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Neurology 2011;76;910
DOI 10.1212/WNL.0b013e31820f2e69

Cortical lesions in children with multiple sclerosis

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ABSTRACT

Objective: Double inversion recovery (DIR) sequences have improved the detection of cortical lesions (CLs) in adult patients with multiple sclerosis (MS). We evaluated the presence and frequency of CLs in pediatric patients with relapsing-remitting MS (RRMS) in comparison to adult patients with MS with the same clinical phenotype.

Methods: Using a 3.0-T scanner, brain DIR, dual-echo, and 3-dimensional T1-weighted scans were acquired from 24 pediatric patients with RRMS, 15 adult patients with RRMS, and 10 pediatric healthy controls. CLs and white matter (WM) lesions were identified, and their volumes measured. Brain gray matter and WM volumes were also calculated. Between-group comparisons were performed using χ^2, Mann-Whitney, and analysis of variance tests. Poisson regressions for count data were used to model the number of lesions of the 2 groups of patients.

Results: Compared to adults, pediatric patients had shorter disease duration and lower disability. WM lesion number and volume did not differ between pediatric and adult patients with MS. CLs were detected in 2 (8%) pediatric and 10 (66%) adult patients. Median CL volume was lower in pediatric than adult patients with RRMS ($p = 0.0003$). Regression analysis showed that pediatric patients had a lower number of CLs than adults ($p = 0.0003$), after adjusting for age, gender, Expanded Disability Status Scale score, and disease duration.

Conclusion: CLs are rare in pediatric patients with MS. Since pediatric patients with MS have a clinical onset closer to the biological onset of the disease than adult patients with MS, our findings indicate that CL formation is likely not to be an initial event in this disease. ***Neurology*® 2011;76: 910–913**

GLOSSARY

CL = cortical lesion; **DE** = dual-echo; **DIR** = double inversion recovery; **ETL** = echo train length; **FA** = flip angle; **FOV** = field of view; **GM** = gray matter; **GMV** = gray matter volume; **LV** = lesion volume; **MS** = multiple sclerosis; **NBV** = normalized brain volume; **RRMS** = relapsing-remitting multiple sclerosis; **TE** = echo time; **TI** = inversion time; **TR** = repetition time; **TSE** = turbo spin-echo; **WM** = white matter; **WMV** = white matter volume.

Although multiple sclerosis (MS) is typically considered a disease of young adults, up to 10% of patients experience their first attack during childhood, and the median time to reach fixed neurologic disability is shorter in patients with adult-onset than in those with pediatric MS.[1]

The use of MRI has contributed to clarify the factors associated with the favorable short- to medium-term clinical evolution of pediatric MS. In this context, one of the main findings was the demonstration that pediatric patients with MS have a relative sparing of the brain gray matter (GM).[2,3]

An aspect that has not been investigated so far in patients with pediatric MS is the presence and extent of focal lesion within the cortex. Pathologic studies have demonstrated that such lesions are frequently seen in adult patients with MS[4] and that they can be classified as mixed WM–GM lesions (type I), or purely intracortical lesions (types II, III, and IV).[5] Recently, double inversion recovery (DIR) sequences have markedly improved our ability to detect in vivo cortical lesions (CLs) in patients with MS.[4]

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Disclosure: Author disclosures are provided at the end of the article.

Table 1 Main demographic and clinical characteristics of the 3 groups of subjects studied

	Pediatric healthy controls	Pediatric patients with RRMS[a]	Adult patients with RRMS
No. of subjects	10	24	15
F/M	6/4	15/9	10/5
Median age, y (range)	14.1 (9–18)	15.5 (7–18)	33.3 (20–51)
Median EDSS score (range)	—	1.5 (0–3)	1.5 (1.0–4.5)
Median disease duration, y (range)	—	2.0 (1–8)	4.0 (2–6)
Therapy: none/IFNβ1a/glatiramer acetate/mitoxantrone	—	5/15/4/0	2/7/5/1

Abbreviations: EDSS = Expanded Disability Status Scale; IFNβ1a = interferon-β 1a; RRMS = relapsing-remitting multiple sclerosis.
[a] Note that the characteristics of these patients are similar to those reported in previous cohorts of pediatric patients.[2,3]

Against this background, we wished to use a DIR sequence to assess the presence, frequency, and type of CLs in pediatric patients with relapsing-remitting MS (RRMS). To test the hypothesis that GM involvement in pediatric patients with MS is less pronounced than that seen in patients with an adult onset of the disease, we compared the results obtained in pediatric patients with those of adult patients with RRMS with similar disease clinical phenotype.

