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MR Evaluation of Early Myelination Patterns in Normal and Developmentally Delayed Infants

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This study demonstrates the ability of MR imaging to show progression of myelination in 64 infants and young children (ages 4 days to 36 months). T2-weighted spin-echo pulse sequences, frequently used for routine screening of intracranial disease, were used. Gray-white matter differentiation was seen in all patients, and changes occurring with age were documented. Three distinct patterns were seen, and age ranges were established for each pattern in developmentally normal children: (1) infantile (birth–6 months); (2) isointense (8–12 months); and (3) early adult (10 months onward). There was a statistically significant difference between the age ranges of the normal and developmentally delayed children showing all three patterns.

These data should be helpful for identifying and following sequentially both infants with clinically suspected developmental delay and those with dysmyelinating or demyelinating disease.

Myelination is a dynamic process starting during intrauterine life and continuing after birth and can thus be used as an index of brain maturation. This is particularly true in the first 2 years, when changes are occurring most rapidly. Since MR imaging of the brain in infants and young children is being performed with increasing frequency when developmental delay is suspected clinically, it offers a unique opportunity to study myelination in vivo in normal and abnormal children both sequentially and relative to a known standard. Such children are routinely screened using combinations of long and short TR and long and short TE spin-echo pulse sequences. It is therefore imperative for the radiologist to be familiar with the normal appearance of the progression of myelination on these sequences if delay in myelination or abnormalities involving the white matter are to be detected and accurately diagnosed at the earliest possible time. It is also important that the normal appearance of the brain of infants, which is different from that of the adult, not be mistaken for myelination abnormalities.

Previous studies evaluating the brain of a small number of infants using spin-echo pulse sequences suggest isointensity between gray and white matter in the first 3 months of life [1–3]. Following a transient appearance of white matter hyperintensity relative to gray matter at 4 to 6 months, gray-white differentiation has reportedly reverted to an early adult pattern at approximately 9 months to 1 year [3]. As our preliminary observations were discrepant with these findings, we reviewed all MR studies of the brains of children under 3 years old obtained in the previous 2 years. This study establishes the spin-echo MR appearance of the progression of myelination and the gray-white matter differentiation patterns in developmentally normal infants from birth to 3 years and demonstrates the ability of MR to detect slower progression of the myelination process in developmentally delayed children.

Materials and Methods

All MR images of the brains of children under 3 years old obtained between December

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1984 and November 1986 were reviewed. Studies demonstrating severe structural anomalies, hydrocephalus, or demyelinating disease, or those that were suboptimal due to motion artifacts, were excluded. The study population thus consisted of 64 children, ages 4 days to 36 months (mean age, 12.4 months), whose age distribution is shown in Figure 1. Thirty-nine were boys and 25 were girls.

Technique

All studies were performed with either a 0.3-T permanent magnet* or a 0.35-T superconducting magnet.† T2-weighted spin-echo pulse sequences (SE 2000/80 or 84) were obtained for all patients, 58 in the axial plane and six in the coronal plane. The thickness of the slices obtained was either 5-mm contiguous cuts or 7-mm cuts with 3-mm gaps between adjacent cuts. Additional short TR, short TE pulse sequences (SE 300 or 500/18, 28, or 30) were obtained for the majority of patients. All patients were scanned with standard adult head coils. Patients were routinely sedated before scanning with either chloral hydrate 50–75 mg/kg orally, or a combination of Demerol 2 mg/kg, Thorazine 1 mg/kg, and Phenergan 1 mg/kg administered intramuscularly 30 min before scanning.

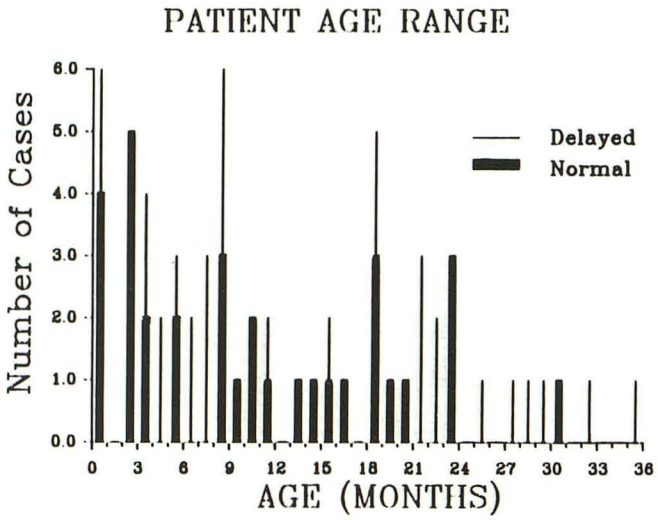

Fig. 1.—Age range of clinically normal and developmentally delayed infants.

