

Vanishing MS T2-bright lesions before puberty

A distinct MRI phenotype?

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ABSTRACT

Background: Multiple sclerosis (MS) onset before puberty may have a distinct clinical presentation. Pediatric patients with MS may less often meet MRI diagnostic criteria for adults. Whether initial MRI presentation is distinct in prepubertal patients is unknown.

Methods: We queried the UCSF MS database for pediatric patients with MS (onset ≤ 18 years) who underwent brain MRI within 3 months of initial symptoms. The overall number of lesions and the number of well-defined and ovoid, large, confluent, and gadolinium-enhancing lesions were compared between patients with earlier-onset (EOPMS) (< 11 years) and later-onset (LOPMS) (≥ 11 years) pediatric MS. The next available brain MRI scan was used to evaluate lesion resolution.

Results: Thirteen children with EOPMS (median age 8.90 years, range [3.58–10.98], 38% girls) and 18 with LOPMS (median age 14.47 years, range [11.78–18.00], 61% girls) were identified. While the overall number of T2-bright lesions was similar in the two groups, patients with EOPMS had fewer well-defined ovoid T2-bright lesions (median = 7, range [0–29] vs 21.5, [4–100]; $p = 0.004$) and more often had confluent lesions (31% of patients vs 0%; $p = 0.02$) on their first MRI compared with patients with LOPMS. Ninety-two percent of patients with EOPMS had a reduction in the number of T2-bright lesions on the second scan compared to 29% of patients with LOPMS ($p = 0.002$).

Conclusions: The distinct prepubertal multiple sclerosis (MS) MRI phenotype suggests that underlying biologic processes may differ in earlier-onset pediatric MS compared to later-onset pediatric MS. These findings may delay diagnosis in that age range. MRI criteria for MS diagnosis may need to be revised before puberty. *Neurology*® 2008;71:1090–1093

GLOSSARY

ADEM = acute disseminated encephalomyelitis; **CIS** = clinically isolated syndrome; **EOPMS** = earlier-onset pediatric MS; **LOPMS** = later-onset pediatric MS; **MS** = multiple sclerosis.

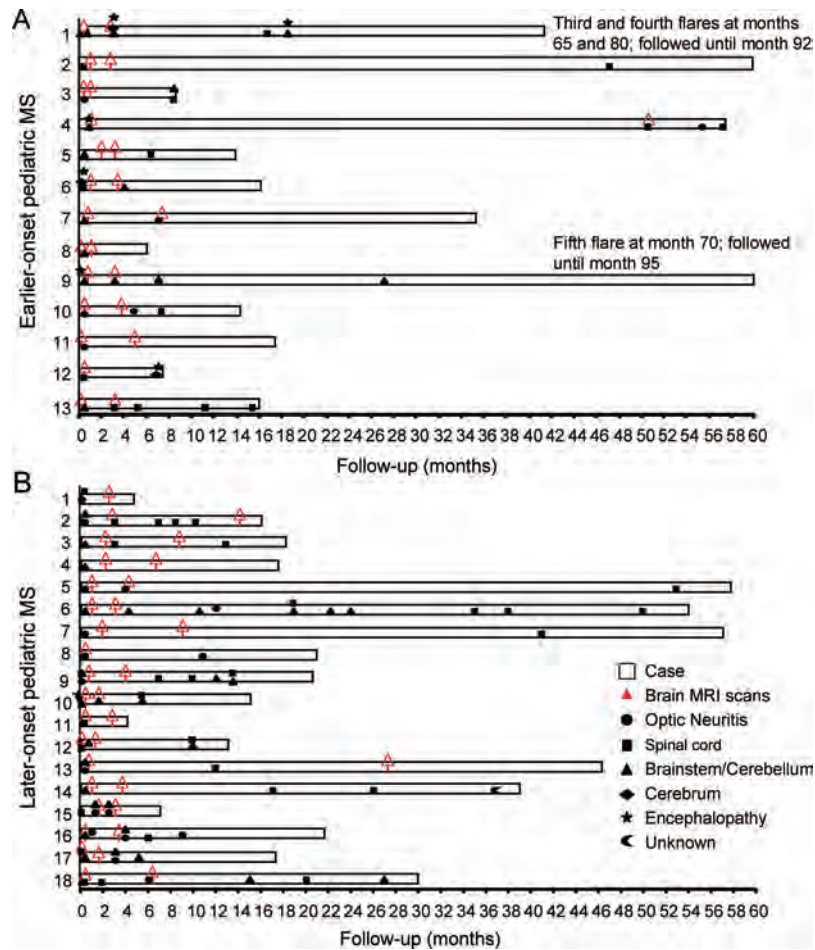
Multiple sclerosis (MS) onset before puberty is rare, likely occurring in 0.2–0.6% of all MS cases. It is more challenging to diagnose pediatric MS at the initial presentation, partly because the differential diagnosis is broader and the clinical presentation more variable than in adults.^{1,2} Children with MS onset before puberty may have an even more distinct presentation; some have encephalopathy (Chabas et al., submitted), and a higher proportion of patients are boys. Furthermore, pediatric patients do not always meet the MRI criteria developed for adult-onset MS.³ For example, the MRIs of pediatric patients with MS often have a lower overall number of, but more tumefactive, T2-bright lesions.^{4,5} Possible explanations include a more recent biologic onset of the disease, immaturity of the immune system, incomplete myelination, or a different capacity of children to remyelinate and repair. In order to improve our understanding of MRI findings in pediatric MS, we compared initial brain MRI features in children with MS