METHODS

Patients. From February 2008 to April 2010, we recruited consecutively 24 patients with pediatric RRMS[6] among the patients attending to the neurologic departments of the participating institutes. Fifteen adult patients with RRMS and 10 healthy pediatric controls were selected among the population of patients with MS and controls enrolled for research studies during the last 2 years at our unit to match as close as possible the demographic and clinical characteristics of pediatric patients with MS (table 1). All patients were relapse-free and steroid-free for at least 3 months.

Standard protocol approvals and patient consents. Approval was received from the local ethical standards committee on human experimentation and written informed consent was obtained from all children's parents and adult patients participating in the study.

MRI acquisition. Using a 3.0-T scanner (Intera Philips Medical Systems), the following sequences were collected: 1) DIR (repetition time [TR]/echo time [TE] = 18,000/125 msec; inversion time [TI] = 3,000 msec; delay = 100 msec; echo train length [ETL] = 27; matrix = 256 × 256; field of view [FOV] = 240 × 240 mm^2; 44 axial 3-mm-thick slices); 2) dual-echo (DE) turbo spin-echo (TSE) (TR/TE = 2,599/16–80 msec; ETL = 6; flip angle [FA] = 90°; matrix = 256 × 256; FOV = 240 × 240 mm^2; 44 axial 3-mm-thick slices); and 3) 3-dimensional T1-weighted fast field echo (TR/TE = 25/4.6 msec; flip angle = 30°; matrix = 256 × 256; FOV = 230 × 230 mm^2; 220 axial slices; voxel size = 1 × 1 × 1 mm).

MRI analysis. All images were assessed by consensus of 2 experienced observers blinded to subjects' identity. On DIR images, attention was paid to exclude artifacts, and CLs were identified. CLs included 1) lesions confined to the cortical ribbon without involving the underlying subcortical WM (pure intracortical lesions) and 2) mixed WM/GM lesions (type I) with a prominent extension within the GM (around 75% or greater). WM lesions (including those located juxtacortically) were identified on DE images. CL and WM lesion volumes (LV) were measured.[2] Normalized brain volumes (NBV), GM volumes (GMV), and WM volumes (WMV) were measured using SIENAx software.

Statistical analysis. Categorical variables were reported as frequencies (percentages), and between-group comparisons were performed using a χ^2 test. Skewed non-normal distributed continuous variables (i.e., age, disease duration, EDSS, LVs) were reported as medians (ranges), and between-group comparisons were performed using the nonparametric Mann-Whitney *U* test. Normal continuous variables (i.e., NBV, GMV, WMV) were reported as means (SDs), and between-group comparisons were performed using analysis of covariance models adjusting for age. The numbers of lesions were reported as medians and ranges. Poisson regressions for count data were used to model the number of lesions adjusting for age, gender, disease duration, and EDSS. The sample recruited was powered to detect the observed difference in lesion number between pediatric and adult patients with MS with a power ≥0.90 and a type I error = 0.05.[7] A p value <0.05 was considered for statistical significance.