Analysis

Subjective analyses of the relative intensity of the gray and white matter (i.e., opinions of observers about relative signal intensities in a given MR slice) were made in the regions of the anterior and posterior limbs of the internal capsule, anterior and posterior centrum semiovale, frontal and temporal lobes, and posterior fossa. These evaluations were carried out by two of the authors simultaneously in each case, with discussion as necessary to agree on the grade assigned to minimize observation variation. The readers graded all cases without prior knowledge of patient age or clinical history. The signal intensity of each area was graded from 0 to 10 (0 = air, 10 = subcutaneous fat).

Although our grading system is subjective, we believe it is a more accurate reflection of assessment of gray-white matter differentiation than are quantitative T1 and T2 measurements or computer-density measurements because of the small size of the areas that would be sampled compared with the slice thickness of the scans obtained.

Clinical correlation was obtained in all cases and developmental delays noted. The patient population was divided into two groups: (1) children with normal neurologic development (34 cases) and (2) children with clinical evidence of developmental delay (30 cases).

The images obtained of the developmentally normal group were reviewed in chronological order to establish the normal appearances in progression of myelination with age. Images of the children with developmental delay were also evaluated to see if there was a significant delay in the progression of the myelination patterns or abnormal myelination patterns as compared with the normal group.

Results

Images obtained in both groups were of diagnostic quality. In all patients scanned, gray-white matter differentiation was demonstrated on SE 2000/80 or 84 sequences using both the 0.3-T and 0.35-T magnets. Although developmentally normal children showed a spectrum of relative intensities of gray and white matter, the gray-white matter patterns observed fell into three distinct groups (see Table 1). In the first, white matter had higher signal intensity than gray matter (subjective rating of white matter was two grades or more higher than gray matter at the level of the centrum semiovale). This pattern was observed in all children under 7 months old and was thus classified as the infantile pattern (Figs. 2 and 3). No child in this age group demonstrated isointensity between the gray and white matter. An early adult pattern (subjective rating of gray matter two grades or more higher than white matter) was seen in all normal children over 12 months old (Fig. 5).

The youngest child with this pattern was 10 months old. Children between the ages of 8–12 months demonstrated a transient isointense phase with poor differentiation of gray and white matter (subjective rating of gray and white matter differed by less than two grades) (Fig. 4). This transient pattern was rarely seen throughout the entire brain at one time. Patients more frequently showed an infantile-isointense

TABLE 1: Patterns of Gray-White Matter Differentiation

Pattern	No. of Children	Age Range of Normal Children	Age Range of Developmentally Delayed Children
Infantile (White matter is two grades or more lighter than gray matter)	24	6 days–6 mos.	1–9 mos.
Isointense (Gray and white matter differ by less than two grades)	15	8–12 mos.	8–33 mos.
Early adult (Gray matter is two grades or more lighter than white matter)	25	10–31 mos.	12–36 mos.
Total	64		

* Fonar B-3000 body imager, Melville, NY.
† Diasonics MT/S whole body imager, Milpitas, CA.

