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MR Assessment of Brain Maturation: Comparison of Sequences

Karl Hittmair, Daniela Wimberger, Thomas Rand, Lucas Prayer, Guenther Bernert, Josef Kramer, and Herwig Imhof

PURPOSE: To evaluate the role of short-inversion-time inversion-recovery (STIR) sequences in assessment of brain maturation. **METHODS:** Twenty-seven infants and young children with normal neurologic development were examined by 1.5-T MR using a circularly polarized head coil. Axial T1-weighted and T2-weighted and spin-echo and STIR images were obtained. Signal intensity of different anatomic structures at individual sequences was classified relatively to reference sites and temporal sequence of signal intensity was observed. **RESULTS:** Signal intensity changes on T1-weighted and T2-weighted spin-echo sequences occurred at ages described in various previous publications. On STIR images intensity changes became apparent at a time between T1-weighted and T2-weighted images. The advantages of the STIR sequence were improved assessment of myelination of subcortical cerebral white matter from 6 to 14 months and good contrast between white matter lesions and cerebrospinal fluid. **CONCLUSION:** Our results suggest that from 0 to 6 months myelination can be assessed best using a combination of T1-weighted and T2-weighted images; from 6 to 14 months a combination of T2-weighted and STIR images seems to be advantageous; after 14 months the use of only T2-weighted sequences is sufficient. After 14 months STIR images may be useful in detecting small periventricular white matter lesions or in cases with retarded myelination and isointensity between gray matter and white matter.

Index terms: Brain, growth and development; Brain, magnetic resonance; Brain, anatomy; Magnetic resonance, in infants and children; Magnetic resonance, technique

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Myelination of white matter proceeds in a pre-determined way. Magnetic resonance (MR) imaging offers a unique opportunity to monitor this process. Besides conventional T1-weighted and T2-weighted spin-echo sequences, inversion-recovery sequences have proved capable of mapping brain maturation (1-15).

A problem with conventional spin-echo sequences is the low sensitivity of T1-weighted images to white matter lesions and a poor gray-white differentiation in lobar cerebral white matter on T2-weighted images during the second half-year of life (2, 12). It is during the second half of

the first year of life that infants suffering from myelination disorders often show first neurologic abnormalities and are submitted to an MR examination (12, 15). In these cases a sequence that improves the assessment of lobar cerebral white matter, a site where early white matter lesions are expected, would be useful. The poor gray-white differentiation on T2-weighted images during this period of life could not be improved sufficiently by using longer repetition times (3000) and longer echo times (120) in trials preliminary to this study.

We used a short-inversion-time inversion-recovery (STIR) sequence which in our and other authors' experience (12) proved helpful in detecting small demyelinated white matter lesions. The aim of this study was to evaluate the role of STIR sequences in assessment of brain maturation.

Subjects and Methods

From September 1990 to June 1992 38 infants and young children between 3 days and 3 years of age were examined. In cases of preterm birth, the age was corrected

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for the prematurity. Reasons for investigation were mild hydrocephalus, exclusion of infection, macrocephaly, microcephaly, cerebral seizures, small brain tumors, or chromosomal abnormalities with normal psychomotor development. Eleven patients were excluded from this study because lesions revealed by MR did not allow proper assessment of myelination; thus, data of 27 patients without or with only minor pathologies and normal neurologic development were used for further evaluation (0 to 1 month, two patients; 1 to 3 months, four patients; 3 to 6 months, four patients; 6 to 9 months, four patients; 9 to 12 months, five patients; 12 to 24 months, five patients; and 24 to 36 months, three patients).

The study was performed on a 1.5-T system (Magnetom 63 SP, Siemens, Erlangen, Germany) using a circular polarized head coil. Standard axial T1-weighted (600/15/1 [repetition time/echo time/excitations]) and T2-weighted (2500/90/1) spin-echo sequences as well as STIR sequences (2500/20/1, inversion time 140) were obtained. On the STIR sequence the magnitude reconstruction method was used for converting signal intensity into gray level. Scan times for the entire brain were 2 minutes 36 seconds for T1-weighted sequences, 10 minutes 44 seconds for T2-weighted sequences, and 10 minutes 44 seconds for STIR sequences.

White-matter age was determined using the atlas of Barkovich (1).

