The role of classic spin echo and FLAIR sequences for the evaluation of myelination in MR imaging

Betül Kızıldağ, Ebru Düşünceli, Suat Fitoz, İlhan Erden

PURPOSE
The aim of this study was to assess the features of the normal brain development in terms of myelination in infants and young children on fluid-attenuated inversion recovery (FLAIR) magnetic resonance (MR) imaging, and to determine if FLAIR imaging is superior to spin echo MR sequences.

MATERIALS AND METHODS
T1-weighted (T1W) fast spin echo T2-weighted (FSE T2W), and FLAIR images were obtained in 76 pediatric patients between the ages of 0 and 48 months, on a 1 Tesla MR unit. On these images, the signal intensities of 16 different white matter regions were compared to those of adjacent gray matter, and for each brain region. Comparisons between the gray and white matter signal intensities were scored by the consensus of two radiologists on a scale of -1 to +1 for each patient.

RESULTS
In the first 6 months, hypointense white matter signal intensity changed to hyperintensity on T1W images. After the first 6 months, white matter progressed from hyperintense to hypointense on T2W images. Except for the cerebral white matter, FLAIR images showed the same signal transition, though slightly later than what was seen on T2W images. The deep cerebral white matter, which was hypointense on birth, became hyperintense early in the first several months of life, and finally, reconverted to hypointense during the second year of life on FLAIR images.

CONCLUSION
Myelination, which is an indicator of brain maturation, was successfully demonstrated both in classic spin echo sequences and on FLAIR images. These imaging techniques are an essential component of routine MR imaging of the dating of and differentiation between normal and pathological brain development.

Key words: • magnetic resonance imaging • myelination • brain

RESULTS

White matter, which forms the majority of the central and peripheral nervous systems, primarily consists of myelin. Myelination, one of the key steps of nervous system development, is in fact a process that starts in the second trimester of fetal development. As an indicator of maturation, myelination continues until adulthood, although it is most rapid during the first two years after birth. Therefore, magnetic resonance (MR) imaging is used as an objective method for the evaluation of developmental delays of the nervous system within this period. In contrast to computed tomography (CT) and ultrasonography, with which pathologies can not be demonstrated except when there are significant white matter changes, information related to the myelin structure and myelination process can be obtained with MR imaging. This ability of MR imaging has been the focus of numerous studies related to this process. Today, in addition to normal developmental processes, changes in pathological development such as metabolic diseases can be evaluated with MR imaging, which is the only method available that allows for the evaluation of myelination in vivo (1-8).

Changes related to myelination on T1- and T2-weighted (T1W, T2W) images have been studied by many authors. Fluid-attenuated inversion recovery (FLAIR) imaging, which has recently become a must in routine pediatric brain MR studies, is a technique that forms image contrast based on T1 and T2 relaxation times. Cerebrospinal fluid (CSF) signals are suppressed using an appropriate inversion time with FLAIR pulse sequence, in order to obtain heavily T2W images. Suppression of CSF signal enhances the detection of lesions adjacent to the ventricles (7, 8). In this regard, the study of signal changes during the myelination process using FLAIR imaging has become extremely important in differentiating pathological processes from normal ones. Diffusion tensor imaging, which has been recently developed, is a technique sensitive to even the smallest movements of water molecules, allowing for quantitative measurement of anisotropic changes observed during maturation (1-5). Currently, not all imagers have been equipped with the appropriate software and hardware for this technique and therefore classic spin echo sequences and FLAIR imaging remain valuable techniques.

In this study, our aim was to demonstrate the properties of the normal brain in newborns and infants with FLAIR images and define its place in comparison to classic sequences.