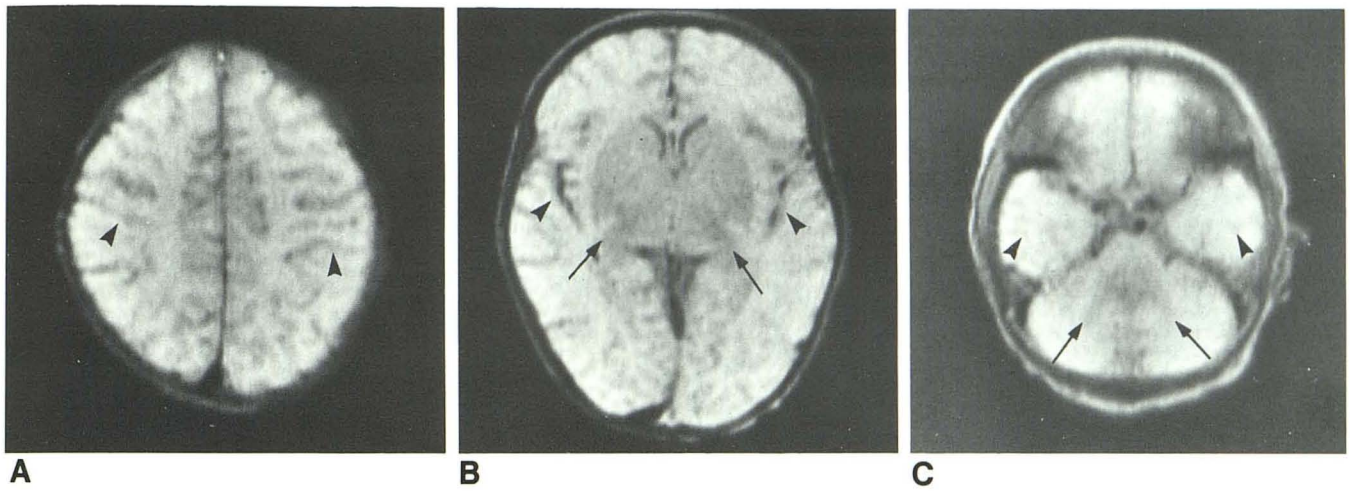

Fig. 2.—Infantile pattern in 6-day-old boy. Axial MR images (SE 2000/84). Supratentorial white matter has diffusely higher signal intensity than gray matter (*arrowheads*) at all levels.
***A*, Level of centrum ovale.**
***B*, Level of basal ganglia.**
***C*, Level of temporal lobes and posterior fossa. Areas of myelination (*arrows* in *B* and *C*) already present in cerebellum and thalami.**

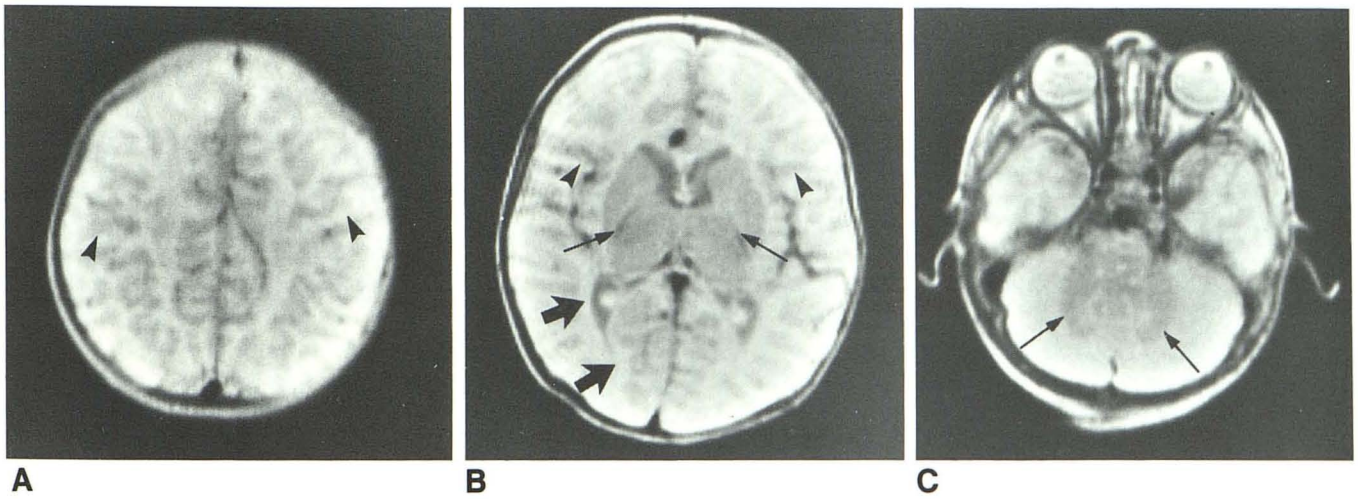

Fig. 3.—Infantile pattern in 3-month-old boy. Axial MR images (SE 2000/84).
***A*, Level of centrum ovale white matter has higher signal intensity than gray matter (*arrowheads* in *A* and *B*), as in the 6-day-old boy (Fig. 2).**
***B*, Development of myelination in posterior limb of internal capsule (*thin arrows*) and optic radiation (*thick arrows*) is seen as low signal intensity.**
***C*, Myelinated area of cerebellum (*arrows*) is larger than in 6-day-old boy.**

transition phase or an isointense-adult transition phase. In one 11-month-old child all three patterns were identified concomitantly (Fig. 6). When more than one pattern was seen in different areas of the brain of the same child, the more immature pattern was always present in the areas of later myelination.

As the process of myelination progressed, the previously nonmyelinated, high signal intensity, infantile supratentorial white matter developed lower signal intensity. This generally followed established patterns [2–7] (Fig. 7); that is, myelination first seen in the thalamus followed by the posterior limb of the internal capsule, the optic radiations, the anterior limb of the internal capsule, centrum ovale, and finally subcortical extension to the frontal and temporal lobes. In children under 1 month old, both the posterior and anterior internal capsule had high signal intensity, as did all the white matter. As myelination progressed in specific areas, the affected white matter, which had high signal intensity prior to this time, developed decreasing signal intensity. In all normal children over 1 month old, the development of myelination was seen in the region of the posterior limb of the internal capsule. As myelination continued, areas of lower signal intensity were also identified sequentially in the regions of the optic radiations to the occipital lobes (3 months), the anterior limb of the

