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MR Assessment of Myelination in Infants and Children: Usefulness of Marker Sites

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A retrospective study was made of 60 patients, 1 month to 3 years old, to determine the normal progression of white matter myelination on MR imaging. All examinations were performed with a 1.5-T unit, and axial T1- and T2-weighted images were evaluated in each patient. Multiple sites in the cerebral hemisphere and cerebellum were examined in each case for the presence and degree of myelination. The results show that MR imaging is sensitive to the early changes of white matter myelination, and imaging patterns correlate with known patterns from pathologic studies. At the time of birth in a full-term infant the posterior limb of the internal capsule, central corona radiata, and cerebellar peduncles show visible myelination. Myelination in the centrum semiovale then proceeds anteriorly and posteriorly. Both T1- and T2-weighted images show these changes, which are best explained by a decrease in the water content of white matter as myelination progresses. Knowledge of these normal myelination patterns is essential in evaluating MR imaging studies in infants and children and in diagnosing delayed myelination.

Myelination is a dynamic process in the developing infant brain and for this reason is an excellent marker of brain maturation. MR imaging has for the first time provided a method for imaging the evolution of myelination in vivo [1–4]. The purpose of this study is to identify specific marker sites on MR imaging that aid in assessing the normal progression of myelination in children.

Materials and Methods

Normal MR scans in 60 patients, aged 1 week to 3½ years old, were evaluated. The patients were referred for a multitude of various clinical conditions; however, only those initially and retrospectively interpreted as normal were included in the study. Patients with clinical conditions known to be associated with delayed myelination, such as developmental delay, preterm delivery, or congenital anomalies were excluded from the study. The degree of myelination in each patient was ranked by a consensus of two observers on an ordinal scale of −1 to +3 using the posterior limb of the internal capsule as an internal standard (Table 1). Both T1-weighted, 600/20 (TR/TE) and T2-weighted, 2500/80, spin-echo images were evaluated in each patient. The intermediate or proton density weighted images, 2500/40, were not used in the evaluation because of relative gray/white matter isointensity on this pulse sequence. Scanning was performed on a 1.5-T MR system* with a 256 × 256 acquisition matrix. In each patient the degree of myelination on T1- and T2-weighted images versus age was plotted graphically and smoothed curves were constructed from the data points (Fig. 1).

Results

The general overall appearance of the cerebral white matter in our patient population was categorized by three age groups. Patient age distribution is presented in Figure 2. From birth to approximately 4 months the cerebral white matter was of relatively low signal intensity on T1-weighted images and of high signal

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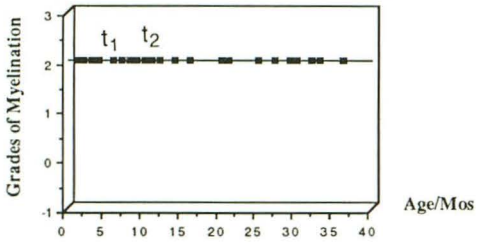
* General Electric, Milwaukee, WI.

Post. Limb Internal Capsule



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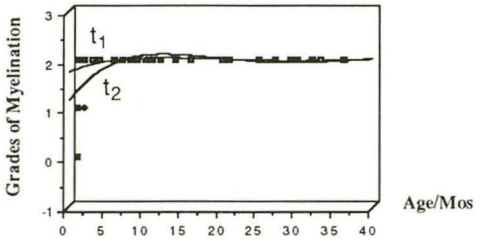

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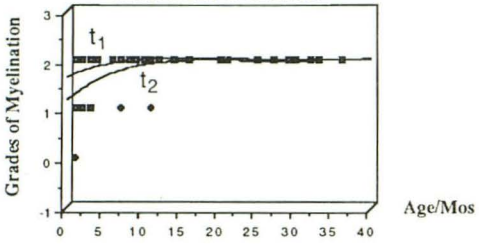

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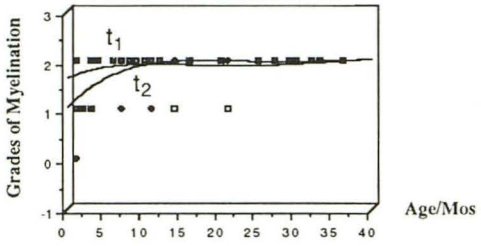

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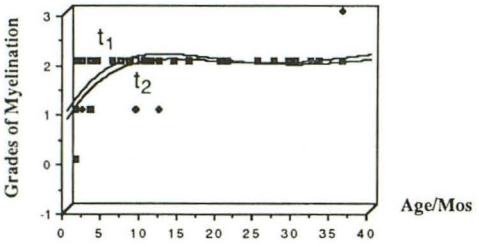

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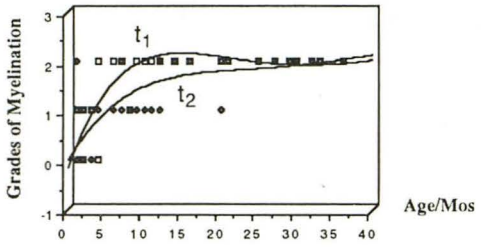

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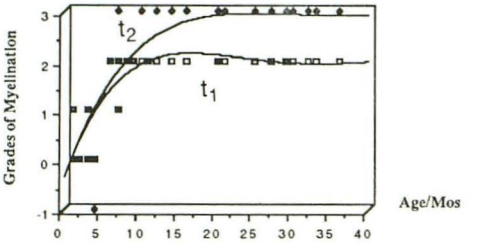
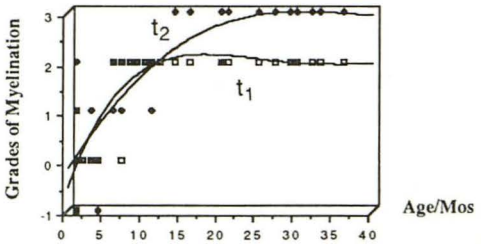


