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Normal myelination of anatomic nerve fiber bundles: MR analysis.

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Normal Myelination of Anatomic Nerve Fiber Bundles: MR Analysis

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PURPOSE: In order to establish milestones of brain maturation by MR imaging, we examined the initiation of myelination of fiber bundles and of surrounding white matter.

METHODS: The subjects included 54 healthy infants ranging in age from 35 to 145 weeks by corrected gestational age. Images were obtained on a 1.5-T MR unit. In 24 sites of 18 fiber bundles in eight cross sections obtained perpendicular to the long axis of the brain stem, we analyzed the initiation of myelination and the age at which fiber bundles become indistinguishable owing to myelination of the surrounding white matter (blurring).

RESULTS: The fiber bundles were classified into two groups on the basis of the presence or absence of blurring. The first group (no blurring) was further divided into group 1A, in which myelination began at 35 weeks or less, and group 1B, in which myelination began at 44 weeks or later. The second group (blurring) was divided into group 2A, in which myelination began at 35 weeks or less and blurring occurred at 43 to 49 weeks; group 2B, in which myelination started at 35 weeks or less and blurring began at 67 to 145 weeks; and group 2C, in which myelination began at 36 weeks or later and blurring occurred at 67 to 145 weeks.

CONCLUSION: The time of blurring, when myelinated fiber bundles become indistinguishable from surrounding white matter owing to the initiation of myelination, is considered to be a useful parameter of brain maturation in infancy.

Myelination of the cerebral white matter starts in the third trimester of the fetal period and progresses rapidly through infancy. Even though some myelination progresses into the third decade or later (1), the majority occurs within the third trimester and the first 2 years of life. Therefore, the degree of myelination has been studied pathologically and anatomically as a parameter of brain maturation in early childhood (1–3). Observation of myelination in vivo by CT has been attempted (4–6), but this technique has recently been replaced by MR imaging, which gives considerably more information on myelination (7–16).

The white matter of the brain consists of numerous fiber bundles that represent organized functional and anatomic collections of axons (eg, anterior commissure) surrounded by nonbundled fibers. With progression of myelination of fiber bundles, the MR signal intensity of white matter changes from low to high on T1-weighted images, and from high to low on T2-weighted images (7). Fiber bundles that started myelination earlier than the surrounding white matter can be clearly observed because of the difference in signal intensity, but they become indistinguishable as maturation proceeds and signal intensity of surrounding white matter changes as myelination progresses to those areas.

Myelination does not occur synchronously throughout the cerebral white matter; rather, it is initiated and completed differentially among fiber bundles. To our knowledge, no studies have specifically addressed the myelination period of white matter surrounding fiber bundles. By examining the process of myelination around specific fiber bundles, we may achieve a more detailed assessment of brain maturation. The purpose of this study was to use MR imaging to determine the initiation time of myelination of fiber bundles in detail at various cross-sectional levels and to establish parameters of brain maturation on the basis of myelination of white matter around these fiber bundles.

Methods

The subjects consisted of 54 infants (30 boys, 24 girls) ranging in age from 35 to 145 weeks by corrected gestational age (Fig 1). Indications for MR imaging varied, but all infants were
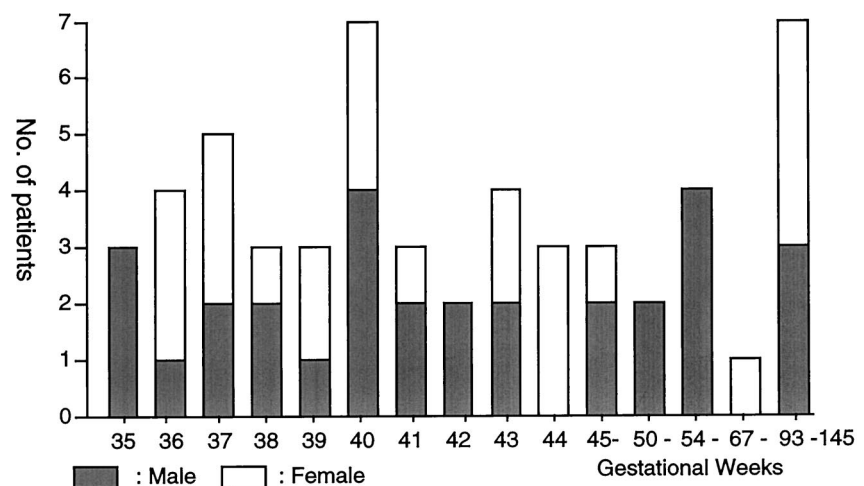
determined to be clinically healthy on the basis of MR imaging results and the clinical course observed by pediatricians. The corrected gestational age was calculated according to the definition set by the World Health Organization, with intrauterine sonographic measurements or postpartum values corrected according to the table of Dubowitz and Dubowitz (17).