Materials and methods
A total of 76 cases, including 25 girls and 51 boys, with ages ranging from 0 to 48 months were included in the study. All cases were referred for routine cranial MR examination with suspected or diagnosed central nervous system diseases. The cases were summarized in Table 1 according to patient age. The clinical histories or the causes for MR imaging referral...
were developmental delay, tumor, cerebral palsy, mental/motor retardation, epilepsy, trauma, attention deficit-hyperactivity disorder, metabolic diseases, tuberous sclerosis, trisomy 21, and congenital anomalies (arthrogryposis multiplex, meningomyelocele, Beckwith-Wiedemann syndrome, congenital giant melanocytic nevus, etc.).

MR imaging studies were performed in superconductive MR systems (Signa, GE Medical Systems, Milwaukee, WI, USA). In cases where sedation was needed, i.e., pons tegmentum [dorsal pons], middle cerebellar peduncle, crus cerebri, peridentate white matter, optic radiations, internal capsule posterior limb, corpus callosum splenium, corpus callosum genu, centrum semiovale [adjacent to paracentral sulcus], occipital central, and peripheral white matter, frontal central and peripheral white matter, and temporal central and peripheral white matter), where white matter was predominant, were compared with the gray matter in transverse plane T1W, FSE T2W, and FLAIR images. Similar to the scoring technique stated in the literature (6-8), hypointense areas as compared to the gray matter were graded as -1, isointense areas as 0, and intense areas as +1, by a consensus of both radiologists. The changes in signal evolution were matched with age and compared in T1W, T2W, and FLAIR images. The average values of signal changes, as compared with age, were defined in the specified regions (Table 3). Cases in which delayed myelination was detected in classic spin echo sequences were excluded from the study.

Table 1. Numbers of cases in the study by age intervals

<table>
<thead>
<tr>
<th>Months of age</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>11</td>
</tr>
<tr>
<td>4-6</td>
<td>9</td>
</tr>
<tr>
<td>7-9</td>
<td>6</td>
</tr>
<tr>
<td>10-12</td>
<td>7</td>
</tr>
<tr>
<td>13-18</td>
<td>6</td>
</tr>
<tr>
<td>19-24</td>
<td>11</td>
</tr>
<tr>
<td>25-36</td>
<td>14</td>
</tr>
<tr>
<td>37-48</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 2. MR imaging sequence parameters used in the study

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Slice thickness (mm)</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>TI (ms)</th>
<th>FOV (cm)</th>
<th>NEX</th>
<th>Matrix</th>
<th>Time (min:sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1W</td>
<td>4-5</td>
<td>460-540</td>
<td>12-14</td>
<td></td>
<td></td>
<td>2.5</td>
<td>256x192</td>
<td>2:16</td>
</tr>
<tr>
<td>FSE T2W</td>
<td>4-5</td>
<td>3700-5160</td>
<td>79-113</td>
<td></td>
<td>22x16</td>
<td>4-24</td>
<td>320x224</td>
<td>2:50</td>
</tr>
<tr>
<td>FLAIR</td>
<td>4-5</td>
<td>9002-10002</td>
<td>99-105</td>
<td>2050-2300</td>
<td>22x22</td>
<td>1 256x160</td>
<td>3:00</td>
<td></td>
</tr>
</tbody>
</table>

TR: time to repeat, TE: time to echo, TI: time of inversion, FOV: field of view, NEX: number of excitations

Table 3. Ages in which signal changes on three MR sequences were observed related to myelination

