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**ORIGINAL
RESEARCH**

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BACKGROUND AND PURPOSE: A common isolated reported finding in brain imaging studies on developmentally delayed children is delayed myelination. We hypothesized that brain MR imaging scans of these children would show delayed subcortical myelination of white matter with specific involvement of the subcortical U-fibers as these represent terminal zones of myelination and are the last areas to myelinate.

MATERIALS AND METHODS: A total of 93 children (31 controls, 62 with idiopathic developmental delay [IDD]) aged 17 to 46 months were identified on the basis of having brain MR imaging for evaluation of IDD (cases) or for another condition (controls). Children with diseases that primarily affect white matter or overt intracranial lesions or malformations were excluded. IDD was defined as psychomotor retardation without a clear cause on the basis of history, physical, genetic, metabolic, and neuroimaging examinations. Developmental quotients (DQs) were calculated for all children with IDD on the basis of clinical history, examination, and psychometric testing. Three board-certified pediatric neuro-radiologists examined axial T2-weighted brain images and used a published scoring system to rate the extent of myelination in the frontal, temporal, parietal, and peritrigonal brain regions. In addition, subcortical U-fibers in the frontal, temporal, and parietal lobes were scored separately. Data were analyzed at both the intraobserver and interobserver levels, and scores were compared between groups and tested for interactions with age and DQ.

RESULTS: There were no differences in the timing or extent of myelination in the control and IDD groups at any age in any brain region. In the IDD group, there was no relationship between myelination scores and DQ or developmental domain.

CONCLUSIONS: Our findings did not support the hypothesis that there is a correlation between IDD and the maturity of myelination, including the terminal zones, as seen on conventional brain MR imaging. Neuroimaging evaluation of maturity of subcortical myelination is not a marker of IDD in young children, and the isolated "finding" of delayed myelination should be interpreted with caution.

Myelination of the human brain begins in the prenatal period and proceeds in a series of predictable, well-defined steps. First described in postmortem studies,¹⁻⁴ several groups have also identified changes on brain MR imaging that correlate with progression of myelination.⁵⁻⁷ Both pathologic and imaging studies have shown that subcortical white matter myelination originates at the 1) pericentral gyri, moving toward the poles, and 2) occipital lobes, moving in a posterior-to-anterior direction toward the frontal and temporal lobes. It has been hypothesized that changes in both the composition of myelin and the amount of water present in developing white matter are responsible for the changes in signal intensity on MR imaging.⁸ Because of their relative sensitivities to these factors, T1-weighted images are the most useful in a patient's first 6 months of life, whereas T2-weighted images provide a more detailed picture in patients at older ages.⁵ It has been reported that, with the exception of the peritrigonal area and peripheral subcortical fibers (the so-called terminal zones), the adult pattern of myelination as assessed by T2-weighted

imaging is normally present by 18 months of age.⁹ A more recent study demonstrates that the terminal zones do not complete myelination until the child is closer to 4 years old.²

Several conditions that disrupt normal myelination, such as periventricular leukomalacia, infections, and the leukodystrophies, are associated with significant developmental delays. Brain MR imaging is useful for the identification of morphologic abnormalities in these patients, and studies that include children with identified causes of developmental delay demonstrate concomitant delays in the patterns of myelination.¹⁰⁻¹³ However, no imaging study has evaluated the significance of delayed brain myelination in children with otherwise idiopathic developmental delay (IDD). Subtle findings on MR imaging that specifically involve the timing and extent of myelination are therefore difficult to interpret in the setting of IDD. This is an important issue because the American Academy of Neurology has recently published a practice parameter that calls for neuroimaging in most globally developmentally delayed children¹; it is expected that the number of imaging studies obtained in this patient population will therefore increase significantly.

Our goal was to provide a framework for the analysis of maturity of myelination in young children with IDD. We hypothesized that brain MR imaging scans of these children would show delayed myelination of the subcortical white matter, with specific involvement of the subcortical U-fibers that interconnect cortical gyri and represent a terminal zone of myelination. It was our belief that, because these terminal

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Table 1: Myelination scoring system of Parazzini et al*

Grade	Frontal Lobe		Temporal Lobe			Parietal Lobe	Peritrigonal Area		
	Prerolandic	Polar	Convolution I-II	Lateral	Polar	Postrolandic	Gyri	Posterior	Superior
0	–	–	–	–	–	–	–	–	–
1	+	–	–	+	–	+	–	+	–
2	+	+	–	+	+	+	+	+	+
3	+	+	+						

* The scoring system is binary (0, not myelinated; 1, myelinated).

zones of myelination are the last areas to myelinate in normal brains, they would be the most sensitive to delays in the acquisition of the normal pattern.