Imaging Methods

The apparatus used was a 1.5-T MR unit. T1-weighted images were obtained using spin-echo (400–700/20, TR/TE) or inversion recovery (2000–3000/600/30, TR/TI/TE) sequences, and T2-weighted images were obtained using spin-echo (2000/100) sequences. Sections were perpendicular to the long axis of the brain stem and 5- to 7-mm thick using a matrix of 192×256 and a field of view of 20 or 25 cm.

Analysis of Myelination of Fiber Bundles

Fiber Bundles Analyzed.—Eighteen fiber bundles were analyzed. Changes in myelination were observed at 24 sites in the eight cross sections perpendicular to the long axis of the brain stem (see Table and Figs 2 and 3). Analyzed fiber bundles consisted of sensory pathways (medial lemniscus), special sensory systems (vestibular system: medial longitudinal fasciculus; auditory system: acoustic radiation, brachium of inferior colliculus; visual system: optic radiation), the motor system (corona radiata, anterior and posterior limbs of the internal capsule, cerebral peduncle, corticospinal tract), the limbic system (mamillothalamic tract), commissural connections (anterior commissure, splenium and genu of the corpus callosum), and the cerebellar system (inferior, middle, and superior cerebellar peduncle). The fiber bundles in the cerebral hemispheres were also classified into the projection fibers (corona radiata, anterior and posterior limbs of the internal capsule, optic radiation), the association fibers (acoustic radiation), and commissural fibers (anterior commissure, genu and splenium of the corpus callosum).

Changes in Myelination of Each Fiber Bundle.—When fiber bundles had higher signal intensity than that of gray matter on T1-weighted images, or had lower signal intensity than that of gray matter on T2-weighted images, they were considered to be myelinated. The 24 sites studied in each subject were graded as follows: 1) not myelinated, 2) targeted fiber bundles distinguished by myelination, and 3) fiber bundles difficult to distinguish (blurred) owing to similar signal intensity of surrounding tissue (Fig 4). The studies were staged independently by two observers who had no prior knowledge of the subjects' corrected gestational ages or clinical course.

To determine the normal time course of myelination on the basis of MR findings, the relative abundance of myelination at

List of analyzed fiber bundles

I. Level of inferior cerebellar peduncle
   (1) Inferior cerebellar peduncle (ICP)
   (2) Medial lemniscus (ML)
   (3) Medial longitudinal fasciculus (MLF)
II. Level of middle cerebellar peduncle
   (4) Middle cerebellar peduncle (MCP)
   (5) Superior cerebellar peduncle (SCP)
   (6) Medial lemniscus (ML)
   (7) Medial longitudinal fasciculus (MLF)
   (8) Corticospinal tract (CT)
III. Level of inferior colliculus
   (9) Decussation of superior cerebellar peduncle (SCP)
   (10) Brachium of inferior colliculus (BIC)
   (11) Cerebral peduncle (CP)
IV. Level of superior colliculus
   (12) Optic radiation (OR)
   (13) Anterior commissure (AC)
V. Level of lamina terminalis
   (14) Anterior limb of internal capsule (AIC)
   (15) Posterior limb of internal capsule (PIC)
   (16) Acoustic radiation (Heschl's gyrus) (AR)
   (17) Mamillothalamic tract (MT)
   (18) Fornix (FX)
VI. Level of septum pellucidum
   (19) Genu of corpus callosum (CCG)
   (20) Splenium of corpus callosum (CCS)
   (21) Anterior limb of internal capsule (AIC)
   (22) Posterior limb of internal capsule (PIC)
VII. Level of body of lateral ventricle
   (23) Corona radiata (CR)
VIII. Level of centrum semiovale
   (24) Corona radiata (CR)

different levels in the 24 sites were determined according to the following five criteria: 1) absence of myelination in all subjects belonging to the same age group, 2) myelination in less than half the cases, 3) myelination in half the cases or more, 4) blurring in less than half the cases, and 5) blurring in half the cases or more. The label "NA" was used when there were no available cases within a particular age group.