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Figure 1 Patients' disease course and MRI timing



This figure represents symptoms at multiple sclerosis (MS) onset and for each additional exacerbation in earlier-onset (age <11 years) (A) and later-onset (age ≥ 11 years) (B) pediatric patients with MS. The timing of the two first brain MRI scans is provided with respect to clinical exacerbations. All patients met criteria for pediatric CIS (patient 11 in the earlier-onset pediatric MS group, and patients 1, 4, and 11 in the later-onset pediatric MS group) or pediatric relapsing remitting MS.⁶ Some patients had additional MRI scans that were not used for the analysis but were used to confirm the diagnosis of relapsing remitting MS when needed; these MRIs are not reported in the figure.

onset before the age of 11 (earlier onset pediatric MS [EOPMS]) vs those with onset between the ages of 11 and 18 (later onset pediatric MS [LOPMS]).

METHODS We queried the UCSF Pediatric MS database for patients diagnosed with MS or clinically isolated syndrome (CIS) according to recently published operational definitions⁶ with disease onset before 19 years. The initial brain MRI scans were obtained within 3 months of symptom onset. We used the first subsequent available brain MRI scan to evaluate lesion resolution. MRI scans were performed in various facilities but stored on a UCSF computerized system. All patients had axial or coronal T2-FLAIR images available for review. Initial and second brain MRI scans were blindly reviewed (O.A.G.). The overall number of lesions (defined as foci ≥ 3 mm of increased signal on the T2-FLAIR images), the number of well-defined ovoid and large (≥ 1 cm) lesions, and the number of gadolinium-enhancing lesions at presentation were compared between the two age groups (EOPMS and LOPMS). Areas of confluent T2-FLAIR hyperintensity, defined as involving the white matter of greater than two adjacent gyri, were also compared. Lesion reduc-

tion (defined as any decrease in the number of T2-bright areas) and resolution (defined as $\geq 50\%$ decrease in the number of T2-bright areas) between the first and second MRI scans were evaluated.

RESULTS Patient characteristics at onset. We identified 13 children with EOPMS or CIS (median age 8.90 years, range [3.58–10.98], 38% girls) and 18 with LOPMS or CIS (median age 14.47 years, range [11.78–18.00], 61% girls) for whom initial brain scans were available. Clinical course and MRI timing are presented in figure 1. Monoregional presentation occurred in 85% of EOPMS ($n = 11$) vs 61% of LOPMS ($n = 11$) patients (Fisher exact test $p = 0.24$). Including mono- and polyregional onset, the locations of clinical presentations were similar in the EOPMS and LOPMS groups (optic neuritis 23% vs 44%, $p = 0.28$; brainstem/cerebellar involvement 54% vs 61%, $p = 0.73$; and spinal cord involvement 23% vs 33%, $p = 0.70$). Although encephalopathic