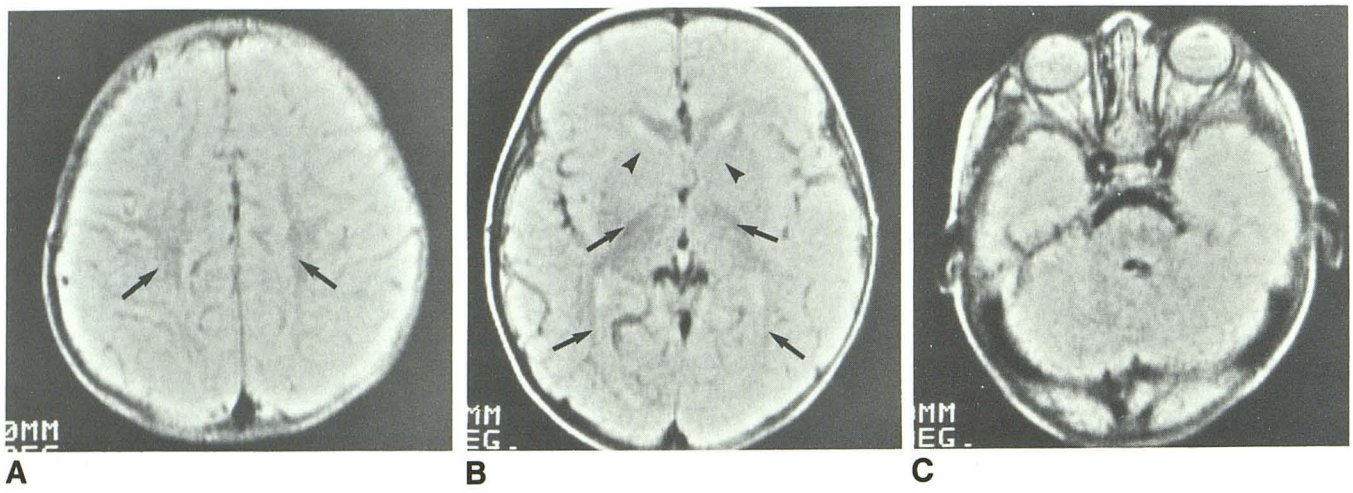

Fig. 4.—Isointense pattern in 10-month-old girl. Axial MR images (SE 2000/84). Signal intensities of gray and white matter are similar at all levels.
A, Myelination present in white matter of centrum semiovale (*arrows*).
B, Myelination is seen in anterior (*arrowheads*) and posterior limbs of internal capsule and optic radiations (*arrows*).
C, There is no significant difference between white matter and gray matter in the cerebellum.

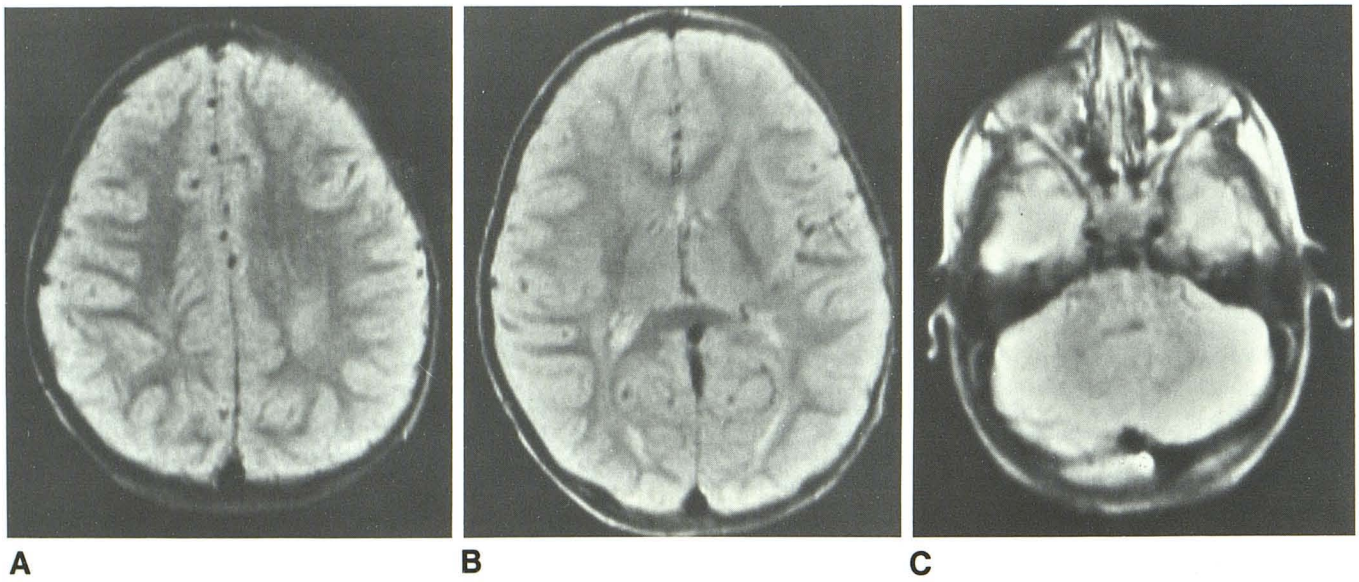

Fig. 5.—Early adult pattern. Axial MR images (SE 2000/84) in 1-year-old boy. White matter now has lower signal intensity than gray matter at all levels. In *B* we believe that the bilateral linear hyperintense signal in medial portion of occipital white matter represents subependymal glial cells.

internal capsule and radiation to the precentral gyrus (6 months), the parietal and frontal central white matter (8 months), and the white matter of the temporal lobes (1 year). After the age of 1 year, the portion of central white matter myelinated increased progressively as myelination occurred in the subcortical fibers, and the gray-white matter signal intensity differentiation increased.