Genu CC



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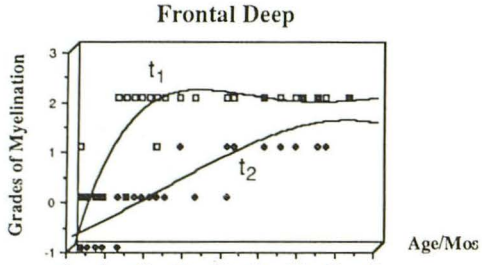
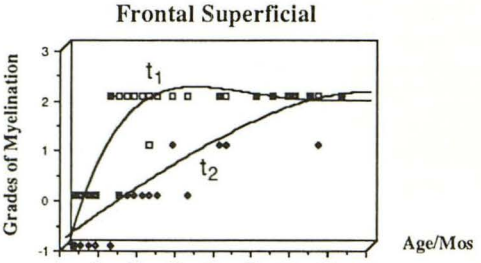


Frontal Superficial



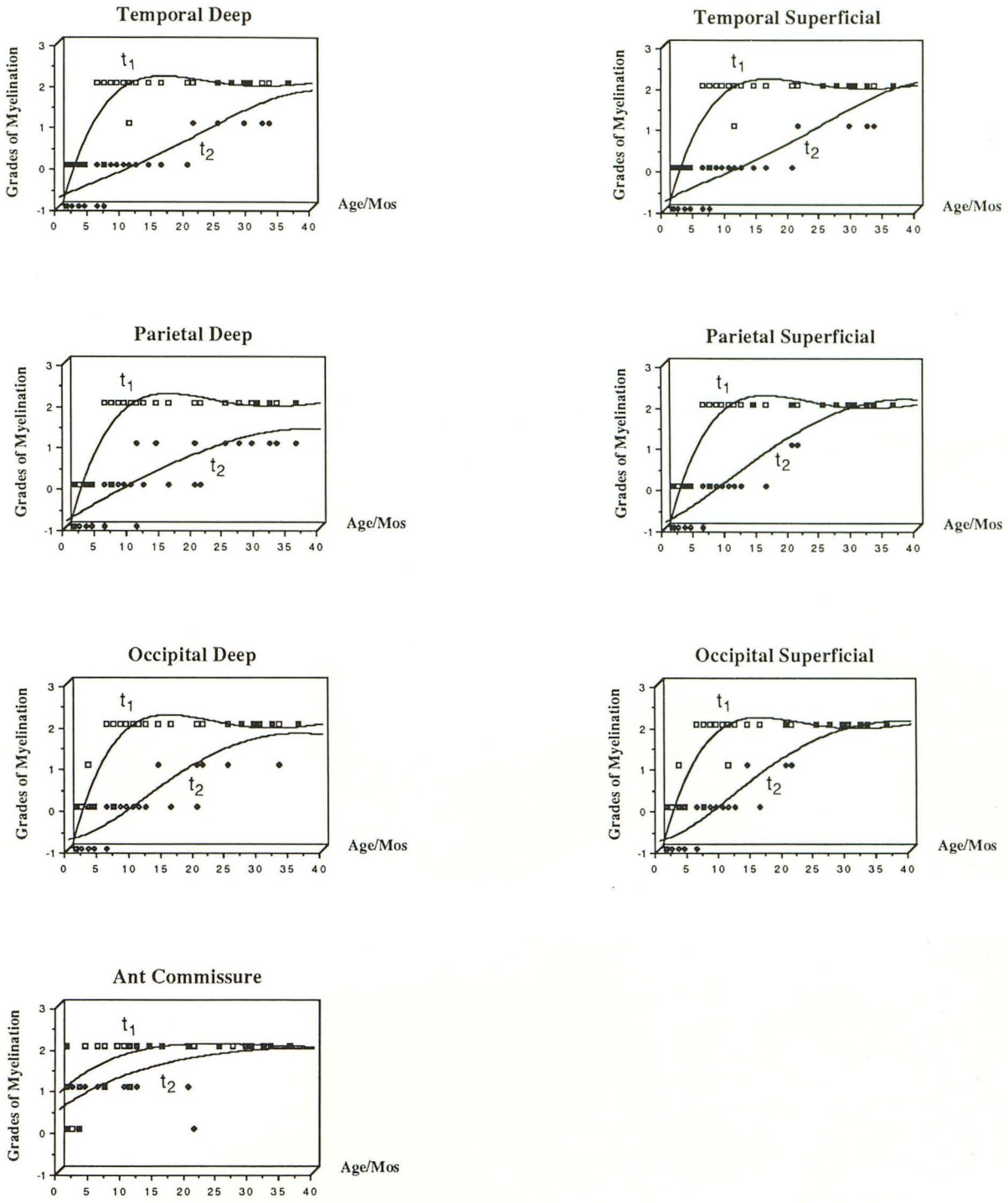


Fig. 1.—Degree of myelination versus patient's age in individual anatomic sites as determined by relative signal intensity on T1- and T2-weighted images.

TABLE 1: Grading Scale: White Matter Intensity

Degree	T1 SI	Degree	T2 SI
−1	< gray matter	−1	> gray matter
0	= gray matter	0	= gray matter
+1	> gray matter < plic	+1	< gray matter > plic
+2	= plic	+2	= plic
+3	> plic	+3	< plic

Note.—SI = signal intensity, plic = posterior limb internal capsule.

intensity on T2-weighted images (Fig. 3). Between approximately 4 and 10 months of age the cerebral white matter became the relatively highest brain signal intensity on T1-weighted images but remained of higher signal intensity than gray matter on T2-weighted images (Fig. 4). After approximately 10 months the white matter remained the highest signal intensity on T1-weighted images and developed pro-

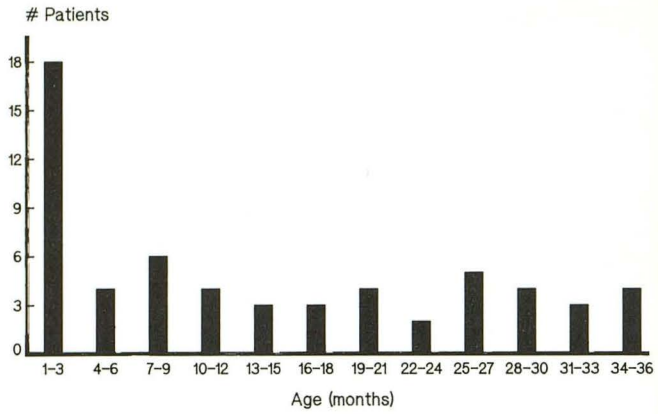


Fig. 2.—Age distribution of patients in study group. There were 60 patients ranging in age from 1 week to 3.5 years.