Table MRI findings	First MRI		p Value	Second MRI		
	<11 y, n = 13	≥11 y, n = 18		<11 y, n = 12	≥11 y, n = 17	p Value
	No. of T2-bright lesions, median (range)	21 (4-55)		21.5 (4-100)	0.59	13 (1-40)
No. of well-defined, ovoid T2-bright lesions, median (range)	7 (0-29)	21.5 (4-100)	0.004	6 (0-16)	26 (4-100)	0.0004
No. of large T2-bright lesions (>1 cm), median (range)	8 (0-22)	2.5 (0-26)	0.23	3.5 (0-17)	2 (0-21)	0.24
No. of enhancing lesions, median (range)	1.5 (0-22)	7 (0-66)	0.16	0 (0-17)	1 (0-13)	0.85
Change in no. of T2-bright lesions on second scan (%)	NA	NA	NA	-41.3	16.3	0.0004
% Patients with confluent T2-bright lesions (no.)	31 (4)	0 (0)	0.02	16 (2)	0 (0)	0.16
% Patients with subcortical T2-bright lesions (no.)	92 (12)	83 (15)	0.62	75 (9)	88 (15)	0.62
% Patients with deep gray matter T2-bright lesions (no.)	54 (7)	22 (4)	0.13	58 (7)	29 (5)	0.15
% Patients with brainstem T2-bright lesions (no.)	62 (8)	61 (11)	1	58 (7)	59 (10)	1
% Patients with cerebellar T2-bright lesions (no.)	46 (6)	44 (8)	1	25 (3)	53 (9)	0.25
% Patients with reduction in the no. of T2-bright lesions (no.)	NA	NA	NA	92 (11)	29 (5)	0.002
% Patients with more than 50% reduction in the no. of T2-bright lesions (no.)	NA	NA	NA	33 (4)	5.9 (1)	0.13

MRI characteristics of initial and repeat brain scans are provided for earlier-onset (age <11 years) and later-onset (age ≥11 years) patients with pediatric multiple sclerosis.

changes occurred only in 23.1% of the EOPMS vs 5.6% of the LOPMS group ($p = 0.28$), 69% of patients with EOPMS were initially misdiagnosed with acute disseminated encephalomyelitis (ADEM) (vs 17% of patients with LOPMS, Fisher exact test $p = 0.0075$).

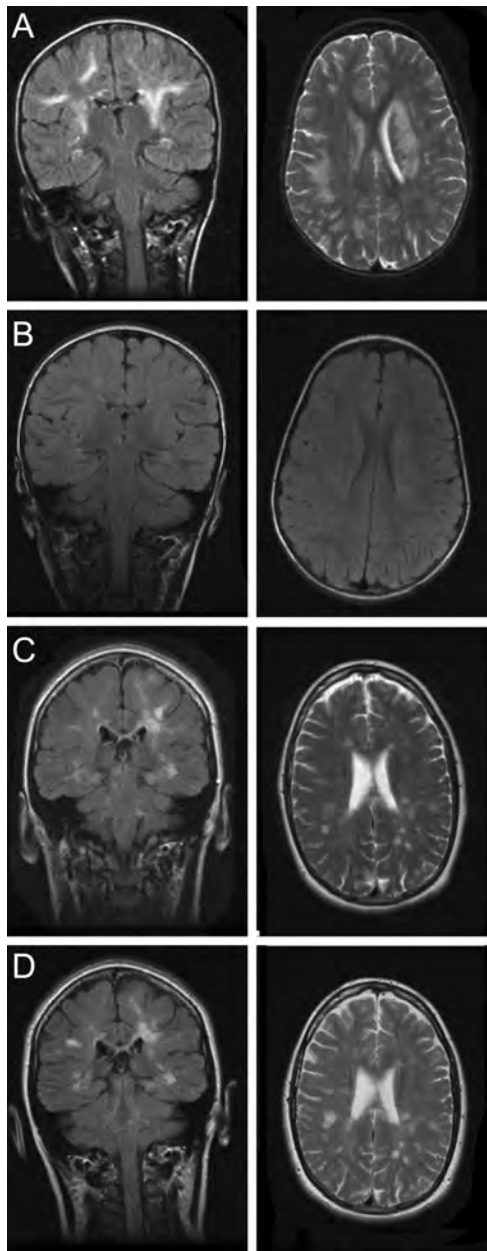
Initial brain MRI scan. The MRI findings of the first scans are summarized in the table. Time between symptom onset and first MRI scan was similar in both groups (median = 8 days [range, 0–64] vs 15 days [range, 0–68], Wilcoxon rank sum test, $p = 0.69$). Patients with EOPMS had fewer well-defined, ovoid T2-bright lesions and more often had confluent lesions on their first MRI than those with LOPMS (table). Younger patients tended to have fewer enhancing lesions and more deep gray matter involvement compared to older patients. The number of T2-bright or large T2-bright lesions and the proportion of patients with subcortical, brainstem, or cerebellar involvement did not differ between the two groups. We repeated the statistical analysis excluding the four patients who had encephalopathic changes during their first exacerbation; results were similar (not shown).