Signal intensity of white matter in different sites was classified into four categories as explained in Table 1, thus eliminating the influence of window setting. Image assessment was done by three neuroradiologists independently; final results were achieved in consensus. Signal intensities of categories -1 and 0 were regarded to represent unmyelinated white matter, categories 1 and 2 myelinated white matter. Looking at complex anatomic structures such as medulla oblongata, brain stem, and midbrain primarily, we took into account only the areas of most advanced myelination, neglecting the subtle alterations in signal intensity within these structures (13, 14).

To compare the contrast of the sequences within the brain stem and medulla oblongata, we looked at the following anatomic structures: substantia nigra, nucleus ruber, colliculi superiores and inferiores, medial lemniscus, and corticospinal tracts. Contrast and delineation of these structures were compared between one sequence and another, and sequences were classified equal, better, or worse.

Results

For the present population, white-matter age, as assessed using the atlas of Barkovich (1), showed maximum deviations from chronological age of less than 1 month during the first 6 months of life, less than 2 months up to 1 year, and less than 4 months thereafter. The periods when white-matter signal intensity changes from categories -1 and 0 (representing unmyelinated white matter) to category 1 or 2 (representing myeli-

TABLE 1: Classification of white-matter signal intensity (WM) referring to the signal intensity of the posterior limb of the internal capsule (IC) and the cortical cerebral gray matter (GM)

Category of Signal Intensity	T1	T2	STIR
-1	WM < GM	WM > GM	WM > GM
0	WM = GM	WM = GM	WM = GM
1	GM < WM < IC	GM > WM > IC	GM > WM > IC
2	WM ≥ IC	WM ≤ IC	WM ≤ IC

TABLE 2: Age (in months) at which myelination becomes apparent

	T1	T2	STIR
Medulla oblongata	0	0	0
Midbrain and brainstem	0	0	0
Cerebellar peduncles (central parts)	0	0-1	0
Peripheral parts of midcerebellar peduncles	2-3 ^a	4	2-3 ^a
Folia cerebelli	7 ^b	6-7	6-7
Capsula interior (posterior limb)	0	0	0
(anterior limb)	4-5	9-10	5
Corona radiata	0	0-1	0-1
Corpus callosum (splenium)	4-5	6	5-6
(genu)	5-7	7-9	5-9
Optic radiation	0-1	0-1	0-1
Lobar cerebral white matter (central portion)			
paracentral	2	5-7	5-6
occipital	4-6	10-12	7-9
frontal	5-6	11-14	8-12
Completed cerebral white matter arborization			
paracentral	3-6 ^a	10-12	7-9 ^a
occipital	7-9 ^a	18-20	14-16 ^a
frontal	8-10 ^a	18-22	14-16 ^a

^a Unreliable assessment because remaining peripheral unmyelinated white matter cannot be differentiated from gray matter.

^b Unreliable assessment because of poor contrast even in much older subjects.

nated white matter) occurred in individual sites are listed in Table 2. A considerable difference in the age of maturation was noted from sequence to sequence: first alterations were observed on T1-weighted images; changes were significantly later on T2-weighted images and lay somewhere between on STIR images (Table 2).

Regarding delineation and contrast of small anatomic structures within the medulla and the brain stem, T1-weighted sequences were classified as equal or worse, T2-weighted sequences as equal or better than the other sequences in all subjects. STIR sequences were inferior to T2-weighted sequences in all 10 subjects under 6 months of age. In the older age groups STIR images showed similar contrast as T2-weighted

images and were classified as inferior to T2-weighted images only in five of 17 cases.

Inferior, superior, and central parts of the middle cerebellar peduncles were myelinated in the youngest individuals. Myelination progressed peripherally, and maturation of peripheral parts of the midcerebellar peduncles was completed at 4 months. This peripheral progression of myelination was assessed most reliably by determining the amount of peripheral cerebellar unmyelinated

white matter, which was demonstrated as areas of signal intensity of category -1 only on T2-weighted images (Fig 1). On T1-weighted and STIR images unmyelinated white matter could not be discriminated from gray matter, and the amount of cerebellar unmyelinated white matter could not be quantified. Maturation of subcortical cerebellar white matter (folia cerebelli) was completed (featuring a signal intensity of category 2) at an age of around 7 months. Myelination of