Classification of Fiber Bundles According to Progression of Myelination

The fiber bundles were classified according to the presence or absence of blurring, the age at which myelination was initi-
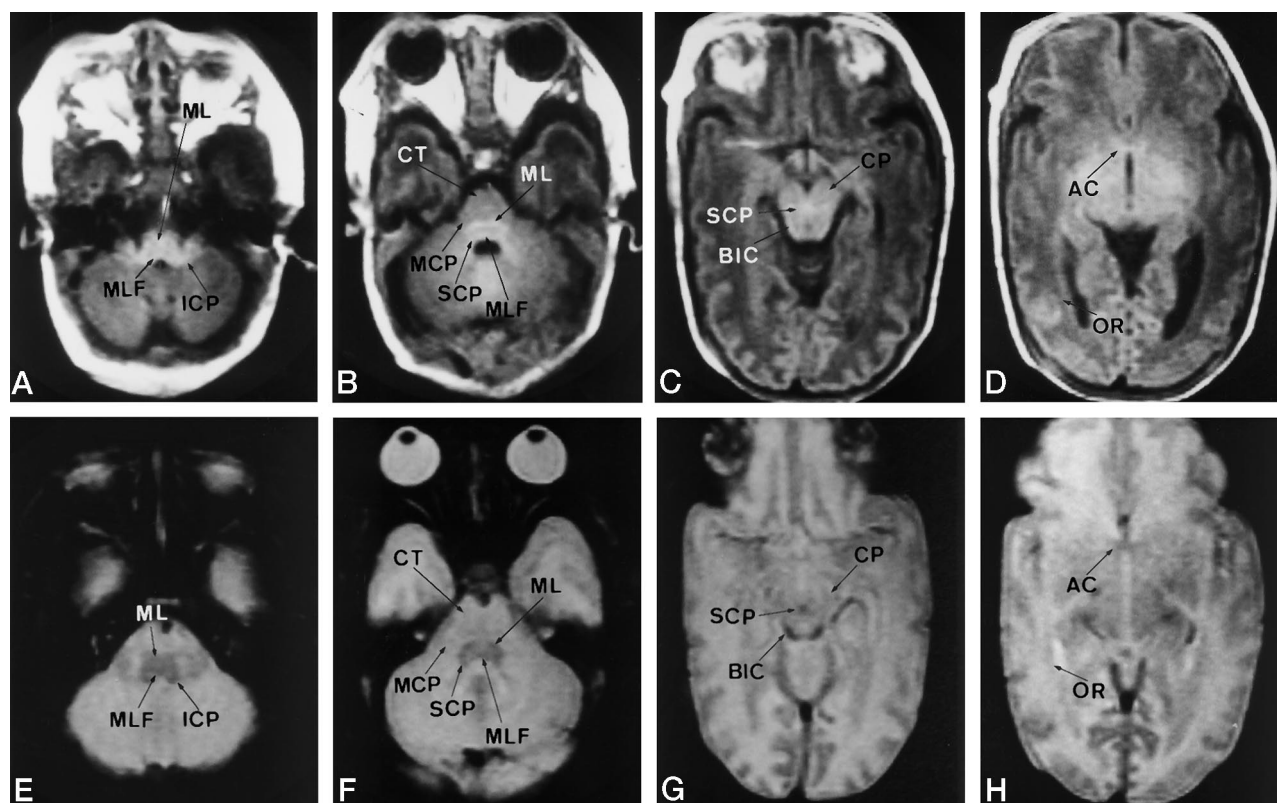
FIG 2. T1-weighted (500/20/4) (*A–D*) and T2-weighted (2000/100/2) (*E–H*) spin-echo MR images of an infant in the 38th gestational week. *A* and *E* are at the level of the inferior cerebellar peduncle; *B* and *F* are at the level of the middle cerebellar peduncle; *C* and *G* are at the level of the inferior colliculus; *D* and *H* are at the level of the superior colliculus. The inferior cerebellar peduncle, medial lemniscus, medial longitudinal fascicles, superior cerebellar peduncle, and brachium of the inferior colliculus were already myelinated and showed high signal intensity on T1-weighted images and low signal intensity on T2-weighted images. (See Table for explanation of abbreviations.)

ated, and the age at which blurring started. Statistical comparisons of progression and degree of myelination were made by using a contingency table method with χ^2-test analysis.

Results

Progression of Myelination of Fiber Bundles

Figure 5 shows the progression of myelination in the 24 sites of fiber bundles. For each number in parentheses, the top line represents the T1-weighted image and the bottom line represents the T2-weighted image. There were no interobserver differences in the results.

The age at which myelination began differed among fiber bundle sites, prompting three categories of classification: those in which myelination began at 35 weeks or less, those in which myelination began at around 44 to 45 weeks, and those in which myelination occurred after 56 to 67 weeks. Early myelination (before 35 weeks) was observed in the inferior cerebellar peduncle, the medial lemniscus, the medial longitudinal fasciculus, the superior cerebellar peduncle, the brachium of the inferior colliculus, the posterior limb of the internal capsule, and the corona radiata (on the T1-weighted image), all except the posterior limb of the internal capsule and the corona radiata representing fiber bundles in the brain stem.

Myelination at 44 to 45 weeks was observed in the middle cerebellar peduncle, the cerebral peduncle, the optic radiation, and the corona radiata. Myelination at 54 to 67 weeks was observed in the corticospinal tract, the anterior commissure, the anterior limb of the internal capsule, the acoustic radiation, the mamillothalamic tract, the fornix, and the genu and splenium of the corpus callosum, in all of which no blurring was seen except in the corticospinal tract.