<table>
<thead>
<tr>
<th>White matter region</th>
<th>T1W sequence</th>
<th>T2W sequence</th>
<th>FLAIR sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pons tegmentum (dorsal pons)</td>
<td>Birth</td>
<td>Birth-1st month</td>
<td>3rd-4th month</td>
</tr>
<tr>
<td>Middle cerebellar peduncle</td>
<td>Birth</td>
<td>Birth-1st month</td>
<td>3rd-4th month</td>
</tr>
<tr>
<td>Crus cerebri</td>
<td>3rd month</td>
<td>3rd month</td>
<td>4th-5th month</td>
</tr>
<tr>
<td>Peridentate white matter</td>
<td>3rd month</td>
<td>3rd month</td>
<td>6th month</td>
</tr>
<tr>
<td>Optic radiation</td>
<td>4th month</td>
<td>5th-6th month</td>
<td>6th month</td>
</tr>
<tr>
<td>Internal capsule posterior limb</td>
<td>Birth</td>
<td>Birth</td>
<td>3rd month</td>
</tr>
<tr>
<td>Internal capsule anterior limb</td>
<td>3rd month</td>
<td>6th month</td>
<td>8th-9th month</td>
</tr>
<tr>
<td>Corpus callosum splenium</td>
<td>3rd-4th month</td>
<td>3rd-4th month</td>
<td>6th month</td>
</tr>
<tr>
<td>Corpus callosum genu</td>
<td>4th-5th month</td>
<td>5th-6th month</td>
<td>6th-7th month</td>
</tr>
<tr>
<td>Centrum semiovale</td>
<td>Birth</td>
<td>1st month</td>
<td>4th-5th month</td>
</tr>
<tr>
<td>Occipital central white matter</td>
<td>4th month</td>
<td>7th month</td>
<td>2-3rd to 12th month</td>
</tr>
<tr>
<td>Frontal central white matter</td>
<td>6th month</td>
<td>11th month</td>
<td>2-3rd to 14th month</td>
</tr>
<tr>
<td>Temporal central white matter</td>
<td>8th month</td>
<td>12th month</td>
<td>2-3rd to 22nd month</td>
</tr>
<tr>
<td>Occipital peripheral white matter</td>
<td>6th-7th month</td>
<td>11th month</td>
<td>14th month</td>
</tr>
<tr>
<td>Frontal peripheral white matter</td>
<td>11th month</td>
<td>18th month</td>
<td>20th month</td>
</tr>
<tr>
<td>Temporal peripheral white matter</td>
<td>12th month</td>
<td>20th-22nd month</td>
<td>24th month</td>
</tr>
</tbody>
</table>

* Triphasic signal change in the cerebral hemispheric white matter in comparison with the adjacent gray matter; first signal change from hypointensity to hyperintensity, second signal change from hyperintensity to hypointensity.

Results

Image quality in all 76 cases included in the study was technically adequate. The radiological findings were not compatible with a delay of myelination or dis-/demyelinating pathologies.

On T1W images, the evolution of white matter hypointensity in the first six months of life to adult form hyperintensity took twelve months. The average age in which white matter regions turn into hyperintense areas secondary to myelination was calculated (Table 3). Accordingly, hyperintensity was present in the pons dorsal region, middle cerebellar peduncle, internal capsule posterior limb, and centrum semiovale adjacent to paracentral gyrus, where myelination was already present at birth (Figure 1a-c). Evolution to hyperinten-
signal was visualized in the third month in crus cerebri, peridentate white matter, and internal capsule anterior limb, whereas it was observed in the optic radiation in the fourth month, in the corpus callosum splenium in the third-fourth months, and in the corpus callosum genu in the fourth-fifth months. Signal changes related to myelination were detected in the central regions of cerebral hemispheric white matter starting from the occiput in the fourth month, progressing to frontal regions in the sixth month, and temporal regions in the eighth month (Figure 2a-c). Myelination progressed to the cortical

Figure 1. a-i. On transverse T1W (a-c), T2W (d-f), and FLAIR (g-i) MR images of an 8-day-old newborn (a, d, g), 6-month-old infant (b, e, h), and 25-month-old infant (c, f, i), signal changes were observed in the myelinated white matter tracts in the centrum semiovale at the level of the paracentral gyrus. These areas, which were hyperintense from birth on T1W images (a-c), are hyperintense on T2W images in the newborn (d) and hypointense in the sixth month (e) and the twenty-fifth month (f). Signal changes similar to T2W images were observed on FLAIR sequences (i).
convolutions and was detected in the occipitals in sixth-seventh months, frontals in eleventh month, and temporals in twelfth month.