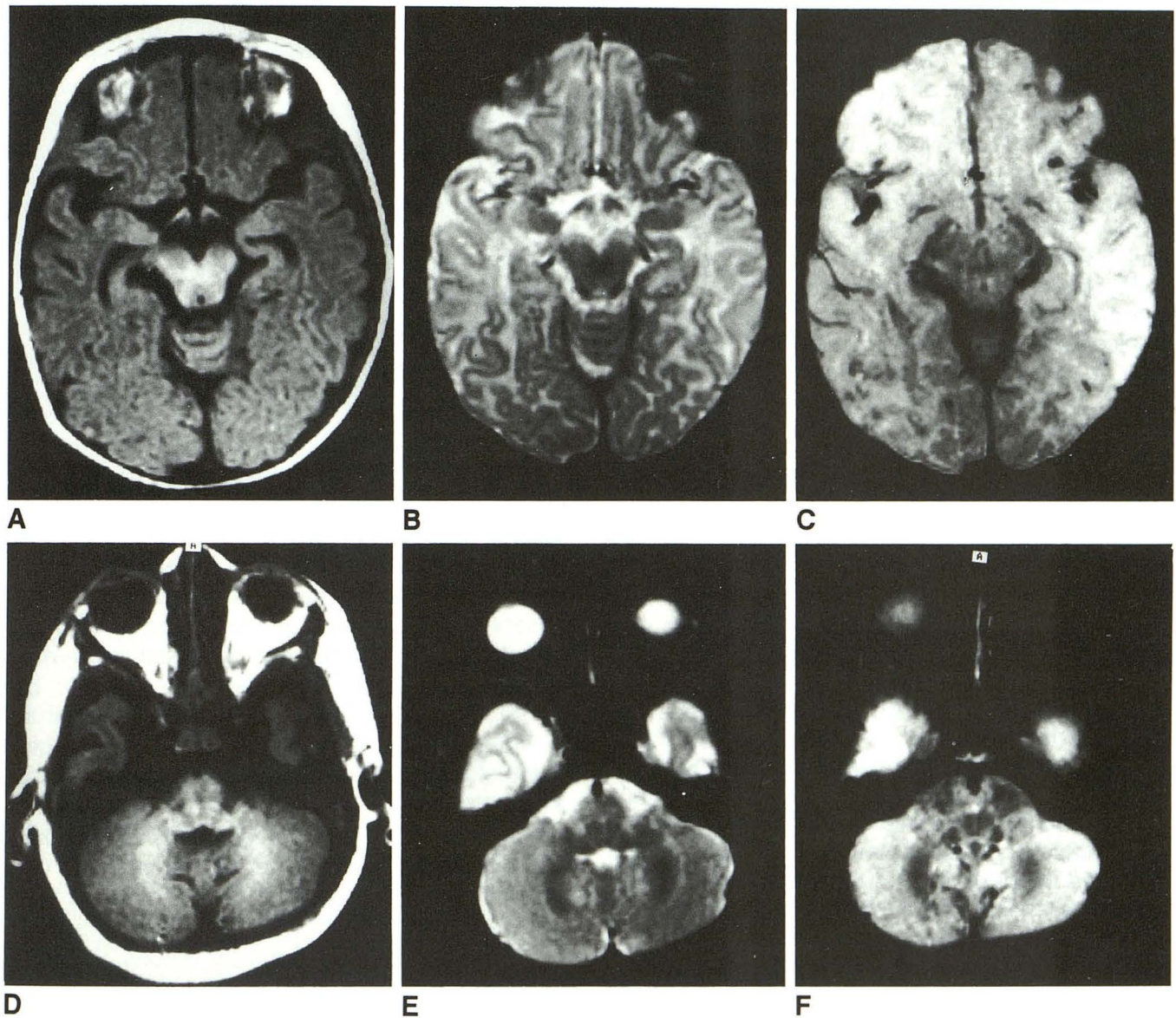


Fig. 1. Two-and-a-half-month-old girl. Better delineation and contrast of small structures within the brain stem on T2-weighted (2500/90/1) (B) compared with T1-weighted (600/15/1) (A) and STIR images (2500/20/1, inversion time 140) (C). Remaining peripheral unmyelinated white matter of the midcerebellar peduncles is demonstrated only on T2-weighted images (2500/90/1) (E) as areas of high signal intensity but not discriminable from gray matter on T1-weighted (600/15/1) (D) and STIR images (2500/140/20) (F). Peripheral extension of cerebellar myelination is therefore best determined using T2-weighted images.

these thin sheets of subcortical white matter was mirrored nearly equally on T2-weighted images and STIR images but markedly worse on T1-weighted images in all cases after 7 months.