In the inferior cerebellar peduncle, the medial lemniscus, and the medial longitudinal fasciculus, blurring appeared at 43 to 49 weeks, whereas in other structures (ie, the corticospinal tract, the superior cerebellar peduncle, the brachium of the inferior colliculus, the cerebral peduncle, the optic radiation, the acoustic radiation, and the corona radiata) it started to appear at 67 to 145 weeks.

Classification of Fiber Bundles According to Progression of Myelination

The fiber bundles were classified into two groups: group 1, in which fiber bundles could be identified after growth, owing to the absence of blurring; and group 2, in which blurring was observed. Based on the age at which myelination was initiated, group 1 was further divided into subgroups A and B, and group 2
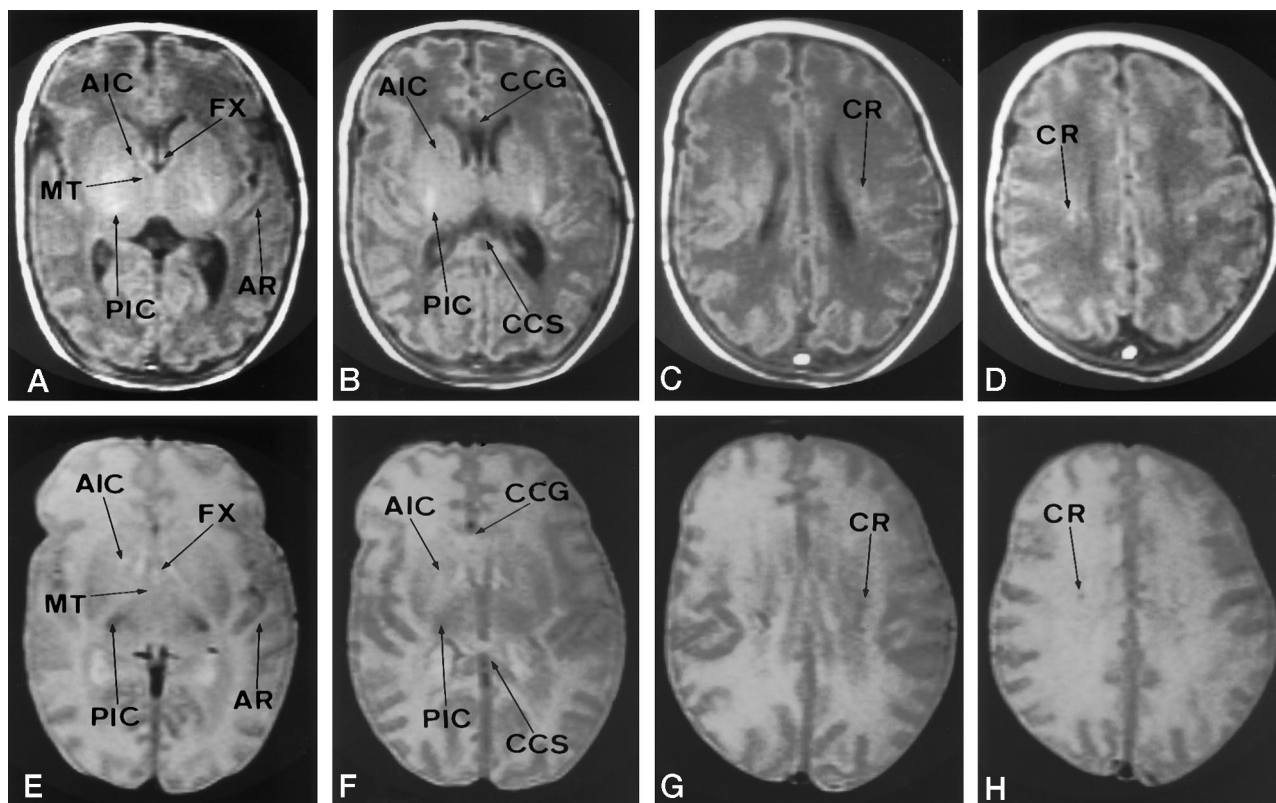
Fig 3.   T1-weighted (500/20/4) (*A–D*) and T2-weighted (2000/100/2) (*E–H*) spin-echo MR images of the same subject as Figure 2. *A* and *E* are at the level of the lamina terminalis; *B* and *F* are at the level of the septum pellucidum; *C* and *G* are at the level of the body of the lateral ventricle; *D* and *H* are at the level of the centrum semiovale. The posterior limb of the internal capsule and the corona radiata at the level of the body of the lateral ventricle were already myelinated. (See Table for explanation of abbreviations.)

was subdivided into subgroups A, B, and C (Fig 6). The results of the contingency table analysis for this five-subgroup classification were as follows: *df* was 8, χ^2 value expected for this df with a critical rate of 0.5% was 21.96, and the obtained χ^2 value was 877.4 (T1-weighted image) and 774.0 (T2-weighted image). These results were statistically significant.