On T2W images during the first two years of life, the white matter hyperintensity changed into hypointensity. Hypointensity was present in the internal capsule posterior limb at birth. While hypointensity was detected in the first month in the pons dorsal region, middle cerebellar peduncle, and centrum semi-
In FLAIR images, the hemispheric white matter appears hypointense as compared to the gray matter. In the same images in the first year of life, a change from hypointensity to hyperintensity lasting till the twenty-fourth month. When the scores of the two radiologists were compared, the amount of mismatch was calculated as 7% (45 mismatches in a total of 648 scores). The difference of variation in the scoring system was not more than 1 unit. However, the final decision was reached through the agreement of both radiologists.

**Discussion**

Myelination, which is a dynamic process in the developing brain, is the most important indicator of brain maturation. MR imaging, which has been in routine use lately, is the only method that allows for the evaluation of myelination in vivo (9-12). Changes related to myelination on T1W and T2W images have been extensively studied by many authors (13-19). FLAIR imaging, which has recently become as a must in routine pediatric imaging, has its contrast based on T1 and T2 relaxation times. In this manner, evaluation of signal changes in FLAIR images during the myelination process becomes an important tool to differentiate pathological processes from normal ones (7, 8).

Brain myelination occurs in a predictable and symmetrical sequence following general rules. Generally, myelination in the brain is from caudal to rostral, posterior to anterior, and from central to peripheral (8). Myelination starts in the fourth-fifth months of gestation and completes in the twentieth-twentieth months (8-10, 20, 21). According to the histological data on developing brains, the most active myelin synthesis occurs in the first 8 postnatal months, and the most active period of myelin maturation is the eighth-fifteenth postnatal months (20-21).

The water content of white matter is higher in the neonatal period as compared to older infants. Myelin has relatively less water and because the mature brain contains more white matter, a decrease in the water content of white matter is observed along with maturation (8-11, 23, 24). While unmyelinated white matter on T1W images has low signal intensity, with myelin maturation it becomes hyperintense. On T2W images, unmyelinated white matter appears hypointense and is followed by a decrease in signal intensity with maturing myelin (8-11).

This study was performed by retrospective analysis by two experienced radiologists of pediatric brain studies reported to have normal myelination in concordance with age, on transverse T1W, T2W, and FLAIR images. Cases that had pathological clinical findings were also included in the study, because presently there is no information as to whether myelination delay in any of these diseases is predictable. In published reports, the normal myelination process is mentioned, even in cases in which there is a superimposition of pathological delay (17, 25).

In our study, signal changes related to myelination on T1W images were similar in age as has been reported in the literature (Table 3). However, the age of appearance of signal changes on T2W images was earlier than in other studies (16). For instance, splenium and genu of the corpus callosum, internal capsule anterior limb, occipital, as well as frontal and temporal white matter regions were hypointense a few months earlier on T2W images as stated in the literature (16). While T2W images were obtained using conventional spin echo techniques in other studies, in our study, FSE T2W techniques were used (1, 6-8, 13, 16). In accordance with this technical change, hypointensity related to myelin maturation was detected earlier on T2W images. Findings in our study were similar to age related signal changes on T2W images observed in a study by Murakami et al. using FSE T2W sequence (7). With multislice FSE

Determination of signal changes on T1W and T2W images, cerebral white matter signal intensity demonstrated a triphasic pattern in FLAIR images. In our cases, we observed the evolution of cerebral hemispheric white matter from hypointensity to hyperintensity in T1W images in the first year of life in comparison to the gray matter. In the same regions in T2W images, a change from hyperintensity to hypointensity was observed in the eighth-twentieth month as compared with the gray matter. However, in FLAIR images, the hemispheric white matter appeared heterogeneously hypointense in the newborn and signal intensity changed around second-third month in the occipital, frontal, and temporal central white matter. Hypointensity was again observed in the twelfth month in the occipital, fourteenth month in the frontals, and twenty-second month in the temporals (Figure 2 g-i). In the cerebral white matter, myelination started first in the occipital lobes and last in the temporal lobes.