Follow-up MRI scan. The MRI findings of the second scans are summarized in the table. Median time be-

tween first and second scans was 111 days (range, 25–1,530) in the EOPMS vs 107 days (range, 34–814) in the LOPMS patients (Wilcoxon rank sum test, $p = 0.96$). Second scans were available in 12 of the EOPMS and 17 of the LOPMS patients. Significant differences were reported for both overall and well-defined T2-bright lesions. Ninety-two percent of younger patients had a reduction in the number of T2-bright lesions on the second scan compared to 29% of older patients (Fisher exact test $p = 0.002$). A greater than 50% reduction tended to be more frequent in the younger group. Excluding patients with encephalopathic changes at onset did not substantially change the findings (not shown). Two examples of typical scans for EOPMS and LOPMS are provided in figure 2.

DISCUSSION Although initial clinical characteristics were fairly similar in EOPMS vs LOPMS patients, several brain MRI features were strikingly different. In particular, initial T2-bright lesions in very young patients were less well-defined. Furthermore, a significant number of these lesions vanished on follow-up imaging, suggesting that demyelinating lesions may be different in younger children. Additional differences, although only found as trends in

Figure 2 Examples of MRI findings in a very young patient and in an adolescent patient



The brain MRI scan of a 4-year-old patient (A,B, patient 10) shows the absence of well-defined, ovoid T2-bright areas (A: first scan, coronal FLAIR and axial T2-weighted sequences). The repeat scan shows a dramatic decrease of T2-bright areas (B: second scan, coronal FLAIR and axial FLAIR sequences). The same type of images obtained in a 13-year-old patient (C,D, patient 4) show typical ovoid T2-bright areas suggestive of MS (C: first scan, coronal FLAIR and axial T2-weighted sequences). The repeat scan in this adolescent does not show any significant decrease in the number of T2-bright areas (D: second scan, coronal FLAIR and axial T2-weighted sequences).

this small cohort, include a higher rate of deep gray matter involvement and less enhancement in young patients. It is our impression that MRI features in adolescents are similar to those reported in adults.

There are no published pathologic data regarding MS lesions in very young patients, so the extent to which MS pathology differs in that age category is unclear. Rather than representing demyelination, less well-defined brain MRI abnormalities that vanish over time in very early-onset MS may actually represent nonspecific reactive edema, a distinct microglial activation pattern, less axonal loss, or an enhanced ability to remyelinate compared to adults.

The majority of EOPMS patients (69%) were misdiagnosed with ADEM at onset before being referred to the UCSF Regional Pediatric MS Center. These patients did not meet the recently published criteria for ADEM⁶; we presume that the diagnoses were given based on the presence of encephalopathy in a minority of the patients (23% of the patients), the young age at onset, or the extensiveness and vanishing nature of the T2-bright lesions on the initial MRI scans. All EOPMS patients eventually met the diagnostic criteria for pediatric MS or CIS according to the International Study Group definitions.⁶ Thus, although our study is limited by its small sample size and the lack of a uniform MRI protocol, it is likely that the distinct MRI phenotype we report in the EOPMS group considerably contributes to the misdiagnosis of the majority of younger patients. MRI criteria for the diagnosis of MS may need to be revised in prepubertal children to account for the poorly defined T2-bright lesions in that age category. Further studies should be performed prospectively with a uniform MRI protocol and analytic method to confirm our findings. Finally, nonconventional imaging techniques may enhance our understanding of disease processes at play.

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REFERENCES

1. Ruggieri M, Polizzi A, Pavone L, et al. Multiple sclerosis in children under 6 years of age. *Neurology* 1999;53:478–484.
2. Mikaeloff Y, Husson Adamsbaum C, et al. MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. *Brain* 2004;127:1942–1947.
3. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria.” *Ann Neurol* 2005;58:840–846.
4. Hahn CD, Shroff M, Blaser S, et al. MRI criteria for multiple sclerosis. Evaluation in a pediatric cohort. *Neurology* 2004;62:806–808.
5. Balássy C, Bernert G, Wöber-Bingöl C, et al. Long-term MRI observations of childhood-onset relapsing-remitting multiple sclerosis. *Neuropediatrics* 2001;Feb 32:28–37.
6. Krupp LB, Banwell B, Tenenbaum S, et al. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology* 2007;68 suppl 2:S7–S12.