In group 1A, myelination of fiber bundles started before 35 weeks and showed no blurring. The posterior limb of the internal capsule belongs to this group.

In group 1B, myelination started at 44 weeks (1 month) or later and showed no blurring. The middle cerebellar peduncle, the anterior commissure, the anterior limb of the internal capsule, the acoustic radiation, the mamillothalamic tract, the fornix, and the genu and splenium of the corpus callosum belong to this group.

Group 2A is the group in which blurring occurred at 43 to 49 weeks and myelination started before 35 weeks. The inferior cerebellar peduncle, the medial lemniscus, and the medial longitudinal fasciculus belong to this group.

In group 2B, blurring started at 67 to 145 weeks and myelination started before 35 weeks. The superior cerebellar peduncle, the brachium of the inferior colliculus, and the corona radiata belong to this group.

In group 2C, blurring started at 67 to 145 weeks and myelination started at 36 weeks or later. The corticospinal tract, the cerebral peduncle, the optic

radiation, the acoustic radiation, and the corona radiata belong to this group.

Discussion

Myelination of Fiber Bundles

The development of myelin sheaths around fiber bundles is one of the slowest processes in brain maturation, starting at about 16 weeks' gestational age, progressing rapidly from about 24 weeks to the perinatal period, and continuing until puberty (1). Active myelination from the perinatal period onward can be identified at imaging, and thus the progression of myelination provides an excellent parameter of brain maturation.

Attempts to image the process of myelination were first made with CT (4–6), but neither density resolution nor space resolution was sufficient for evaluation of myelination of individual fiber bundles. When MR imaging was first introduced for this purpose, resolution was again insufficient for observation of individual fiber bundles (7–12). However, with advances in MR technology, resolution improved significantly over the years, enabling observation of myelination of individual fiber bundles and use of this process as a parameter of brain development (13, 18).

Studies in which MR imaging has been used to study the initiation time of myelination of individual
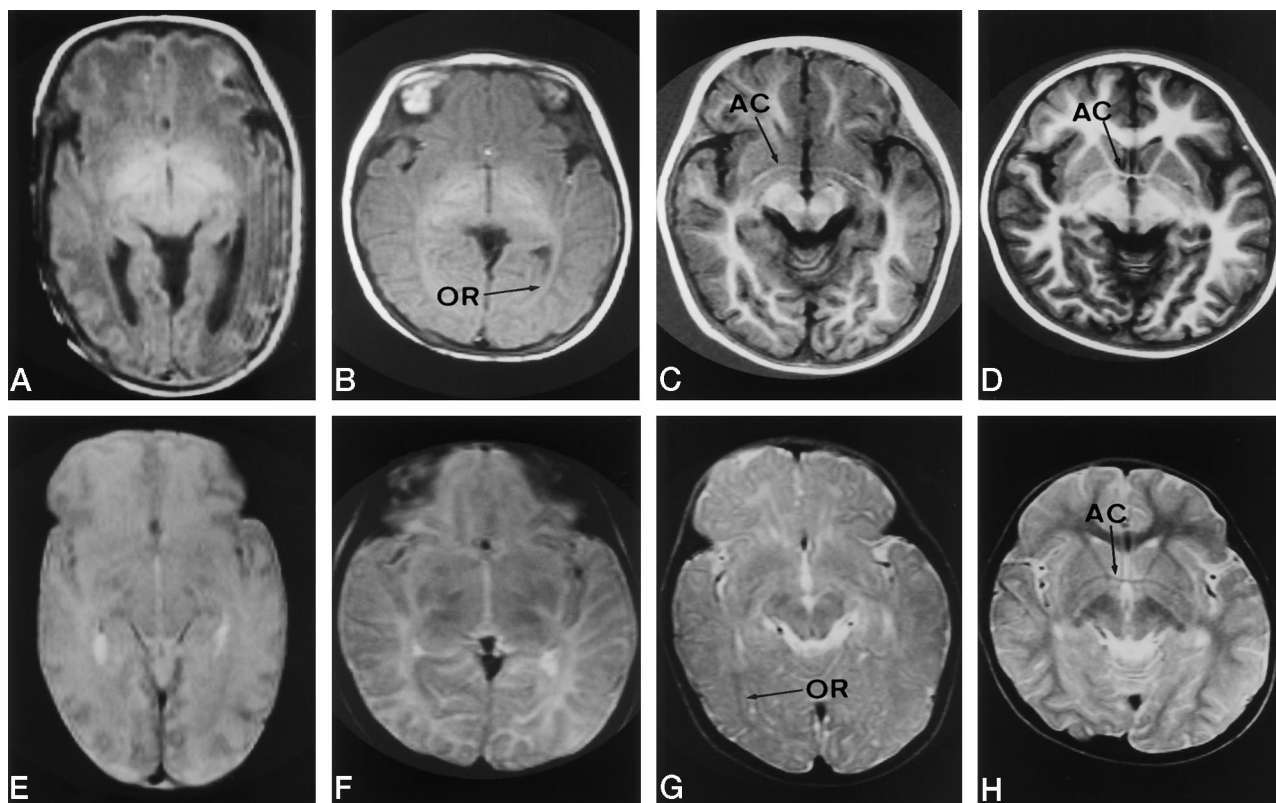
FIG 4. Progression of myelination at the level of the superior colliculus. *A–D* are T1-weighted images, *E–H* are T2-weighted images. *A* (spin-echo 600/20/4) and *E* (spin-echo 2000/100/2) are at 35 gestational weeks; *B* (spin-echo 600/20/4) and *F* (spin-echo 2000/100/2) are at 43 gestational weeks; *C* (inversion recovery 2500/600/30) and *G* (spin-echo 2000/100/2) are at 84 gestational weeks; *D* (inversion recovery 2500/600/30) and *H* (spin-echo 2000/100/2) are at 145 gestational weeks. The optic radiation (group 1C) and the anterior commissure (group 2B) are not myelinated at 35 gestational weeks. The optic radiation begins myelination at 43 gestational weeks (*B, F*) and becomes blurred at 145 gestational weeks (*D, H*). The anterior commissure begins myelination at 84 gestational weeks (*C, G*). (See Table for explanation of abbreviations.)