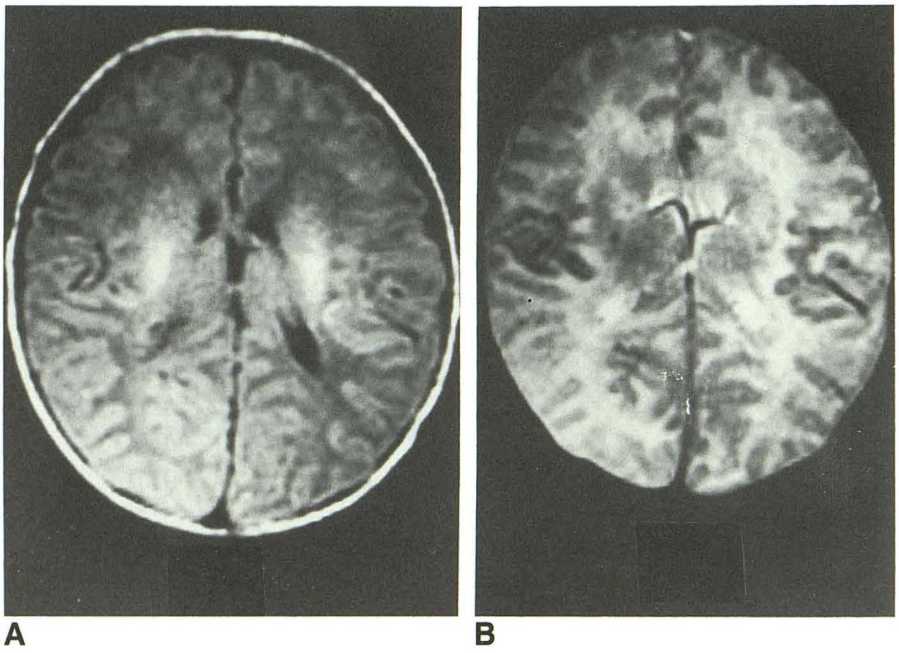


Fig. 3.—*A* and *B*, 1-month-old infant. Axial T1-weighted, 600/20 (*A*) and T2-weighted, 2500/80 (*B*), images. Signal intensity is predominantly decreased in cerebral white matter on T1-weighted image and increased on T2-weighted image. Myelinated central corona radiata has increased signal intensity on T1-weighted image and decreased signal intensity on T2-weighted image.

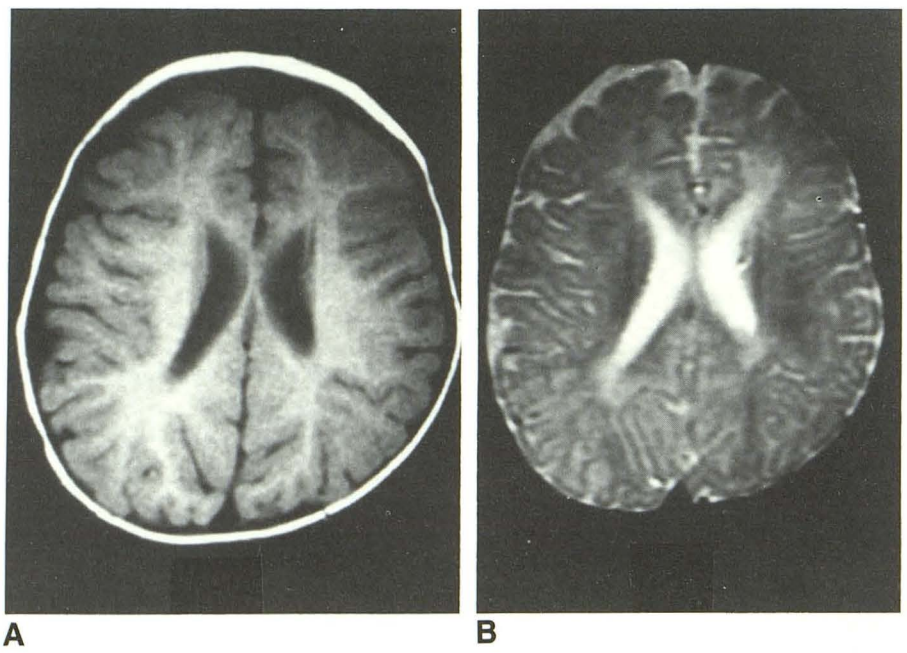


Fig. 4.—*A* and *B*, 10-month-old infant. Axial T1-weighted, 600/20 (*A*) and T2-weighted, 2500/80 (*B*), images. White matter has a "mature" appearance of increased signal intensity on T1-weighted image while T2-weighted image still shows relatively increased signal intensity in frontal and parietal lobes.

gressively lower relative signal intensity on T2-weighted images (Fig. 5).

In the specific anatomic locations evaluated there was a marked diversity in the onset, rate, and appearance of changes associated with myelination. Three of the evaluated areas consistently demonstrated a mature appearance of myelination at birth and in the neonatal period. Besides the posterior limb of the internal capsule these areas were the cerebellar peduncle and corona radiata in the region of the central sulcus (Figs. 6–8). An area that demonstrated little, if any, visible changes of myelination at birth but rapidly progressed to a mature appearance (compared with the posterior limb of the internal capsule) during the first 6 months was the optic radiation (Fig. 9). Locations that demonstrated no visible changes of myelination at birth and progressed to advanced degrees of myelination between 5 months and 1 year included the corpus callosum and anterior limb of the internal capsule (Fig. 10). The genu and splenium of the corpus callosum consistently demonstrated an apparent greater degree of myelination (relatively lower T2 signal intensity) than the posterior limb of the internal capsule on T2-weighted images after approximately 10 months of age (Fig. 11). The splenium of the corpus callosum appeared to myelinate slightly before the genu. The central white matter of the frontal, temporal, occipital, and parietal lobes showed the slowest progression of changes associated with myelination. On T2-weighted images