Table 2 Main MRI findings in pediatric controls and pediatric and adult patients with RRMS[a]

	Pediatric healthy controls	Pediatric patients with RRMS	Adult patients with RRMS
Median no. of WM lesions (range)	—	20 (8–123)	42 (6–150)
Median WM LV (range), mL	—	2.4 (0.7–19.6)	3.6 (0.5–43.3)
Median no. of CLs (range)	—	0 (0–1)	1 (0–8)
Median no. of ICLs (range)	—	0 (0–0)	0 (0–4)
Median no. of mixed GM/WM lesions (range)	—	0 (0–1)	1 (0–4)
Median CLs volume (range), mL	—	0 (0–0.04)	0.07 (0–1.0)
NBV (SD), mL	1,762 (66)	1,713 (69)	1,551 (105)
WMV (SD), mL	920 (120)	872 (128)	826 (81)
GMV (SD), mL	841 (92)	841 (120)	724 (111)

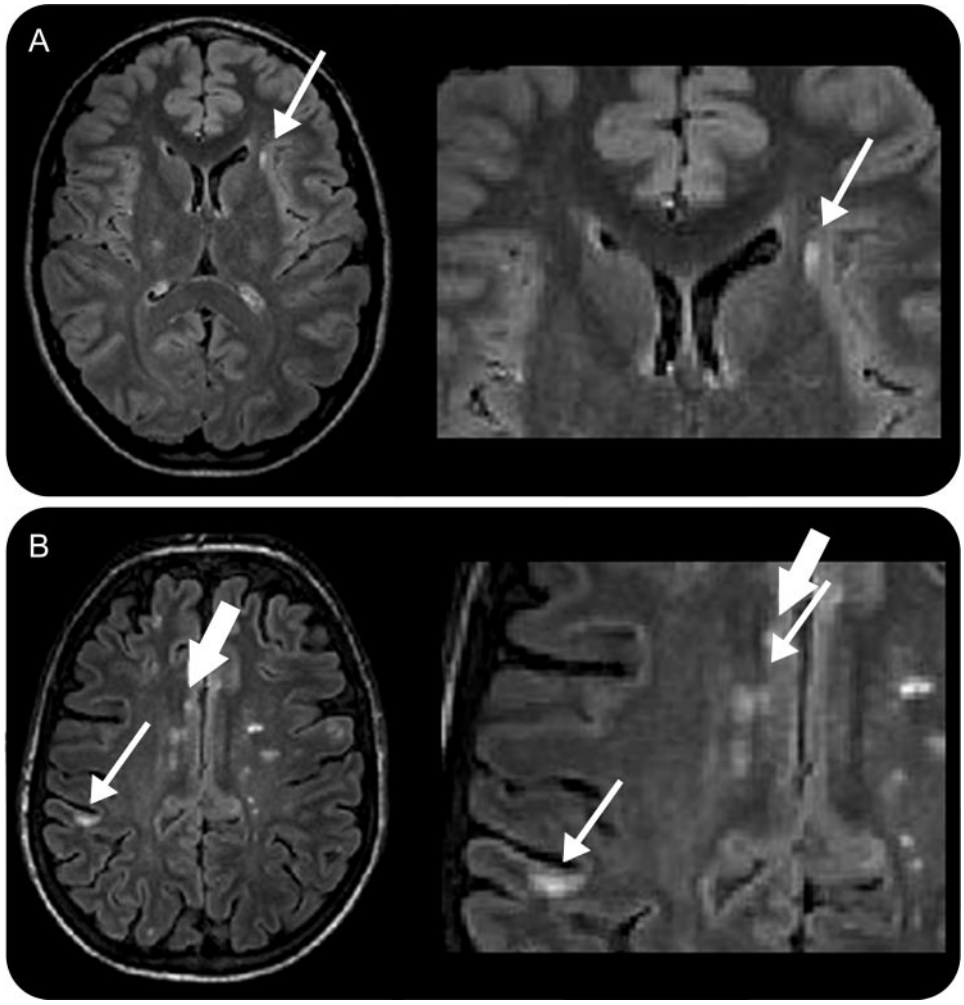
Abbreviations: CL = cortical lesion; GM = gray matter; GMV = gray matter volume; ICL = intracortical lesion; LV = lesion volume; NBV = normalized brain volume; RRMS = relapsing-remitting multiple sclerosis; WM = white matter; WMV = white matter volume.
[a] See the text for statistical analysis.