fiber bundles have been carried out by Barkovich et al (15), Bird et al (16), and Hittmair et al (18). Barkovich and his group (15) used a 1.5-T MR unit to examine 82 infants aged 4 days to 2 years. In their study, as well as in ours, the fiber bundles examined included the posterior limb of the internal capsule, the genu and splenium of the corpus callosum, the middle cerebellar peduncle, the anterior limb of the internal capsule, and the corona radiata. The initiation times of myelination observed in the posterior limb of the internal capsule and in the genu and splenium of the corpus callosum were the same in both studies; however, in the middle cerebellar peduncle, Barkovich et al found an initiation age of 40 weeks (based on T1-weighted images) whereas ours was 44 weeks. In the anterior limb of the internal capsule, Barkovich et al obtained an initiation age of 2 to 3 months, whereas our result indicates 6 months. On T1-weighted images of the corona radiata, Barkovich et al noted an initiation age of 2 to 4 months, whereas our results were 36 to 38 weeks; and on T2-weighted images of the corona radiata, their finding of 7 to 11 months differs considerably from the 2 months in our study. According to findings in the corona radiata, we think that their example of a 1-month-old infant in Figure 3A of their article (15) shows myelination.

Bird et al (16) examined 60 infants aged 1 week to

3 years using a 1.5-T MR imager. The fiber bundles examined in both their study and ours included the posterior and anterior limbs of the internal capsule, the corona radiata, the cerebral peduncle, the optic radiation, the splenium and genu of the corpus callosum, and the anterior commissure. They analyzed the degree of myelination by comparing the signal intensity of gray matter with that of the posterior limb of the internal capsule, classified the signal into four degrees of intensity, and evaluated the findings by means of a graphical method. Although they did not state which degree corresponded to the initiation of myelination, the high signal on T1-weighted images and the low signal on T2-weighted images in our study seem to best fit their grade 1. Taking grade 1 as the initiation time of myelination, our results agree with theirs in the posterior and anterior limbs of the internal capsule, the corona radiata, the cerebral peduncle, the optic radiation, and the genu and splenium of the corpus callosum. In the anterior commissure, however, they reported initiation of myelination at 0 month by T1-weighted images and at 5 months by T2-weighted images, whereas our results indicate an initiation age of 6 months and 12 months, respectively. Because they did not provide any example of myelination in the anterior commissure, we cannot speculate as to the exact reason for this difference.
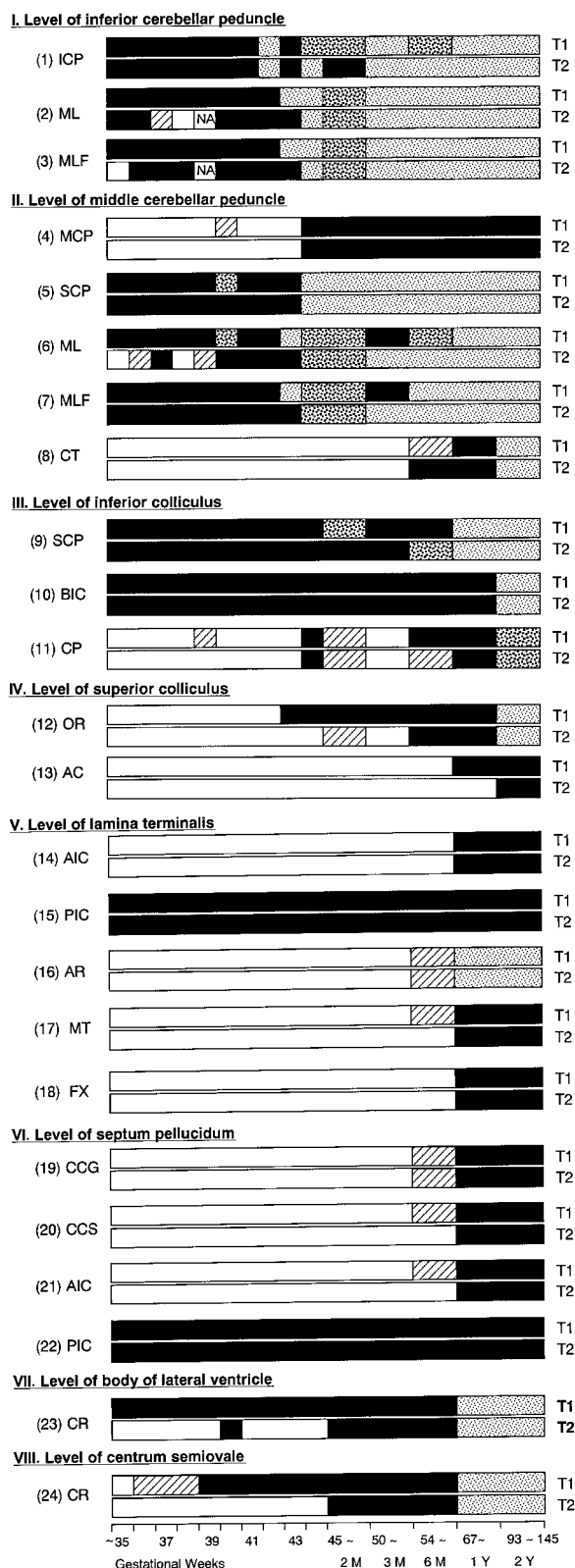