Above the tentorium, myelinated white matter appeared first in the deep, phylogenetically older white matter in a temporal sequence shown in Table 2. As opposed to cerebral lobar white matter there was no contrast observable within the individual anatomic structures of deep supratentorial white matter on any of the sequences; the structures as a whole changed their signal intensity simultaneously. Intervals between characteristic signal intensity changes were shortest on T1-weighted images occurring during the first 7 months of life. On T2-weighted images the process of myelination of deep white matter was mirrored up to 10 months of age, but intervals between significant signal intensity changes were longer, allowing a less detailed temporal classification of maturation of deep supratentorial white matter. STIR sequences lay between T1-weighted and T2-weighted sequences.

Myelination of lobar cerebral white matter featured a ventriculofugal course, beginning in the paracentral region and being detectable markedly later in the occipital and finally in the frontal region (Table 2). In the youngest individuals supratentorial lobar white matter showed a signal intensity of category -1 on all sequences. During the process of maturation, signal intensity changed, passing an isointense stage (signal intensity of category 0), and finally reaching category 2.

On T1-weighted images a signal intensity of category -1 in unmyelinated white matter was observed only in the first 4 months. After that time unmyelinated white matter showed a signal intensity of 0 and could not be discriminated from gray matter. Most of the supratentorial lobar white matter reached a signal intensity of category 2 by the age of 8 months without significant contrast within the white matter. After 8 months no significant alterations were observable on T1-weighted images except a distinct further peripheral progression of myelination of subcortical white matter, which was hardly quantifiable.

On T2-weighted images peripheral subcortical cerebral white matter showed signal intensity of category -1 until 22 months of age, while at the same time the central portions of subcortical cerebral white matter featured a signal intensity of category 2. Hence, maximal dynamic range of signal intensities and highest contrast between

various stages of myelination was observed on T2-weighted images. There were different signal intensities seen within myelinated white matter on T2-weighted images, which cannot be attributed to artifacts or partial volume effects.

In patients between 6 and 14 months, large areas of lobar cerebral white matter showed signal intensity around category 0 with isointensity and therefore poor contrast to gray matter (signal intensity of 0 per definition) (Figs 2 and 3). During that period it was difficult to discriminate cerebrospinal fluid (CSF) from unmyelinated white matter or white matter from gray matter, and to assess the peripheral extension of myelinated white matter.

On STIR images, supratentorial lobar white-matter maturation occurred at a time between that on the T1-weighted and T2-weighted sequences (Table 2). There was a stage with isointensity between cerebral white matter and gray matter on STIR images, too; however, this stage was before that observed on T2-weighted images. In all sites with isointensity of lobar cerebral white matter and gray matter on T2-weighted images, the stage of isointensity on STIR images had already passed (seven of seven cases), and STIR images provided better gray-white differentiation (Figs 2 and 3). In contrast to T1-weighted images, myelinated white matter did not appear homogeneous on STIR images but showed signal intensities of categories 1 to 2 and thus contrast within myelinated white matter. The lower signal intensity areas on STIR images corresponded to that observed on T2-weighted images and could not be attributed to artifacts. Contrast was only slightly lower on STIR images.

CSF featured a low to intermediate signal intensity (around category 0 to 1) on STIR images.

Initial experiences with STIR in white-matter lesions revealed good contrast of white-matter lesions (signal intensity category -1) to surrounding myelinated white matter (signal intensity category 1 to 2), comparable to the contrast seen on T2-weighted images. High contrast was also provided between white-matter lesions, unmyelinated white matter (both signal intensity of category -1), and CSF (signal intensity around category 0 to 1) on STIR images, whereas white-matter lesions, unmyelinated white matter, and CSF featured a similar signal intensity (category -1) on T2-weighted images (Fig 4).