Methods

Subjects

The Institutional Review Boards at Baylor College of Medicine and Texas Children's Hospital in Houston, Texas, approved the study. A total of 93 children (31 controls, 62 with IDD) between 17 and 46 months old who had brain MR imaging between November 2000 and November 2003 were included in the study. Subjects were assigned to the control group only if they had documented normal development; these children received brain MR imaging for a variety of reasons. These included nonsyndromic hearing loss,¹³ idiopathic febrile seizures,⁸ macrocephaly,² spasms nutans,² and 1 each of the following: breath-holding, headache, myofibroma, nystagmus, and precocious puberty. All children with nonsyndromic sensorineural hearing loss included in the control group had neuropsychologic testing scores that were in the average to superior range for developmental milestones other than verbal expressive and receptive language. IDD was defined as a delay in development without a known identifiable cause (perinatal insult, infection, genetic disorder, metabolic disease, etc). Not all subjects had formal psychometric evaluations. For those who did not, an experienced clinician performed a developmental evaluation and generated a developmental age for different domains of development. The clinician was unaware of the MR imaging evaluations. We calculated a developmental quotient by dividing the developmental age by the chronologic age. Laboratory testing included chromosomal analysis (with or without subtelomeric probes), DNA analysis of the MeCP2 gene, fragile X syndrome, serum lactate, serum ammonia, serum amino acids, urine organic acids, serum lead levels, and thyroid function tests. All patients in the IDD group did not have an identifiable cause for their developmental delay as of December 2004, regardless of when their brain imaging was done. Children with diseases that primarily affect white matter or overt intracranial lesions or malformations, or both, were excluded.

Imaging and Scoring of Maturity of Myelination

We obtained brain MR imaging scans on an Intera 1.5T scanner (Philips Medical Systems, Best, the Netherlands) by using a quadrature head coil. All study subjects had axial T2-weighted images (TR, 4000–5000 ms; TE, 100 ms) of 5-mm thickness with 6-mm spacing. The field of view was 22–24 cm, with an echo-train length of 14–16.

Three board-certified pediatric neuroradiologists (J.V.H., J.Y.J., M.C.M.) used a previously published scoring system² (Table 1) to assess the maturity of subcortical white matter myelination in 4 separate brain regions (frontal, parietal, temporal, and peritrigonal). The presence of subcortical U-fiber myelination in each of these areas was scored separately with use of a binary scoring system (0, not myelin-

ated; 1, myelinated) developed at Baylor. The raters were blinded to the clinical diagnoses, clinical MR imaging readings, and group assignments of the subjects. All studies were rated independently, and the raters did not discuss their findings with each other. Additional imaging abnormalities, if present, were also noted.

We did not use T1-weighted images in our study because T1 milestones are usually completed in children up to 8 months, and the age range for the children was 17 to 46 months. Furthermore, our study was initiated because, in our experience, so-called abnormal T2 signal intensity in the subcortical regions is frequently reported in children with developmental delay. We wished to test the validity of this when evaluating MR studies that use routine clinical protocols. At the time of our study, T1 with magnetization transfer was not part of our standard protocol.

Statistical Analysis

Group sizes were selected to provide a power of 0.80 to detect a 10% difference in myelination scores between the control and IDD groups. We used SPSS version 11.0.3 (SPSS, Chicago, Ill) for all statistical analyses except as noted below. The Fisher exact test was used to determine if sex composition varied between groups. We compared intrarater group scores (control vs IDD) for each region using χ^2 tests (Excel 2000; Microsoft, Redmond, Wash). For each study subject, we calculated the median and mean scores for the 3 raters in each brain region, and we repeated group comparisons using the Mann-Whitney and *t* tests, respectively. We used univariate analysis of covariance to analyze the effect of age on intragroup differences. Regression methods were used to determine the relationship between DQ and myelination scores in the IDD group, and multiple regression analysis was used to evaluate the interaction between DQ, domain of delay, age and sex, and myelination scores. Finally, we assessed interrater variability by calculation of the kappa statistic (Stata 8.2; StataCorp, College Station, Tex).

Results

There were no significant differences in age (mean, 30 months in both groups; $P = .989$) or sex distribution (32% male in control and 52% male in IDD groups, $P = .08$) between the control and IDD groups. Incidental findings in our 31 controls included cerebellar tonsillar ectopia in 2, mild cerebral volume loss in 2, and a pituitary cyst in 1. In the research subjects, incidental findings were mild volume losses in 7; cerebellar tonsillar ectopia in 4; a small arachnoid cyst in 2; pituitary cysts in 2; and 1 of the following: a small venous anomaly; a choroid plexus cyst; and a cavum septum pellucidum.