Despite pathologic reports of intrauterine myelination of the inferior cerebellar peduncles, myelination in the posterior fossa has reportedly not been visualized by MR until age 3 months [3]. In our series, however, areas of myelination were seen in this region as early as 6 days and progressively increased in size with age.

Developmentally Delayed Children

When developmental delay was present, the infantile pattern age range extended to 9 months, and the isointense pattern extended to 33 months in this series (Figs. 8 and 9). Figures 8–10 depict the age ranges for each of these patterns in both the developmentally normal and delayed groups.

There was a statistically significant difference in the age distribution of the normal and developmentally delayed children within all three gray-white matter pattern groups. Figures 11–13 (cases 1–3) show examples of developmentally delayed children.

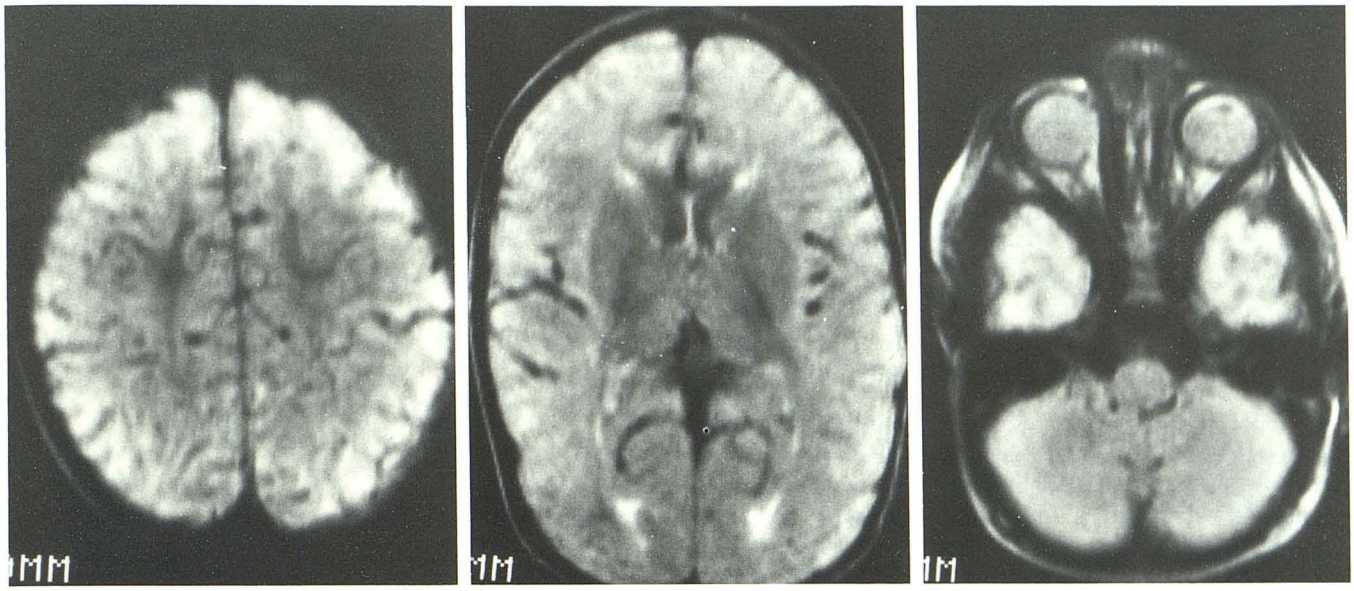

Fig. 6.—Transition pattern in 11-month-old boy. Axial MR images (SE 2000/84).
***A*, At level of centrum ovale, white matter is beginning to show lower signal intensity than gray matter.**
***B*, At level of basal ganglia, white and gray matter of occipital and frontal lobes show isointensity.**
***C*, At level of temporal lobes, white matter has higher signal intensity than gray matter, characteristic of infantile pattern.**

Case 1

This 8-month-old boy (Fig. 11) was noted by his pediatrician to have hypotonia and delayed motor milestones. He was the 7 lb 8 oz product of a full-term gestation following an uncomplicated pregnancy, labor, and delivery. Newborn examination was within normal limits. At 4 months the baby demonstrated persistent head lag and decreased muscle tone. At 8 months the head lag was still present and the child was unable to sit.