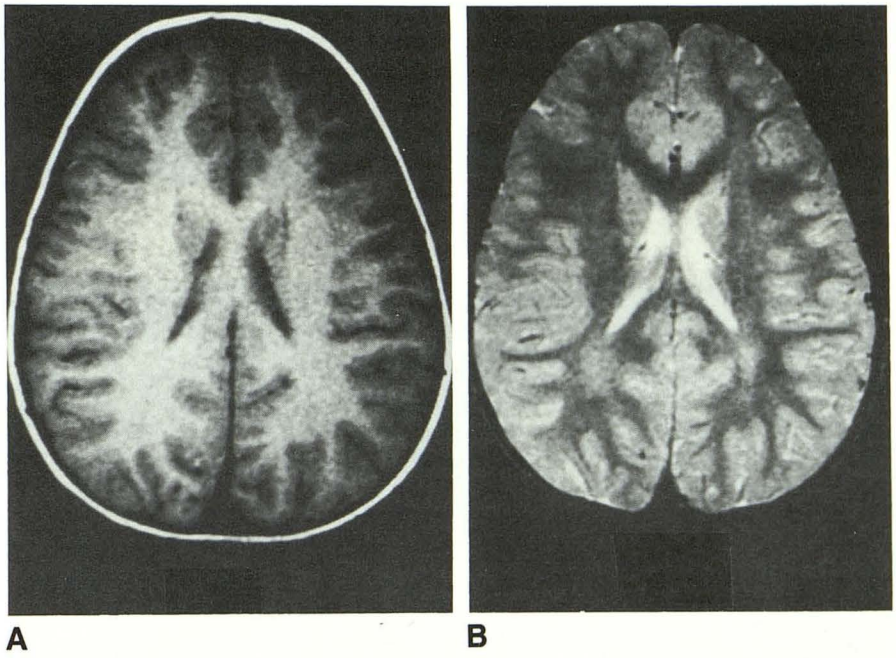


Fig. 5.—*A* and *B*, 2-year-old child. Axial T1-weighted, 600/20 (*A*), and T2-weighted, 2500/80 (*B*), images. T1-weighted image is unchanged in appearance from earlier stage (Fig. 4) while T2-weighted image shows relatively decreased signal intensity in the white matter secondary to progressive myelination. Subcortical white matter has a lower signal intensity than the deep white matter. This is partially due to iron deposition.

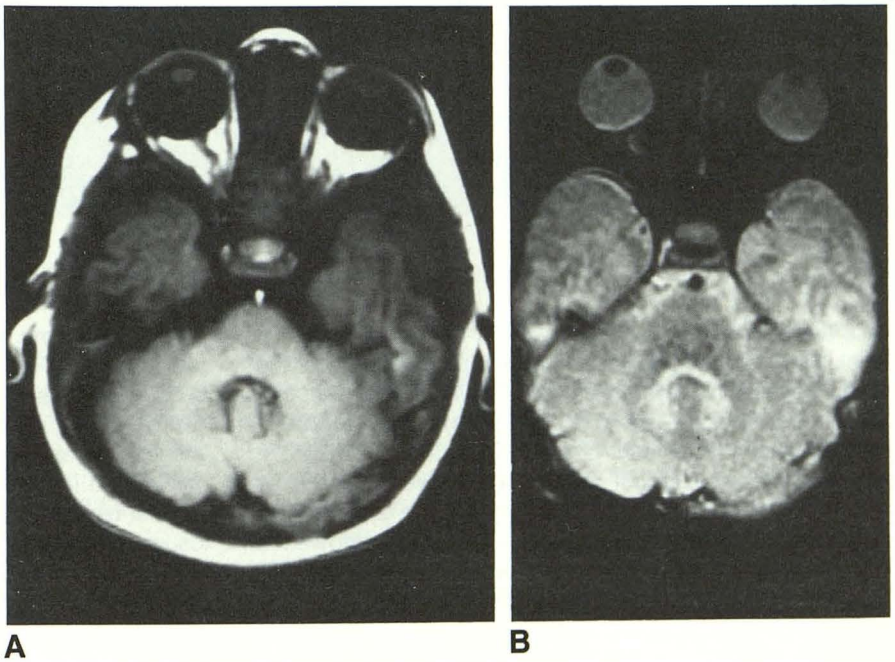


Fig. 6.—*A* and *B*, 1-month-old infant. Axial T1-weighted, 600/20 (*A*), and T2-weighted, 2500/80 (*B*), images. Cerebellar peduncle has increased signal intensity on T1-weighted image and decreased signal intensity on T2-weighted image secondary to myelination.

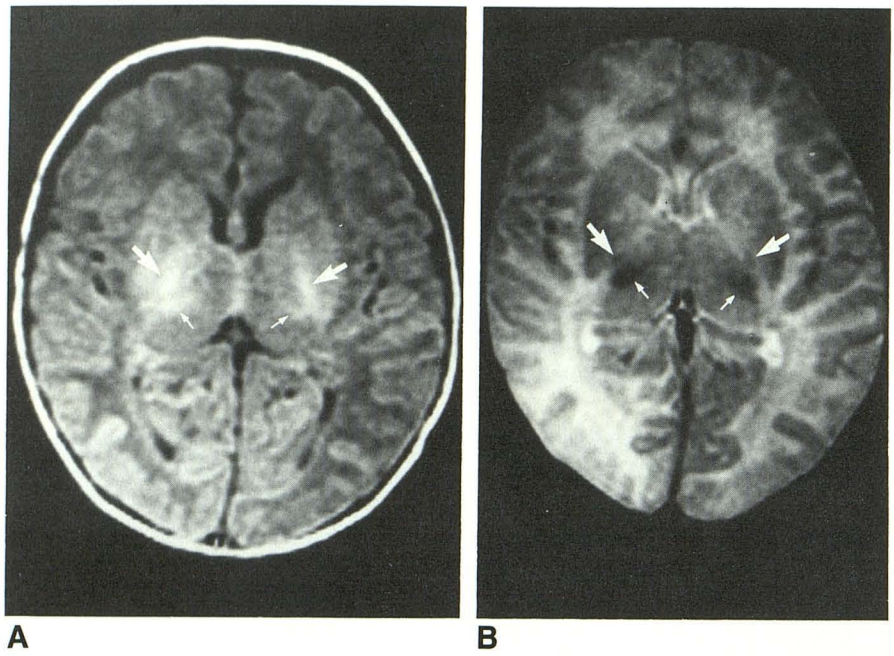


Fig. 7.—*A* and *B*, 1-month-old infant. Axial T1-weighted, 600/20 (*A*), and T2-weighted, 2500/80 (*B*), images. Myelinated posterior limb of internal capsule has increased signal intensity on T1-weighted image and decreased signal intensity on T2-weighted image (*large arrows*). Myelination is also noted in adjacent ventral lateral thalamus (*small arrows*).