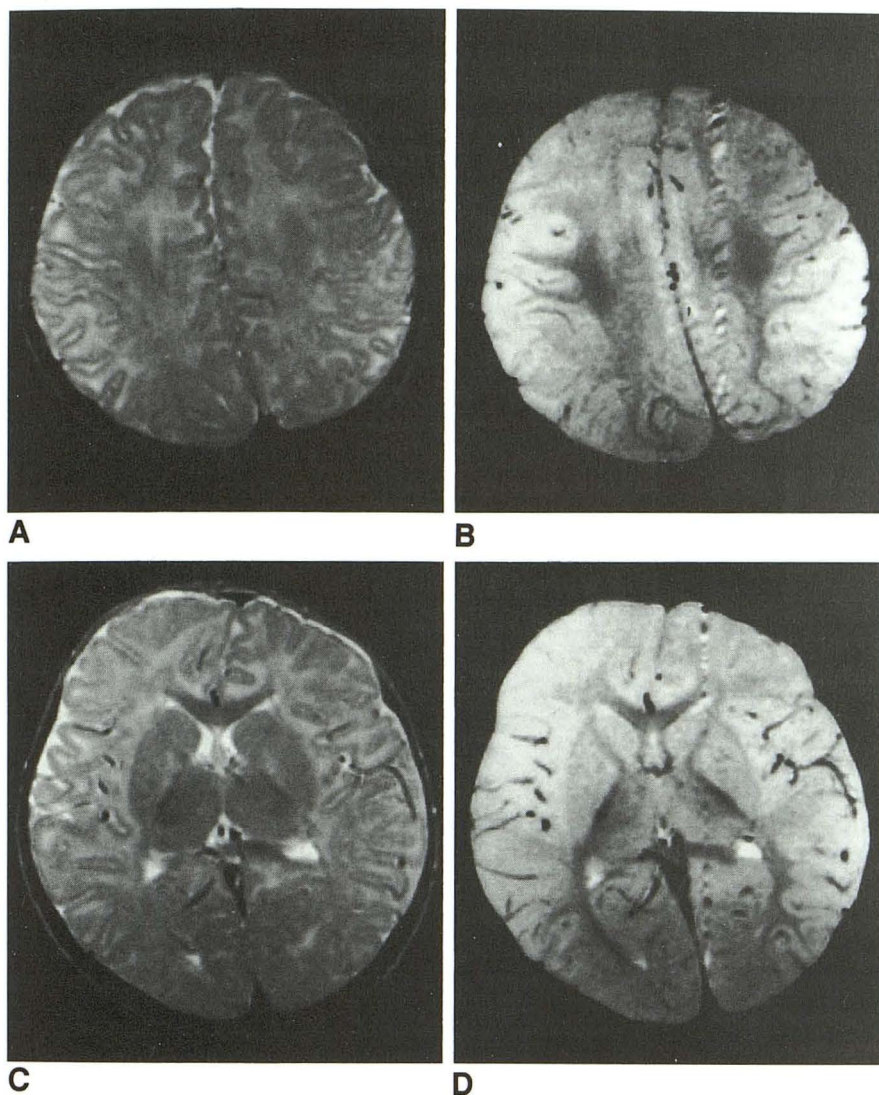


Fig. 2. Nine-month-old girl. On T2-weighted images (2500/90/1) (A and C) white matter shows similar signal intensity as gray matter predominantly in the occipital and parietal lobe but still higher signal intensity than gray matter in the frontal lobe. Within the areas of isointensity on T2-weighted images, STIR images (2500/20/1, inversion time 140) (B and D) provide better gray-white differentiation and thus advantages in the assessment of these areas.

Discussion

The ability of MR (in particular T1-weighted and T2-weighted spin-echo sequences) to demonstrate the process of brain maturation is well established (1–15). Because of a shortening of T1 and T2 relaxation time, white matter turns dark on T2-weighted and bright on T1-weighted images when it becomes myelinated. There are considerable differences in the age when myelination becomes apparent on T1-weighted and T2-weighted images, respectively. Obviously T1 and T2 relaxation times are affected differently by the chemical and structural changes during the process of myelination. T1 and T2 relaxation times of unmyelinated white matter and white-matter lesions are much longer than those of myelinated white matter and are mainly influenced by the state of water protons, because lipid protons do not contribute much to signal intensity

(16). Decrease of water content is one factor responsible for signal-intensity changes observed during myelination. Shortening of T1 and T2 relaxation times caused by interaction of water, protein, and lipid protons of myelinated white matter, however, influences signal intensity, too. This interaction is to a high degree dependent on the presence of cholesterol within the lipids of myelin (17, 18). Because the proportion of cholesterol and glycolipids and the signal intensity on T1-weighted images changes in the same topographic and temporal sequence, a relationship between these two events is postulated (2, 19–22).