As expected, myelination scores increased with age (moved toward more mature values) in each of the areas examined in both groups ($P < .001$ for all regions). However, no differences were found in the degree of subcortical myelination between

Table 2: Control vs IDD comparisons by region*

Brain Region	Control vs IDD Mann-Whitney	Control vs IDD <i>t</i> test	Univariate Age Analysis	DQ Language	DQ Language Age Control	DQ Motor	DQ Motor Age Control
Frontal	0.714	0.801	0.847	0.788	0.901	0.562	0.949
Temporal	0.796	0.778	0.477	0.316	0.185	0.056	0.095
Parietal	0.788	0.785	0.956	0.852	0.980	0.509	0.869
Peritrigonal	0.846	0.750	0.883	0.086	0.059	0.197	0.295
FUF	0.940	0.942	0.255	0.317	0.315	0.575	0.187
TUF	0.867	0.850	0.858	0.846	0.746	0.532	0.751
PUF	0.731	0.739	0.992	0.744	0.841	0.276	0.481

Note:—IDD indicates idiopathic developmental delay; DQ, developmental quotient; FUF, frontal U-fibers; PUF, parietal U-fibers; TUF, temporal U-fibers.
* Numbers in the table are *P* values corresponding to the indicated tests comparing control and IDD groups by brain region.

Table 3: Interobserver comparison

Brain Region	Kappa	Agreement Rating*
Frontal	0.268	Fair
Temporal	0.144	Slight
Parietal	0.339	Fair
Peritrigonal	−0.047	Poor
FUF	0.313	Fair
TUF	0.343	Fair
PUF	0.300	Fair

Note:—FUF indicates frontal U-fibers; PUF, parietal U-fibers; TUF, temporal U-fibers.
* <0 indicates poor; 0–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.0, almost perfect. Adapted from Landis and Koch.¹⁷

the control and IDD groups in any of the regions (Table 2). Moreover, univariate analysis of covariance demonstrated that age did not affect this finding (Table 2).

Although no overall differences were found in the extent or timing of myelination between the control and IDD groups, it remained a possibility that the more severely affected children in the IDD group, or those with delays in a particular domain (language or motor), showed a delayed pattern of myelination. Developmental quotients (DQs) were calculated for language and motor performance; average scores were $DQ_{\text{lang}} = 0.45$ (range, 0.1–1.0) and $DQ_{\text{motor}} = 0.67$ (range, 0.1–1.0). No correlation was found between DQ and myelination scores regardless of chronologic age (Table 2). To determine if there was a relationship between the domain of delay (global, language, or motor) and myelination, the 62 children with IDD were classified into groups on the basis of the domain of delay. No correlation was found between domain classification and degree of myelination.

Finally, we wanted to evaluate the degree of variability between raters in a “real-world” context, so raters were blinded to each other’s readings. The 3 raters scored each region of each study subject separately, and these scores were compared. Interrater variability fell predominantly in the “fair” range (kappa, −0.05–0.34) (Table 3). Individual raters were internally consistent; for example, raters who tended to score myelination as “less mature” did so in all regions (data not shown), and a correlation between IDD and the degree of myelination was not found by any of the individual raters.

Discussion

Our results do not support the assertion that IDD in young children is associated with isolated delays in subcortical myelination as assessed by conventional T2-weighted MR imaging. This result is surprising, given that several previous studies have identified delays in myelination throughout the brain in children with developmental delays.^{10–14} However, those study populations con-

sisted mostly of children with an underlying cause of their psychomotor retardation (perinatal asphyxia, congenital infection, epileptic encephalopathy, metabolic disease, etc). In a study that categorized children by clinical presentation and delay features, only 1 of 58 patients without neurologic findings on examination had delayed myelination on MR imaging,¹⁴ a result that is consistent with our findings. Our study suggests that factors other than delays in myelination are related to clinically diagnosed developmental delay. Such factors may include disruptions of synaptic function or intracellular signaling.¹⁵ In a study by Pujol et al,¹⁶ children with developmental delay were found to have a decreased volume of myelinated white matter on volumetric MR imaging but were reported to have normal conventional MR imaging. However, their study is not strictly comparable with ours. The mean age of their patients (4.4 years) was much higher than ours (30 months). Furthermore, many of their study groups had a specific cause that might be expected to be associated with decreased volume of white matter, such as perinatal insult and genetic disease. We did not include such patients. In addition, their report of a reduction in myelinated white matter was not a feature that characterized children individually and, as the authors stated, only concerned developmentally delayed children studied as a group, with a marked dispersion of measurement and no relationship to severity of delay.