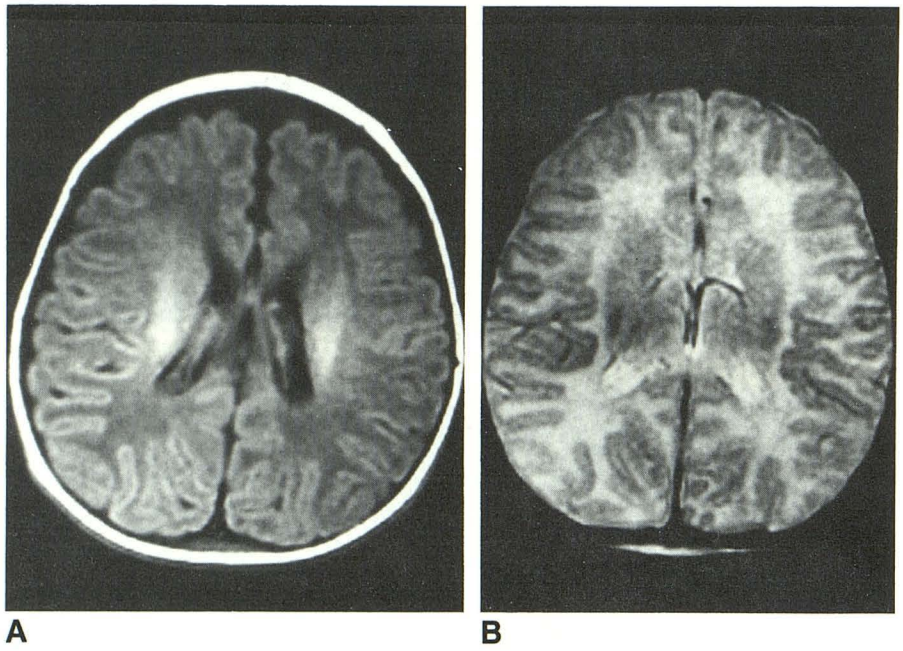


Fig. 8.—*A* and *B*, 1-month-old infant. Axial T1-weighted, 600/20 (*A*), and T2-weighted, 2500/80 (*B*), images. Central corona radiata shows advanced myelination while adjacent frontal and parietal lobes have not yet myelinated.

these areas failed to reach a degree of myelination (i.e., T2 signal hypointensity) equal to that of the posterior limb of the internal capsule by 2 years of age (Fig. 11). Also, the deep parietal white matter showed the slowest progression of myelination beyond 2 years of age (Fig. 1). The T1-weighted images in these areas did achieve a "mature" appearance between 5 and 10 months of age (Fig. 4). The superficial or subarcuate white matter in the cerebral lobes followed a similar pattern to the deep white matter although the T2-weighted images did achieve an appearance similar to that of the posterior limb of the internal capsule by approximately 2 years of age (Fig. 11). A graphic representation of relative brain myelination in different anatomic sites as determined by relative signal intensity changes on T1- and T2-weighted images is presented in Figure 1. The anatomic sequence of myelination (e.g., posterior limb prior to anterior limb of the internal capsule, splenium prior to genu of the corpus callosum, and central corona radiata prior to the poles) was consistently observed in our patient population. The exact timing of this sequence was the only variable noted.

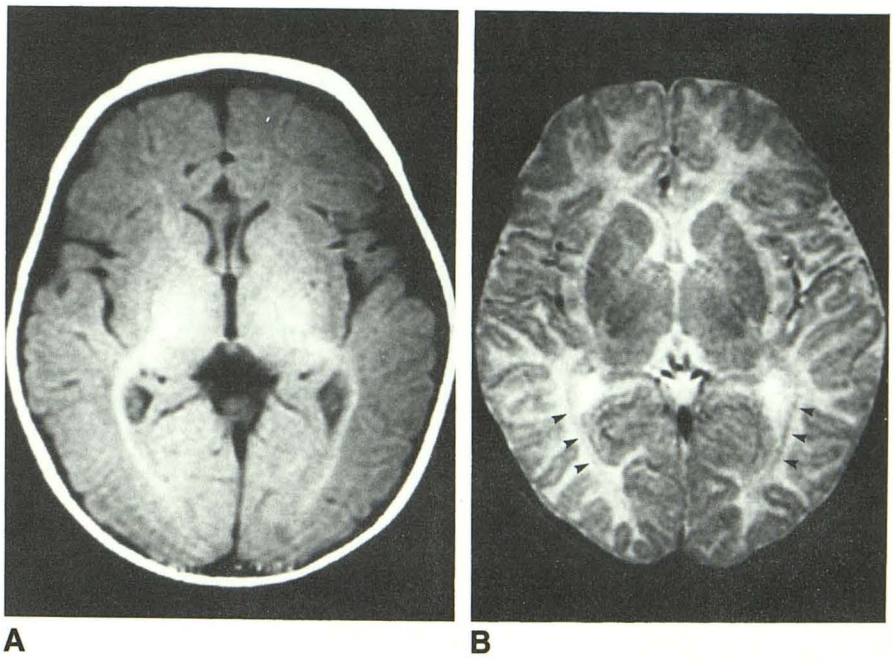


Fig. 9.—*A* and *B*, 4-month-old child. Axial T1-weighted, 600/20 (*A*), and T2-weighted, 2500/80 (*B*), images. Myelinated optic radiation has increased signal intensity on T1-weighted image and decreased signal intensity on T2-weighted image (*arrowheads*). Note the surrounding unmyelinated occipital white matter.