Similar to T1W and T2W images, signal changes in the peripheral white matter followed that of the deep white matter. Change from hypointensity to hyperintensity was detected in the fourteenth month in the occipitals and twentieth month in the frontals. The temporal peripheral white matter was the last region to myelinate and hyperintensity lasted till the twenty-fourth month.

Different from the biphasic white matter signal changes on T1W and T2W images, cerebral white matter signal intensity demonstrated a triphasic pattern in FLAIR images. In our cases, we observed the evolution of cerebral hemispheric white matter from hypointensity to hyperintensity in T1W images in the first year of life in comparison to the gray matter. In the same regions in T2W images, a change from hyperintensity to hypointensity was observed in the eighth-twentieth month as compared with the gray matter. However, in FLAIR images, the hemispheric white matter appeared heterogeneously hypointense in the newborn and signal intensity changed around second-third month in the occipital, frontal, and temporal central white matter. Hypointensity was again observed in the twelfth month in the occipital, fourteenth month in the frontals, and twenty-second month in the temporals (Figure 2 g-i). Peripheral white matter tracts became hypointense and reached the adult form in the eleventh month in the occipitals, eighteenth month in the frontals, and twentieth-twenty-second month in the temporals.

In conventional spin echo sequences, signal changes related to the myelination process were in biphasic pattern in all brain regions (Table 3).

In white matter regions other than the cerebral hemispheric white matter, although signal changes in FLAIR sequences were delayed as compared to T2W images, they were similar to classic T1W and T2W images, displaying a biphasic pattern. In FLAIR images, changes in terms of hyperintensity to hypointensity as compared with the gray matter were as follows: first in the third month in the internal capsule posterior limb, then the middle cerebellar peduncle and pons dorsal regions in the third and fourth month, in the centrum semiovale adjacent to the paracentral sulcus and crus cerebri in the fourth-fifth month, then the peridentate white matter, optic radiation, and corpus callosum splenium in the sixth month, in the genu in the sixth-seventh month, and later in the inner capsule posterior limb in the eighth-ninth month (Figure 1g-i).
imaging, the detection of myelination relatively increased in relation to magnetization transfer (7). In addition, an increase in T2 effect secondary to use of longer TR and effective TE values have made detection of myelinated areas easier. These technical differences explain why myelination was detected relatively earlier on T2W images in our study (7, 16).

Image contrast on FLAIR studies are mainly related to T2 relaxation differences, because in many FLAIR protocols longer effective TE values are used (this value was 99 ms in our study). Selection of an inversion pulse with a longer TI value (the TI value in our study was ranging from 2050 to 2300 ms) suppresses the signals from tissues with very long TI relaxation times. The only tissue that has a high enough relaxation time is the CSF. Similar to our study, on FLAIR images at birth, white matter areas such as pons dorsal regions, cerebellar peduncle, internal capsule posterior limb, and paracentral gyri appear hypointense in comparison to the gray matter. Over the course of time, the white matter loses intensity gradually, and in FLAIR sequence, the brain reaches an adult pattern by the second year of life. While unmyelinated cerebral white matter shows a triphasic pattern on FLAIR images, there is a biphasic pattern on T1W and T2W images. Because of this, brain maturation can be demonstrated definitively on FLAIR images as compared with T1W and T2W images (7).

