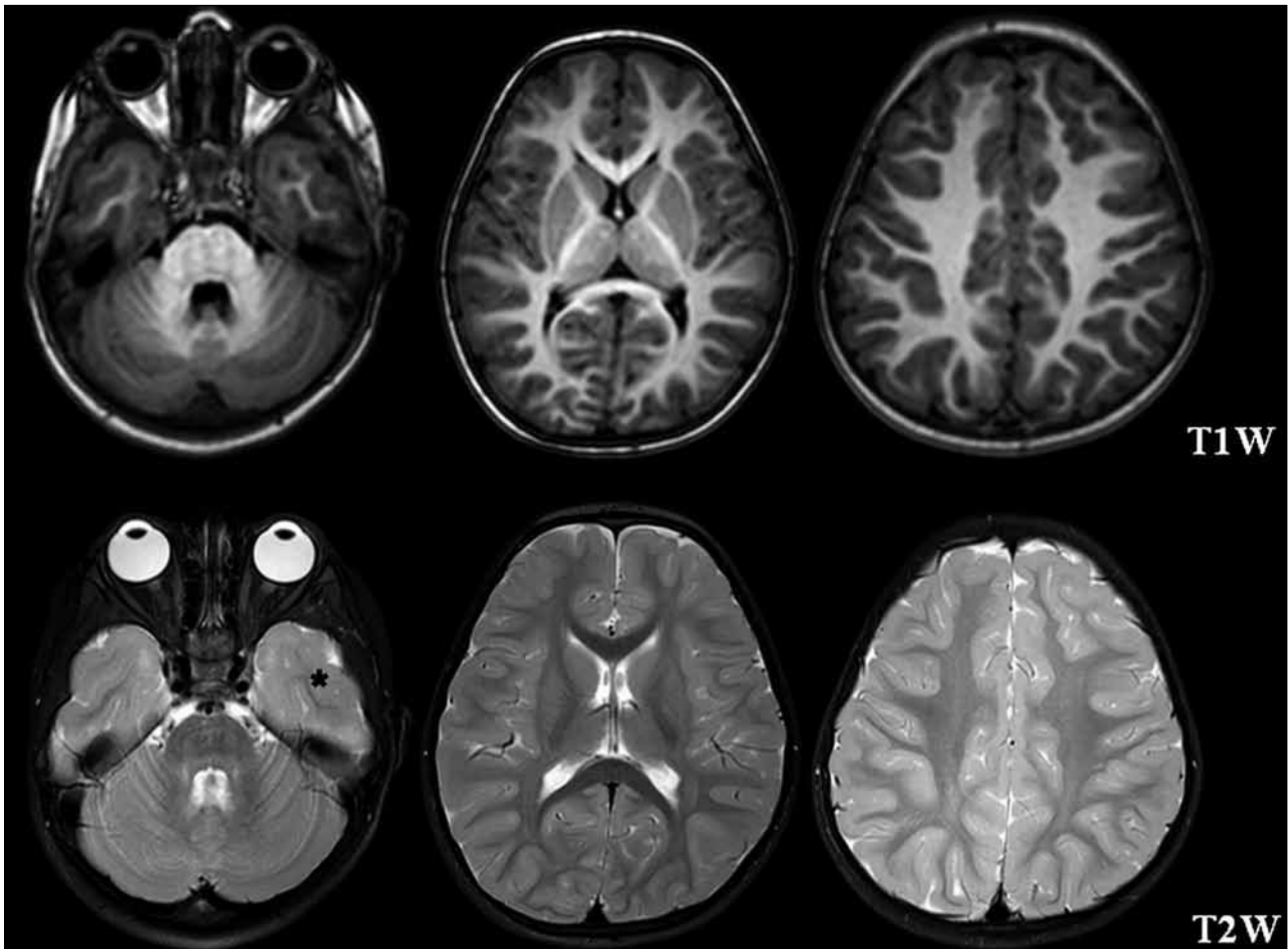
Figure 10. Myelination at 2 years. On axial T1- and T2-weighted images, myelination is complete. The temporal white matter (*) myelinates between 14 and 18 months.

can be confused with periventricular leukomalacia that has a similar appearance. Periventricular leukomalacia is loss of brain tissue with irregularity of the ventricular margin and thinning of the body and splenium of the corpus callosum. Baker et al[7] have noted that a rim of myelinated hypointense white matter is present between the ventricular margin and the terminal zone of high signal intensity in normal individuals. This rim of low signal intensity is lost in the presence of periventricular leukomalacia (Figure 11). The temporoparietal subcortical regions are also considered to be terminal zones of myelination and show persistent T2 hyperintensity up to the age of 3 years.[8]

CONCLUSION

MRI is a useful means to study the normal progression of myelination of the brain. Myelination follows an orderly and predictable sequence of progression. By
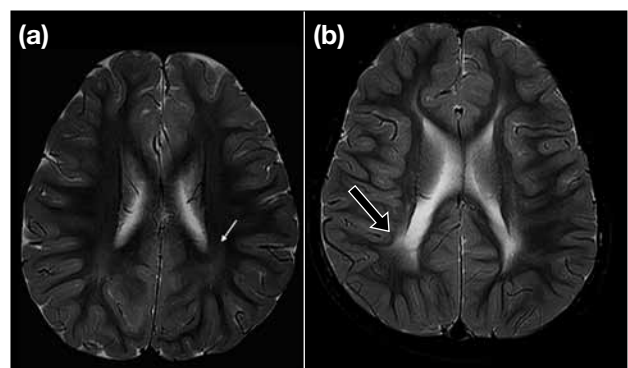

Figure 11. Terminal myelination zones. Axial T2-weighted image of a 3-year-old patient shows (a) normal periventricular white matter hyperintensities that represent terminal myelination zones separated from ventricular margin by myelinated hypointense white matter (white arrow). (b) In comparison, axial T2-weighted image in another patient shows periventricular leucomalacia as abnormal periventricular white matter hyperintensity reaching up to the ventricular margin (thick black arrow) with associated irregularity of the ventricular margin.

evaluating the differential progression of myelination on T1W and T2W images and the various sequential imaging milestones attained, the degree of brain maturation can be determined. Understanding the normal pattern of myelination and identification of an aberrant course can result in early detection of various leukodystrophies and hypomyelinating conditions.

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