FIG 5. Analyzed pattern of progression of myelination. *Open bar*, myelination not seen in any subject; *hatched bar*, myelination seen in less than 50% of subjects; *solid bar*, myelination seen in more than 50% of subjects; *densely dotted bar*, blurring occurred in less than 50% of subjects; *lightly dotted bar*, blurring occurred in more than 50% of subjects; *NA*, no available subjects for this age group. (Numbers in parentheses correspond to those in Table; see Table for explanation of abbreviations.)

Hittmair et al (18) examined 27 infants aged 3 days to 3 years with a 1.5-T MR unit. The fiber bundles examined in both their study and ours included the posterior limb of the internal capsule, the corona radiata, the splenium and genu of the corpus callosum, the optic radiation, the middle cerebellar peduncle, and the anterior limb of the internal capsule. These authors reached almost the same conclusions regarding the first five fiber bundles (the posterior limb of the internal capsule, the corona radiata, the splenium and genu of the corpus callosum, and the optic radiation). However, on T1-weighted images of the middle cerebellar peduncle, they found an initiation age of 2 to 3 months, whereas our results indicate 1 month. On T2-weighted images, they noted 4 months, whereas our results indicate 1 month. In the anterior limb of the internal capsule, their results were 4 to 5 months on T1-weighted images and 9 to 10 months on T2-weighted images, whereas our results were 6 months in both cases. We think that these differences in the periods of myelination in some fiber bundles may be due to the small number of subjects examined.

The mechanism by which myelination affects MR signals differs between T1- and T2-weighted images. Barkovich et al (15) showed that changes in myelination can be seen 2 to 4 months earlier on T1-weighted images than on T2-weighted images. In the present study, myelination of the optic radiation was observed about 3 months earlier on T1-weighted images than on T2-weighted images, and myelination of the anterior commissure was observed about 6 months earlier on T1-weighted images. However, there were no differences between T1- and T2-weighted images in the initiation time of myelination or in the time of blurring in the remaining fiber bundles.

Blurring of Fiber Bundles

It is difficult to distinguish fiber bundles from surrounding tissue by MR imaging in adults. This is because the white matter surrounding each fiber bundle has the same signal intensity as the fiber bundle. However, some fiber bundles are distinguishable by MR imaging after growth. Curnes et al (19) used the term compact to describe those fiber bundles in adults that have low signal intensity on T2-weighted images (the posterior and anterior limbs of the internal capsule, the anterior commissure, the mamillothalamic tract, the fornix, the splenium and genu of the corpus callosum, the optic radiation, the optic tract, the superior frontooccipital fascicles, the cingulum, the uncinate fascicles, and the superior longitudinal fascicles). These authors considered the high density of the fiber bundles and the thick myelin sheaths to be the reasons that fiber bundles have lower signal intensity than surrounding white matter.