Signal-intensity changes on T2-weighted images must be influenced by other chemical and physical alterations in white matter; the decreasing water content is regarded as the most important one (2).

Fig. 3. Twelve-month-old boy. Featureless isointense appearance throughout the cerebral lobar white matter on T2-weighted images (2500/90/1) (A and C). Superior gray-white differentiation on STIR images (2500/20/1, inversion time 140) (B and D).

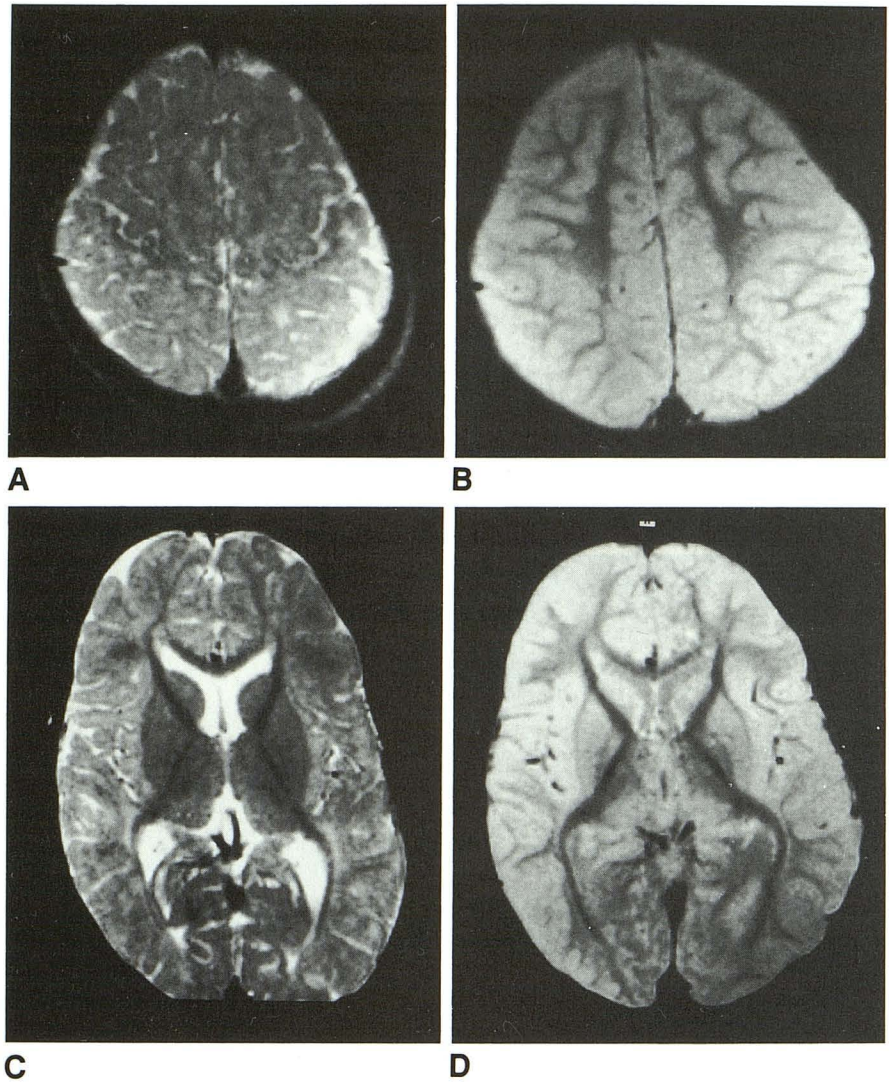
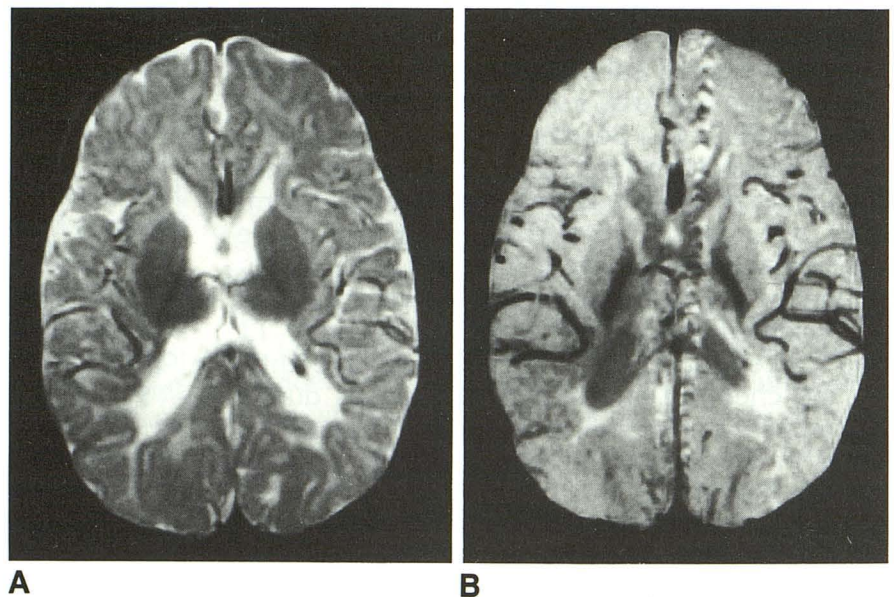