Myelin maturation is detected earlier on T1W images than on T2W. Barkovich et al. stated that in the first 6-8 months of life, T1W images are more appropriate to demonstrate myelin maturation and T2W images are more informative after 6 months (8-10). However, in this study FLAIR images more definitively showed the myelination process from beginning to end as compared to T1W and T2W images. In the spin echo sequences still in use, myelinated white matter appears hyperintense on T1W images and hypointense on T2W images at birth. In contrast to spin echo sequences, on FLAIR images, signal intensities change from hyperintense to hypointense in response to the maturation of myelinated white matter. Except in deep cerebral white matter, white matter areas on FLAIR images change from hyperintense to hypointense during the first 24 months of life. When the presence of T2 relaxation effects on the fundamentals of FLAIR imaging is known, this finding is not surprising. Previous investigators have linked the decrease in white matter signal intensity on T2W images to compression of the myelin spiral around the axon and myelin juxtaposition, or myelin maturation (7, 13, 15, 19). The observed signal change from hyperintensity to hypointensity on FLAIR images in the white matter occurs a little later than similar changes on T2W images (7). This delay may stem from T1 sensitivity of FLAIR imaging. The tendency of the white matter to be hypointense on FLAIR images, secondary to T2 effect, is partially blocked by T1 relaxation effect (7). The net effect of these contradicting forces on image contrast is a relative delay of white matter signal change on FLAIR images as compared to T2W images.

While the deep cerebral white matter demonstrates triphasic signal changes on FLAIR images, there is a biphasic signal change on T1W and T2W images (7). In infants, hemispheric deep cerebral white matter is more hypointense in comparison to the adjacent gray matter. When the T1W images are compared, these white matter areas are relatively more hypointense when compared with the adjacent white matter. However, on T2W images these areas are more hyperintense. Demonstration of deep white matter as distinct areas is difficult on T1W and T2W images because the background white matter is hypointense on T1W images and hyperintense on T2W images. These areas have relatively higher water content (7, 15, 19). It is estimated that free water, by increasing the T1 value, suppresses the signals, and therefore becomes hypointense like CSF on FLAIR sequences (7, 19).

The second stage of the triphasic FLAIR study occurs within the first few months of life. In our study, at birth hypointensity was observed in the occipital, frontal, and temporal white matter in comparison to the adjacent gray matter, and this was similar to T1W images. Later, a change from hypointensity to hyperintensity was visualized in the white matter, starting from the occipital lobe and progressing to the frontal and temporal white matter around the second-third months. In this period, secondary to a decrease in free water due to myelin formation, there is a decrease in T1 relaxation times. This is thought to contribute to the signal increase in white matter on T1W images (7, 13, 15, 19). At the same time, a decrease in T1 relaxation time prevents the suppression of the deep cerebral white matter along with the inversion pulse related suppression of the CSF pulse. As the T1 relaxation time decreases, the T2 relaxation time becomes dominant in the image contrast. This situation results in relative hypointensity of the deep cerebral white matter compared to adjacent gray matter on FLAIR images (7).

The third phase of triphasic FLAIR images is observed in the second year of life. In the last phase of this signal change, white matter becomes isointense with gray matter and then becomes hypointense (7). This sequence was analogous to signal changes on T2W images despite a short delay. Changes in the periphery of cerebral white matter followed the changes in the central regions.

In our study, triphasic signal change on FLAIR images was not observed in the other white matter areas, such as the dorsal pons, middle cerebral peduncle, crus cerebri, peridementate white matter, internal capsule anterior and posterior limbs, corpus callosum splenium and genu, and optic radiation. This most likely stemmed from the absence of enough free water in the regions like the middle cerebellar peduncle, peridementate white matter, crus cerebri, corpus callosum splenium and genu, and optic radiation. The small amount of hypointensity in these areas with partial volume effect caused difficulties in decision-making and a lack of correlation between the scores of the two observing radiologists.

Because the temporal lobes are the last regions where myelination is completed after the frontal lobes, the white matter in these lobes remains hypointense until the twenty-fourth month on FLAIR images (7, 25, 26). In infants within this age group, the normal increase in signal intensity on FLAIR images in the temporal white matter should not be regarded as pathological.

In conclusion, myelination, which is an indicator of brain maturation, was successfully demonstrated both in classic spin echo sequences and on FLAIR images. These imaging techniques are
an essential component of routine MR imaging in the dating of and differentiation between normal and pathological brain development.

References