The fiber bundles in the first group in our study included the posterior and anterior limbs of the internal capsule, the middle cerebellar peduncle, the anterior commissure, the mamillothalamic tract, the fornix, and the genu and splenium of the corpus

Group 1: Blurring (-)

A: PIC(15,22)

B: MCP(4), AC(13), AIC(14,21), MT(17),
FX(18), CCG(19), CCS(20)

Group 2: Blurring (+)

A: ICP(1), SCP(5), ML(2,6), MLF(3,7)

B: SCP(9), BIC(10), CR(23)

C: CT(8), CP(11), OR(12), AR(16),
CR(24)

~ 35   37   39   41   43   45 ~   50 ~   54 ~   67 ~   93 ~ 145
Gestational Weeks   2 M   3 M   6 M   1 Y   2 Y

☐ no myelination

■ fiber bundle isolation is possible by myelination

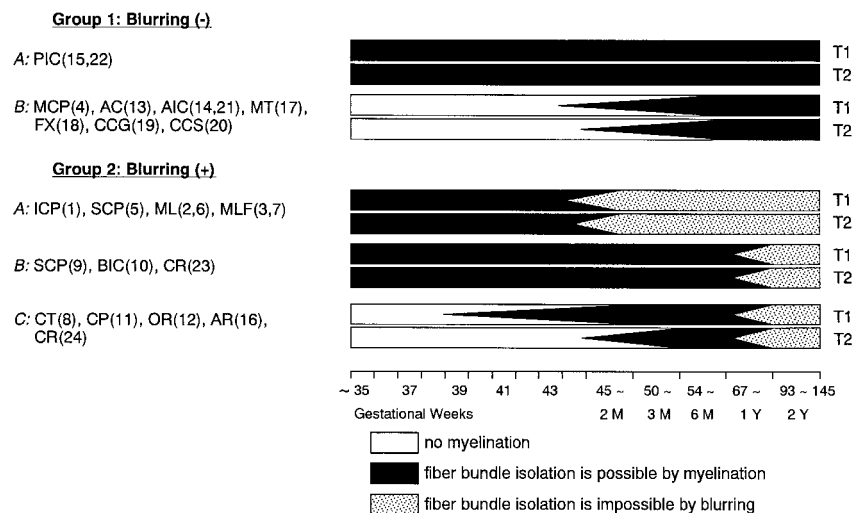▨ fiber bundle isolation is impossible by blurring

Fig 6. Simplified pattern of progression of myelination. In terms of the onset of myelination and blurring of fiber bundles shown in Figure 5, two major groups and five subgroups were identified. (Numbers in parentheses correspond with those in Table; see Table for explanation of abbreviations.)

callosum, and all of them except the middle cerebellar peduncle were compact fiber bundles. These were distinguishable on T1- and T2-weighted images, perhaps because the middle cerebellar peduncle, the fornix, and the genu and splenium of the corpus callosum are surrounded by CSF spaces, whereas the anterior limb of the internal capsule, the anterior commissure, and the mamillothalamic tract are surrounded by gray matter.

The fiber bundles in the second group in our study were blurred, and all were surrounded by myelinated white matter. This supports the notion that, early in development, fiber bundles can be distinguished from surrounding white matter because myelination of fiber bundles precedes that of the surrounding white matter in the neonatal period, but later they become indistinguishable because of the progression of myelination in the surrounding white matter.

The fiber bundles were divided into three groups according to the time when blurring occurred: group 2A, in which blurring occurred at 44 to 50 weeks, and groups 2B and 2C, in which blurring occurred at 67 to 92 weeks or later (7 months to 1 year). Group 2A consisted of the inferior cerebellar peduncle, the medial lemniscus, the medial longitudinal fasciculus, and the superior cerebellar peduncle (midbrain), in all of which myelination started by 35 weeks. These are the fiber bundles of the caudal brain stem in relation to the middle cerebellar peduncles. Presumably, not only the fiber bundles but also the surrounding white matter began myelination early on the caudal side of the brain stem. The superior cerebellar peduncle (decussation of the superior cerebellar peduncle), the brachium of the inferior colliculus, and the corona radiata, in which myelination started by 35 weeks, belong to group 2B, whereas the corticospinal tract, the cerebral peduncle, the optic radiation, and the acoustic radiation, in which myelination started after 36 weeks, belong to group 2C. The superior cerebellar peduncle, the brachium of the inferior colliculus, the corticospinal tract, and the cerebral peduncle are located in the midbrain; the corona radiata, optic

radiation, and acoustic radiation are in the cerebral hemisphere.

Conclusion

Knowledge of the initiation time of myelination of fiber bundles is useful for evaluating brain maturation in the neonatal period, but there have been no appropriate parameters of brain maturation after infancy, when myelination of fiber bundles is complete. The present study shows that the time of blurring in groups 2B and 2C can be a useful parameter of brain maturation after infancy.

Acknowledgment

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