MR showed an infantile-type gray-white matter differentiation pattern. Myelination was present in the posterior fossa and thalami. A small amount of myelination was also seen in the posterior limb of the internal capsule consistent with a developmentally normal child of approximately 1 month.

Case 2

This 18-month-old girl (Fig. 12) demonstrated congenital nephrosis and failure to thrive. She was the 7 lb 12 oz product of a full-term gestation following an uncomplicated pregnancy, labor, and delivery. The baby did well until age 2 months, when she had two seizures. Evaluation at that time revealed acute renal failure, and biopsy documented congenital nephrosis. She has been maintained on peritoneal dialysis since that time. Developmentally, at 18 months she could transfer objects well but could not roll over or sit alone. She was diffusely hypotonic and had bilateral symmetric hyperreflexia.

An MR study revealed myelination in the posterior fossa and optic radiations. A small amount of myelination was also present in the anterior limb of the internal capsule consistent with a normally developing child of 5–6 months.

Case 3

This 20-month-old girl (Fig. 13) presented with fever and cervical adenopathy. She was the 8 lb 1 oz product of a normal pregnancy, labor, and delivery, and was previously healthy. At the time of admission she had been symptomatic for 6 weeks. Routine blood tests revealed hemaglobin of 6.5, and a cervical node biopsy showed histiocytosis X.

MR studies demonstrated early adult-type gray-white matter differentiation pattern. Although myelination was present in the parietal white matter, this was less extensive than would be expected at 20 months and was more consistent with a developmentally normal child of 12 months.

Discussion

Although the process of myelination has been well documented pathologically, in the past with a small number of autopsy infant brains [4–9] and more recently by a more extensive series [10], until the advent of MR, it was not possible to study myelination in vivo or sequentially. Elegant neurochemistry studies have shown myelogenesis to be a dynamic process starting during intrauterine life and continuing after birth. Generally, the most archaic phylogenetic systems are myelinated first, myelination proceeding roughly in a rostral direction, the cortical association fibers being the last [4]. The initiation of myelination appears in different sites at different times, but has begun in most areas by 8 months of age. Myelination proceeds at different rates in different neuronal systems and in different tracts of the same neuronal systems. There is a variable range in the degree of myelination

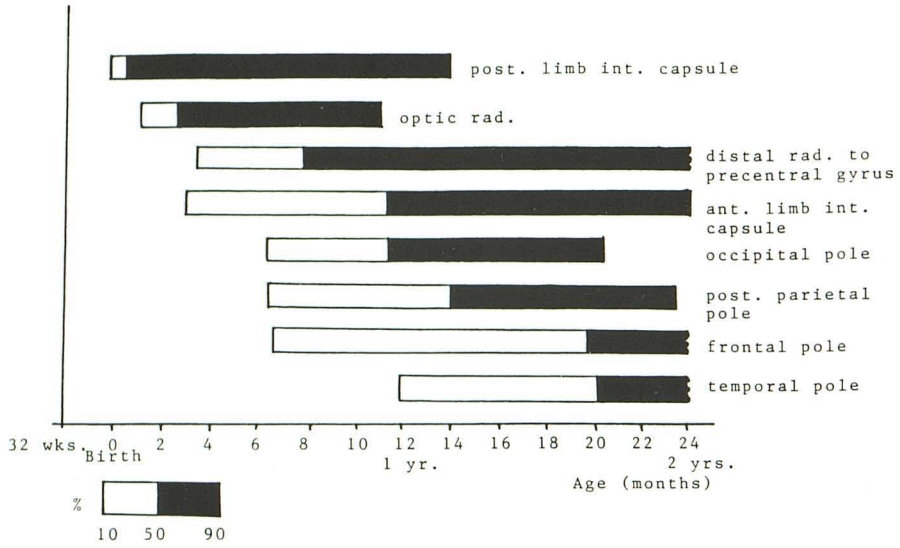

Fig. 7.—Diagram adapted from [10] demonstrating the time sequence of myelination seen in infant brains at autopsy. White zone = 10–50% myelination; black zone = 50–90% myelination.

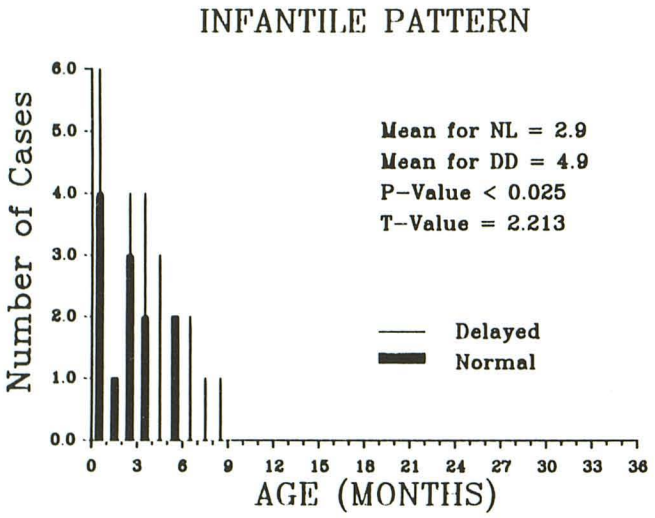

Fig. 8.—Infantile pattern. Age distribution of normal and clinically developmentally delayed children.