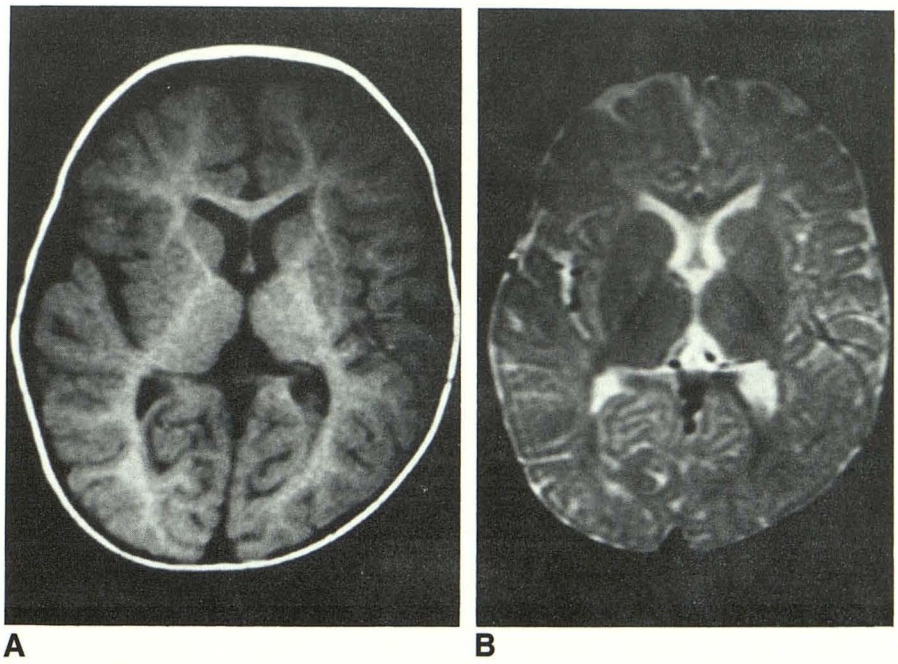
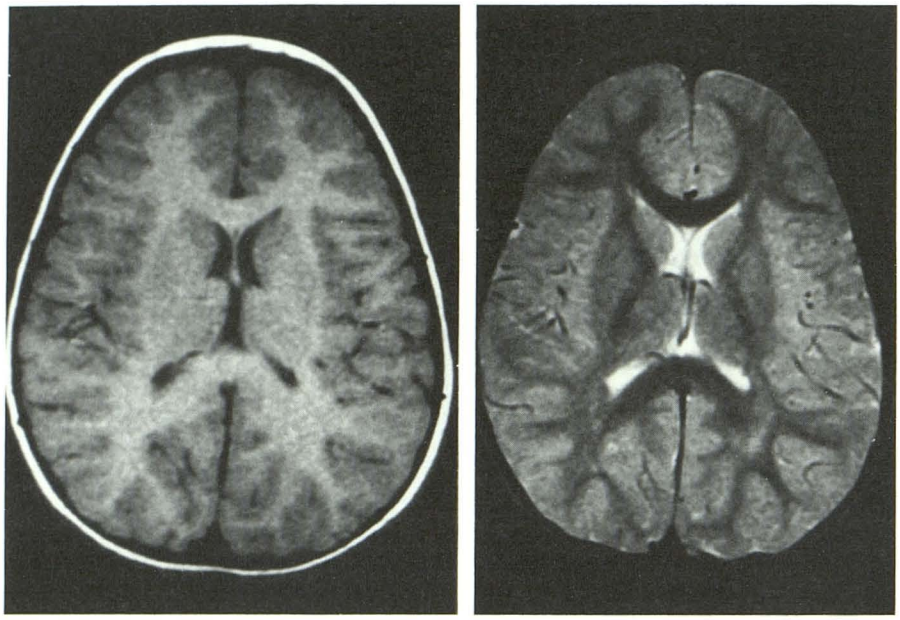


Fig. 10.—*A* and *B*, 10-month-old child. Axial T1-weighted, 600/20 (*A*) and T2-weighted, 2500/80 (*B*) images. Anterior limb of internal capsule and genu of corpus callosum have a degree of myelination comparable to the posterior limb of the internal capsule on T1- and T2-weighted images.

Discussion

MR imaging is a safe, noninvasive method of imaging the entire progression of myelination in infants and children [1–4]. Since many developmental and acquired conditions may affect the progression of myelination, familiarity with the normal sequence of events is essential for identifying any pathologic alteration.

Previous MR analyses of the development of white matter have used different methods to assess the degree of myelination at a given time [1–4]. These include calculation of T1- and T2-relaxation values [1], comparison to the normal adult pattern of myelination [2], and comparison to signal intensities ranging from air to fat [3]. In our study we used the degree of myelination in the posterior limb of the internal capsule as a standard of mature myelination. Myelination in other locations was graded in reference to this internal standard. This method has been applied to the postmortem evaluation of myelination in infancy [5, 6]. The major advantage of this relative intensity method is its ease of comparison, making it



A B

Fig. 11.—*A* and *B*, 2-year-old child. Axial T1-weighted, 600/20 (*A*) and T2-weighted, 2500/80 (*B*), images. On T1-weighted image the signal intensity of the genu and splenium of corpus callosum are similar to white matter in other areas. On the T2-weighted image these areas have lower relative signal intensity than any other white matter, which is partially related to their tightly packed axonal arrangement and, subsequently, to their smaller amount of interstitial water.

useful for practical clinical application. Also, differences in the appearance of images from different MR scanners or the same scanner on different occasions should not cause problems, since an internal standard is employed. The posterior limb of the internal capsule was chosen because it is a readily identifiable structure and is known to attain a mature degree of myelination in the early perinatal period [5]. A limitation of this method is that some increase in the amount of myelin in the internal capsule does occur soon after birth; however, a mature degree of myelination is usually achieved by 1 month of age [6]. The internal capsule myelinates from posterior to anterior so the posterior portion of the posterior limb is first to completely myelinate. This posterior to anterior sequence was also present in other locations, such as the corpus callosum, and has been noted in autopsy studies [6]. Striking myelination is also noted in the adjacent posterior lateral thalamus in the first months of life (Fig. 7). Thalamocortical fibers arising in the ventral posterior lateral nucleus of the thalamus contribute to the early appearance of myelination in the posterior limb of the internal capsule [7].