Fig. 4. Periventricular white matter lesions in a 19-month-old boy with heavily retarded psychomotor development. Retarded myelination with still large areas of unmyelinated cerebral lobar white matter. STIR images (2500/20/1, inversion time 140) (B) provide a better differentiation of white-matter lesions from unmyelinated white matter and CSF, all of which feature a similar signal intensity on T2-weighted images (2500/90/1) (A).



Signal intensity on inversion-recovery images depends on the same tissue parameters as on T1-weighted and T2-weighted images. The properties of both T1-weighted and T2-weighted images are combined on inversion-recovery images, and the effects of prolonged T1- and T2-relaxation times are additive in case of a T1 longer than T0 (null point) and shorter than T_p (peak time). Signal intensity of tissues with a T1 of T0 is nulled. T_p denotes the T1 for which signal intensity is maximal and the maximum value for which the effects of prolonged T1 and T2 are additive. T0 and T_p mainly depend on inversion time and repetition time (23). For an inversion time of 140 and a repetition time of 2500, T0 approximately equals 250 and T_p equals 1100. This range covers the T1 values of white matter between 6 months (around 1100 msec) and 1 year (around 500 msec), respectively (12). Thus theoretically good contrast can be obtained within white matter during the second half-year of life.

The time when signal intensity changes of T1-weighted and T2-weighted images occurred matched well with previous publications (1–3). Minor deviations may be attributed to the relatively low number of subjects and their inhomogeneous age distribution. This population distribution, however, is not expected to reduce the validity of sequence comparison. Contrast behavior of the different sequences changed only slowly during longer periods of time, and enough subjects were examined within these periods to get sufficient data for sequence comparison. This is in particular true because contrast behavior did not show relevant interindividual variation.

Similar to previous papers (13, 15) we found that T1-weighted images showed the poorest and T2-weighted images the best contrast and contrast-to-noise ratio of infratentorial anatomic structures. STIR images were nearly as good as T2-weighted images with regard to contrast and delineation of small structures in the age groups older than 6 months. Before 6 months, however, when infratentorial brain maturation takes place, STIR images were inferior to T2-weighted images. Thus STIR images cannot improve the assessment of infratentorial brain maturation.

On T2-weighted images, but not on T1-weighted or STIR images, unmyelinated white matter remaining in the periphery of the midcerebellar peduncles (signal intensity of category –1) could be discriminated from gray matter (signal intensity of category 0), which improves the classification of the peripheral extension of cerebellar

white-matter myelination. Relating unmyelinated white matter of the midcerebellar peduncles to myelinated white matter provides a more reliable assessment of peripheral extension of myelination than does the mere evaluation of the width of the myelinated part. These features of T2-weighted images and their high sensitivity to white-matter lesions favors the use of T2-weighted images for the assessment of infratentorial brain maturation.

In the deep supratentorial white matter only few signal intensity changes occur on T2-weighted images in the first 6 months of life. At these sites of white matter and during this period of life, the most significant signal intensity changes are seen on T1-weighted images, providing the finest temporal grid for classifying maturation of supratentorial deep white matter. After 6 months, however, T1-weighted images show no further significant signal intensity changes in the deep supratentorial white-matter, and maturation of these white-matter sites has to be monitored by T2-weighted or STIR images; established standards favor the use of T2-weighted images. On STIR images signal intensity changes occur until 9 months, on T2-weighted images until 12 months of age.