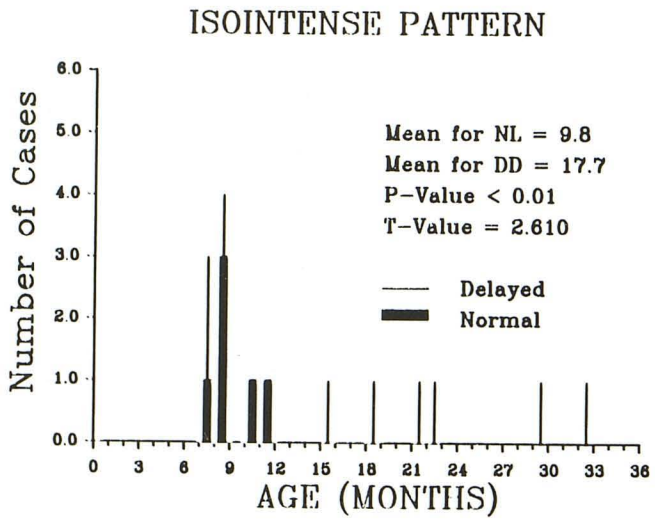

Fig. 9.—Isointense pattern. Age distribution of normal and clinically developmentally delayed children.

within any site at all ages. By age 2 years, the myelination process, although incomplete, has progressed rapidly from the newborn period. Figure 7 is adapted from work by Brody et al. [10] and depicts the time of initiation and completion of myelination in the specific areas analyzed.

With the routine T2-weighted spin-echo pulse sequences normally used to evaluate adult pathology, it is possible to distinguish gray and white matter by MR in infants and to demonstrate early progression of myelination. The progession of myelination shown by MR using spin-echo pulse sequences correlated well with the previously documented pathologic mapping. At birth and generally for the first 8 months, there is reversal of the normal adult pattern seen on T2-weighted images, white matter being more intense than gray matter. It is important that radiologists performing MR are familiar with this pattern and recognize it as a normal phenomenon so as not to confuse this infantile appearance with dysmyelinating or demyelinating disease, edema, or other pathologic processes that may affect the white matter diffusely during this time period. This appearance and its gradual reversion to the adult pattern correlates with an initially greater water content of unmyelinated white matter, followed by subsequent water loss occurring during the myelination process, as myelin is relatively hydrophobic [6, 11, 12]. Evaluation of possible clinical developmental delay is extremely difficult in this early age group. MR images obtained at this time may demonstrate delay in myelination or other pathologic lesions leading to clinical developmental delay such as structural abnormalities, areas of hemorrhage, or changes secondary to anoxia in these patients. Obtaining a baseline study at this time may

also be extremely useful as serial progression and thus possible delay in this progression may be seen on sequential scans.

Despite the fact that the isointense phase is only a transient finding, a significant number of the children we evaluated (23.4%) demonstrated this pattern. This is probably due to the fact that the age range of this pattern in normal children is from 8 to 12 months. At this time infants are achieving well-established milestones such as sitting, crawling, and walking. It may be that this is the time when parents first express concern about possible developmental delay, and thus children of this age range are more frequently evaluated.

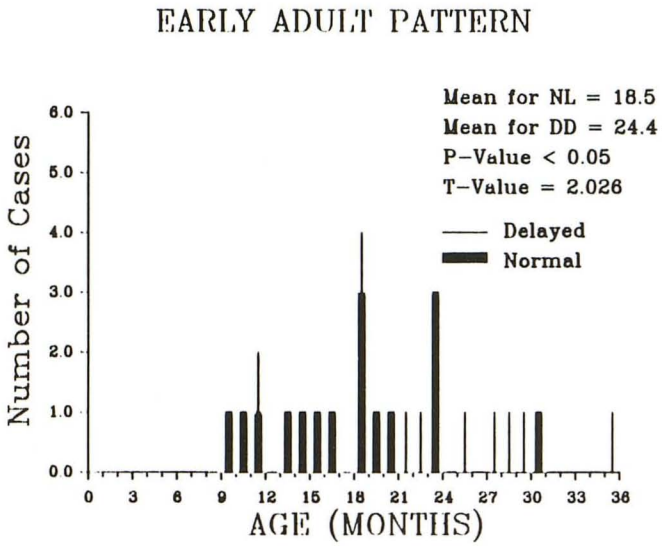

Fig. 10.—Early adult pattern. Age distribution of normal and clinically developmentally delayed children.