Both T1- and T2-weighted images are important for assessing the degree of myelination. In areas such as the posterior limb of the internal capsule, cerebellar peduncle, optic radiation, central corona radiata, and corpus callosum, the degree of myelination on T1- and T2-weighted images is closely parallel (Fig. 1). In other areas, such as the white matter of the frontal, temporal, occipital, and parietal lobes, T1- and T2-weighted images show considerable differences, with the T2-weighted images appearing to have a lesser degree of myelination than corresponding T1-weighted images during the first 2 years (Fig. 1). The reason for this disparity is probably related to two main factors: (1) the T2-weighted images are more sensitive to subtle changes in water content than the T1-weighted images, and (2) the deep white matter in each of the lobes is made up of numerous association tracts, each of which may myelinate at different times [7]. Since these tracts have different myelinogenetic cycles, white matter in these areas is a heterogeneous mixture of myelinated and unmyelinated fiber tracts. In contrast, those areas previously mentioned that have similar-appearing degrees of myelination on T1- and T2-weighted images are predominantly composed of "pure" projection fibers that tend to myelinate uniformly at a given time.

The anatomic arrangement of axons may also influence the apparent degree of myelination. White matter tracts where axons are tightly bundled (e.g., corpus callosum, anterior commissure) may appear to contain greater myelination than areas where axons are not as tightly bundled (centrum semiovale), particularly on T2-weighted images. This is at least partially due to the differences in water content. Areas that are tightly packed have less interstitial water than other areas and therefore have a lower signal intensity on T2-weighted images. In general, projection fibers are more closely packed than association fibers [8]. An additional factor that influences the appearance of myelination on T2-weighted images is iron deposition. Iron first accumulates in the subcortical U fibers during infancy. The effects of ferritin on local field heterogeneity causes the subcortical white matter to appear of lower signal intensity (i.e., relatively more myelinated) than deep white matter even though the reverse is true histologically [5] (Fig. 5).

With the exception of anatomic arrangement and iron deposition, as mentioned above, the sequential alterations in the appearance of white matter undergoing myelination on spin-echo images are primarily related to accompanying changes in water content. As myelination proceeds, the water content of white matter decreases. The graphs of relative signal intensity on T1-weighted images versus age delineated in this study closely correlate with curves of water content versus age [9] (Fig. 1). Even though biochemical studies have shown

that myelin precursors (including lipids) are present where myelination is taking place, they do not appear to be in sufficient quantity to affect the appearance of the MR image as demonstrated by proton chemical shift fat-water imaging [10] (Fig. 12).

To summarize, demonstrable MR changes associated with myelination are multifaceted. The dominant factor producing relative T1 signal hyperintensity and T2 signal hypointensity in myelinating white matter is a concomitant decrease in water content. Myelin precursors or lipid in the myelin sheath do not appear to directly contribute to the MR appearance of myelinating white matter. Secondary factors influencing the appearance of myelination (i.e., relative T2 signal hypointensity) in certain areas include the anatomic arrangement of white matter tracts and iron deposition in the subarcuate white matter.

To establish whether the pattern of myelination in any particular patient during the first 2 years of life is normal, the use of specific marker sites is very helpful. Three sites—the cerebellar peduncle, the posterior limb of the internal capsule, and the central corona radiata—should contain visible myelination (relative hyperintensity on T1-weighted images and hypointensity on T2-weighted images) at the time of birth. By 6 months of age the optic radiation should have a mature myelinated appearance compared with the posterior limb of the internal capsule. Between 6 months and 1 year of age the anterior limb of the internal capsule and the genu and splenium of the corpus callosum should appear similar to the posterior limb of the internal capsule. During the second year of life the corpus callosum should develop a more myelinated appearance (lower signal intensity on T2-weighted images) than the posterior limb of the internal capsule. By 2 years of age the deep white matter of the four cerebral lobes should be relatively hypointense on T2-weighted images but may not yet be as low in signal intensity as the posterior limb of the internal capsule. These general patterns of myelination are very consistent between different patients, and have also been observed pathologically [6]. An example of delayed myelination diagnosed by these criteria is presented in Figure 13.

In conclusion, MR imaging provides a sensitive method for imaging white matter maturation in vivo. Myelination is a heterogeneous process with marked differences between the onset and rate of myelination in different anatomic sites. The use of marker sites is a helpful method of identifying any pathologic alteration in myelination during the first years of life.