Supratentorial lobar cerebral white matter myelinates last during the process of brain maturation. Until 6 months of age most significant signal intensity changes within the cerebral lobar white matter are seen on T1-weighted images. High signal intensity of cerebral lobar white-matter on T2-weighted images during that period of life reduces the sensitivity of T2-weighted images to white-matter lesions. T1-weighted images may be helpful in the assessment of cerebral lobar white matter during the first half year of life. Later, however, T1-weighted images contribute the least information on cerebral lobar white-matter maturation, because of the lowest contrast within white matter, the low sensitivity to white-matter lesions, and a lack of further significant signal intensity changes after 6 to 8 months.

Highest contrast between white matter that myelinated at different stages and high sensitivity to white-matter lesions favors the use of T2-weighted images for assessing lobar white matter after the first year of life. From 6 to 14 months, however, there is a cross-over between T2 relaxation time of lobar cerebral white matter and gray matter, resulting in an isointensity on T2-weighted images with poor gray-white differentiation (1, 2, 12). The isointensity of gray matter

and white matter with the featureless appearance of cerebral lobar white matter may cause difficulties in the assessment of the peripheral extension of myelination, in the differentiation of white-matter lesions from unmyelinated white matter and CSF, and thus in the detection and classification of white-matter lesions. Thus, T1-weighted and T2-weighted images have major disadvantages in assessing the myelination of lobar cerebral white matter from 6 to 14 months. The use of longer repetition times (3000 msec) and longer echo times (120 msec) for T2-weighted images, which is advantageous for imaging brains of persons in their first year of life, did not improve gray-white differentiation in this age group decisively in trials preliminary to this study. STIR images, however, combine features of T1-weighted and T2-weighted images with an improved gray-white differentiation, contrast within lobar myelinated white matter, and sensitivity to white-matter lesions (Figs 3 and 4). Contrast and local signal-intensity difference within myelinated white matter seen on T2-weighted and STIR images cannot be attributed to artifacts as image shading or partial volume effects. This contrast is not found on T1-weighted images and is most probably caused by differences of T2 relaxation times within myelinated white matter. The differences in T2 relaxation time may be caused by a variation in water content within white matter that myelinated at different stages, by local structural differences, or by iron deposition (12).

The features of STIR images with improved gray-white differentiation and simultaneous T2 contrast seem to be helpful in assessing lobar white matter during the stage of isointensity on T2-weighted images. In cases of retarded myelination, this stage can be found in persons older than 14 months, too. In these cases peripheral extension of myelinated white matter is better demonstrated on STIR, and characterization of white-matter lesions may be done advantageously on STIR images. STIR images would then be potentially useful for the differentiation of white-matter lesions from unmyelinated white matter, for the assessment of extension of lesions, and for the assessment of involvement of U fibers. Another advantage of STIR images is the low signal intensity of CSF, which improves the differentiation of CSF and white-matter lesions and thus the detection of small periventricular white-matter lesions (Fig 4).

Van der Knaap and Valk (5) did not see the isointense featureless stage of lobar white matter

on T2-weighted images using an inversion-recovery sequence with different sequence parameters, either, but sensitivity to white-matter lesions has not been discussed. Habord et al (9), who used a similar STIR sequence, did not discuss the issue of isointensity between white matter and gray matter.

Proper assessment of lobar cerebral white matter during the second half of the first year of life is particularly important, because persons suffering from myelination disorders often show first neurologic abnormalities at this age, and early pathologic lesions are expected in these regions (13).

After 14 months the widest dynamic range of signal intensities of white matter is seen on T2-weighted images, resulting in a maximum contrast between different degrees of myelination. This good contrast with the high sensitivity to white-matter lesions and a simultaneous good gray-white differentiation favor the use of T2-weighted images after 14 months. The progression of myelination in the very subcortically located white matter can be assessed most reliably on T2-weighted images because, as opposed to T1-weighted and STIR images, unmyelinated white matter can be discriminated from gray matter on T2-weighted images only at this age. After 14 months STIR images may be useful in detecting small periventricular white matter lesions or in cases with retarded myelination and isointensity between gray and white matter.

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