Our study provides the first dedicated MR imaging analysis of myelination of subcortical U-fibers in the early childhood age group. Subcortical U-fibers form connections between adjacent gyri in the cerebral cortex and, as such, mediate communication both to and from cortical association areas. Myelination of these fibers was not complete by 46 months of age in most children in either the control or IDD groups, and no differences in the acquisition of this pattern were found between the groups. The failure of complete myelination by the end of our study period correlates with the continued development of association areas throughout the first 2 decades of life and beyond.

All the children in the IDD group showed a significant level of psychomotor retardation, with average developmental quotients of $DQ_{\text{lang}} = 0.45$ and $DQ_{\text{motor}} = 0.67$. The use of DQ as an assessment of delay allows comparison across ages because the score is normalized for age. The degree of developmental delay did not correlate with the extent of myelination. These results suggest that IDD, regardless of its severity, is not associated with isolated delays of myelination.

A number of imaging abnormalities other than delays in myelination are associated with developmental delay. In our study population, the MR imaging of 2 (6%) of 31 of the control subjects and 7 (11%) of 62 of the children with IDD dem-

onstrated reported atrophy and volume loss. In a previous study of mentally retarded children,¹⁴ 9 (12%) of 76 were found to have brain atrophy diagnosed on neuroimaging; this number closely approximates our findings in the IDD group. In our study, all of the children in the control group had normal neurologic examinations and normal development, and the mean DQs for the children with IDD and atrophy (language, 0.43; motor, 0.65) did not differ from the IDD group average (language, 0.45; motor, 0.67). These findings suggest that the children were no more impaired than their cohorts. As shown in Table 3, several other incidental findings on MR imaging were present in our study subjects; none of these has been associated with developmental delays.

The low number of children with normal development between 1 and 4 years old who received brain MR imaging made identification of subjects for the control group difficult. Conscious sedation, which is a necessary component of imaging studies in this age group, carries small but measurable inherent risks that preclude recruitment of children for MR imaging with no potential clinical benefit. Therefore, we were limited in the selection of appropriate subjects for the control group. A large proportion of the group (13/31, 42%) was composed of children with nonsyndromic sensorineural hearing loss. We believe this is appropriate because these children did not have developmental delays outside of spoken language, and these patients routinely received brain MR imaging and neuropsychologic testing as part of their evaluation for cochlear implants.

We used a previously published myelination scoring system² developed for the assessment of axial T2-weighted brain MR imaging from children of a similar age range as those of our study patients. Our results followed the same trends seen in that study because the parietal lobe showed the most mature pattern of myelination, whereas the temporal lobe was the last to myelinate. However, Parazzini et al² reported that myelination was essentially complete in all examined areas, including the peritrigonal area, by 40 months of age. In our analysis, only the parietal region demonstrated complete myelination by 46 months of age. In addition, the peritrigonal area showed the least mature pattern of myelination in our study, which was consistent with previously published data demonstrating that this region is often not fully myelinated until the fourth decade of life.⁹

There are several possible explanations for these discrepancies. First, variations in the imaging protocols and the scanners themselves could produce different results. For example, we routinely used longer relaxation times on our T2-weighted sequences (TR, 4000–5000 ms) than Parazzini et al² reported in their study (TR, 2200–5200 ms, depending on spin-echo or turbo spin-echo sequence). Second, it is possible that differences in the study populations are responsible for the different findings. Finally, differences in how the readers in the 2 studies scored the extent of myelination may be responsible. Because there were no differences in the myelination scores between our control and IDD groups, combining these 2 groups made our study the largest (93 children) in this age range. We propose that only the parietal region attains the adult pattern of myelination by 46 months of age, and that incomplete myelination before this time in other subcortical regions is within the range of normal development.

Our neuroradiologists were blinded to the readings of their colleagues to get a sense of the general benefits of a myelination rating scale in a routine clinical setting. The interrater variability¹⁷ seen in this study highlights the challenges of this task. At best, a fair agreement (kappa, 0.21–0.40) between the raters was obtained. It is noteworthy that individual raters were internally consistent, and the lack of difference between the control and IDD groups was present at the individual and pooled rater levels. Numeric scoring scales such as the one used here may suffer from the limitation of universal applicability unless multicenter standardization is implemented, which is often difficult.

In conclusion, we agree that MR imaging is an essential part of the evaluation of children with developmental delay, because several genetic and acquired disorders are clearly associated with abnormalities on neuroimaging. However, these disorders do not have subtle findings on imaging and are usually accompanied by characteristic clinical findings in addition to the delayed acquisition of developmental milestones. We caution against the identification of delayed myelination as an etiologic factor in the pathophysiology of IDD.

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