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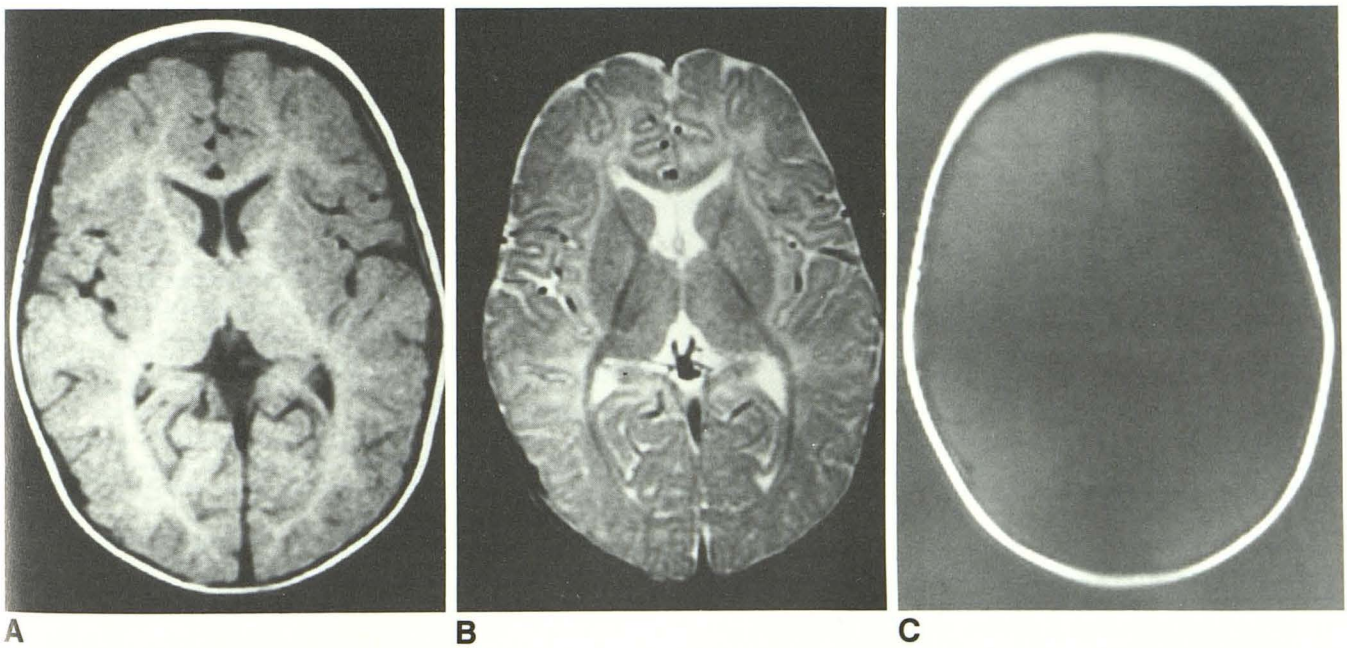

Fig. 12.—*A–C*, 5-month-old child. Axial T2-weighted, 600/20 (*A*), and T2-weighted, 2500/80 (*B*), images. Internal capsule and optic radiation appear myelinated while myelination in the frontal, temporal, and occipital white matter is still progressing. Chemical shift fat-water image, 1000/25 (*C*), at same level as *A* shows high signal intensity from lipid in the scalp but no evidence of lipid signal from the brain even where myelination is still taking place. The water signal was suppressed by presaturation and dephasing.

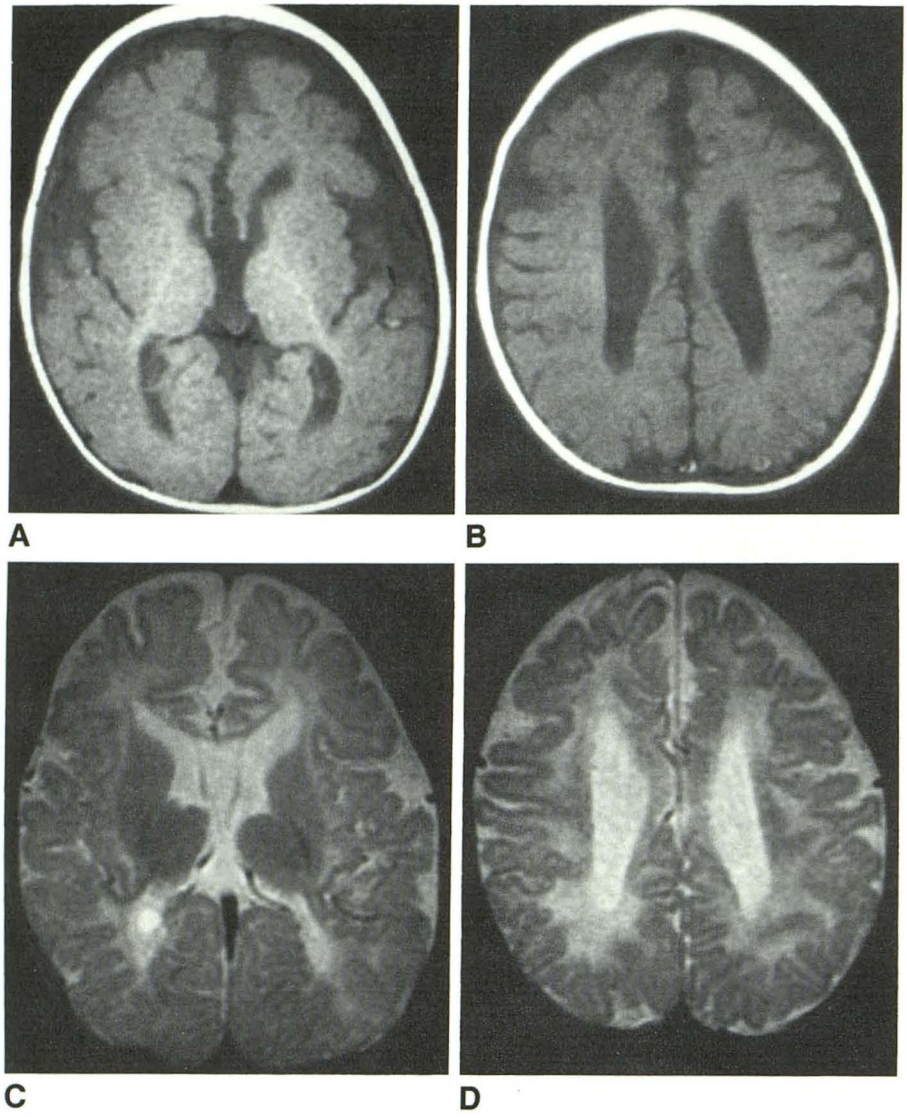

Fig. 13.—1-year-old child with delayed myelination.

***A* and *B*, Axial T1-weighted (600/20) images. Mild dilatation of ventricles and cortical sulci. Increased signal intensity of myelinated white matter is present in posterior limb of internal capsule and central corona radiata. Entire telencephalic white matter should have similar appearance to posterior limb of internal capsule on T1-weighted images at this age.**

***C* and *D*, Axial T2-weighted (2500/80) images. Anterior limb of internal capsule and corpus callosum should have similar signal hypointensity to posterior limb of internal capsule. Frontal and parietal deep white matter normally demonstrate relatively increased signal intensity on T2-weighted images at this age.**

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