The early adult pattern was seen in normal children as early as 10 months of age. Our findings of progression of this pattern subcortically and the development of secondary branching correlated with previously reported findings [3].

The statistically significant differences in the age distribution of normal and developmentally delayed children in three gray-white matter pattern groups implies that the demonstration of a more immature pattern of gray-white matter differentiation or myelination than would be expected at a particular chronological age in infants should raise the suspicion of developmental delay due to a delay or arrest in the myelination process. MR is a noninvasive technique that may prove extremely useful in the evaluation and serial follow-up of such patients.

The discrepancy between our findings and those of previous reports using spin-echo T2-weighted sequences may be due to several factors. If high-field-strength magnets are used it may well be necessary to use sequences with longer TR (in order to counter the increase in T1) before gray-white matter differentiation can be seen, as has recently been reported [13]. In one prior study using a low-field-strength magnet, the images obtained were less T2-weighted (SE 1080/40) than those obtained in our series, and this too may have impaired its visualization [1]. Two other studies, however [2, 3], reported images that were obtained with similar pulse sequences using similar field strength magnets. Different observations may be related to a small number of infants under 6 months old scanned in these particular studies or possibly to poor visualization of gray-white matter differentiation due to patient motion, radio frequency artifacts, or inappropriate windowing during photography.

In conclusion, good gray-white matter differentiation and progression of myelination can be seen on T2-weighted spin-echo MR images in normal infants. This series thus estab-

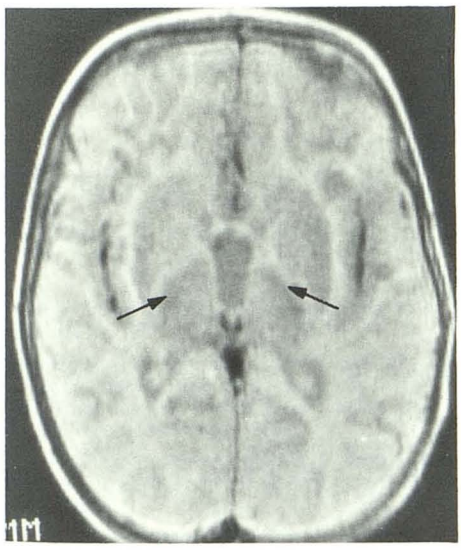

Fig. 11.—Case 1. 8-month old boy with developmental delay. Infantile pattern with myelination only present in the thalami bilaterally (*arrows*).

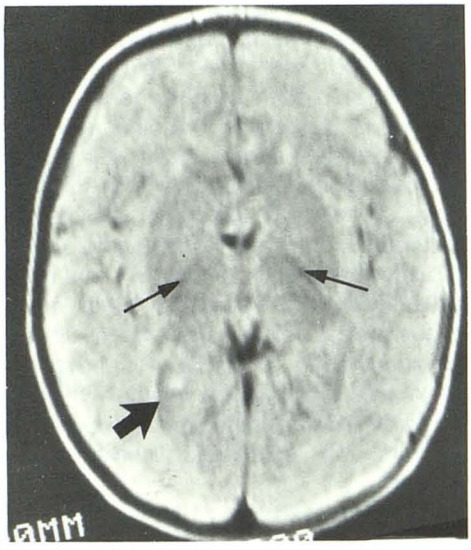

Fig. 12.—Case 2. 18-month-old girl with developmental delay. Isointense pattern with myelination present in posterior limb of internal capsule (*thin arrows*) and optic radiations (*thick arrow*).

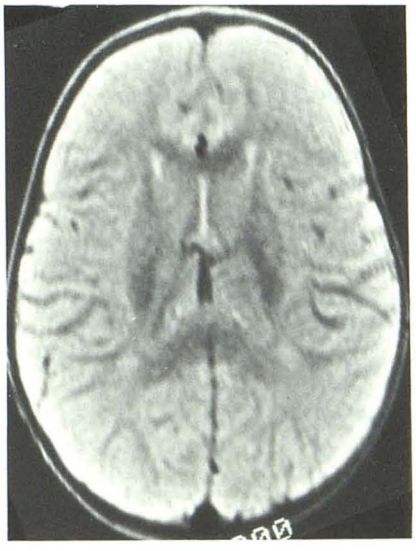

Fig. 13.—Case 3. 20-month-old girl with developmental delay. Early adult pattern consistent with a developmentally normal child of 12 months.

lishes the normal early myelination changes using this pulse sequence. There was a statistically significant difference between the age ranges of the normal and developmentally delayed children showing the infantile, isointense, and adult patterns. Demonstration of a pattern more immature than is normally seen at a particular age correlated with clinical developmental delay.

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