RESULTS

Compared to adult patients, pediatric patients had shorter disease duration ($p = 0.002$) and lower EDSS score ($p = 0.02$). Table 2 summarizes the MRI findings in pediatric and adult patients with RRMS. Brain WM lesions were detected on DE scans of all pediatric and adult patients with MS. The number and volume of WM lesions did not differ between pediatric and adult patients with RRMS ($p = 0.3$ and $p = 0.5$).

Two CLs were identified in 2 (8%) pediatric and 31 CLs were identified in 10 (66%) adult patients

Figure Illustrative axial slices of double inversion recovery sequence in pediatric (A) and adult (B) patients with relapsing-remitting multiple sclerosis (the second row images are magnified)



Thick arrows identify intracortical lesions; thin arrows indicate mixed gray matter/white matter lesions.

with RRMS (figure). All CLs in pediatric MS and 16 CLs in adult patients were mixed WM/GM lesions. Multivariate Poisson regression analysis showed that pediatric patients with MS had a lower number of CLs than adults ($p = 0.0003$) with an estimated mean number of CLs = 0.08 for each pediatric patient and 1.99 for each adult patient. Median CL volume was lower in pediatric vs adult patients with RRMS ($p = 0.0003$).

NBV, GMV, and WMV did not differ between controls and pediatric patients with MS, as well as between pediatric and adult patients with MS, after adjusting for age.

DISCUSSION By suppressing the signal from both WM and CSF, DIR sequences result in an increased lesion contrast, thus improving the detection of CLs. Compared to pathologic assessment, DIR sequences are likely to detect only 10%–20% of CLs.[4] Nevertheless, their use has allowed demonstration of focal CLs in the majority of adult patients with MS. Although such lesions are more frequent in patients with the progressive phenotypes of the disease, they also have been identified in about 40% of patients at presentation with clinically isolated syndromes suggestive of MS.[4]

The main result of this study is the demonstration that CLs are rare in patients with pediatric MS, since we found that less than 10% of our pediatric population had such lesions, in comparison to a figure of 66% in adult patients with MS. Since, by definition, pediatric patients with MS have a clinical onset much closer to the biological onset of the disease than adult patients with MS, our findings indicate that CL formation is not an early event in the course of the disease. This agrees with pathologic studies showing that CLs are much more frequent in the secondary progressive phase of MS.[4]

Two other factors might contribute to explain the paucity of CLs in pediatric MS, i.e., their immuno-

logic profile, which differs from that of adult patients with MS,[8] and the degree of GM maturation, which might yield to a different susceptibility to MS-related damage. Brain GMV show a prepuberal increase, which is followed by a postpuberal loss, consistent with postmortem observations of an increased synaptic pruning and increasing intracortical myelination during adolescence and early adulthood. Furthermore, postmortem studies have demonstrated a late myelination in several cortical regions, including the frontal and parietal cortices.[9] Remarkably, we showed that all CLs in our pediatric patients with MS were located at the boundary between the WM and the GM, a finding which is consistent with the proliferation of myelin into the peripheral cortical neurophil occurring at the interface between the WM and GM during childhood and adolescence. Clearly, we cannot completely rule out that the sequence we used did not have enough sensitivity to detect abnormalities in pediatric patients with MS. However, this sequence has been recently used in a population of healthy individuals ranging from 5 to 80 years, with comparable results in subjects older than 10 years.[10]

DISCLOSURE

Dr. Absinta reports no disclosures. Dr. Rocca serves as consultant to Bayer Schering Pharma and served on the speakers' bureau for Biogen-Dompé. Dr. Moiola, Dr. Copetti, Dr. Milani, and Dr. Falini report no disclosures. Dr. Comi serves on speakers' bureaus for Teva Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck Serono, Bayer Schering Pharma, Biogen-Dompé, Boehringer Ingelheim, and Novartis; and has received speaker honoraria from Teva Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck Serono, Serono Symposia International Foundation, Bayer Schering Pharma, Novartis, Biogen-Dompé, and Merz Pharmaceuticals GmbH. Dr. Filippi serves on scientific advisory boards for Teva Pharmaceutical Industries Ltd. and Genmab A/S; has received funding for travel from Bayer Schering Pharma, Biogen-Dompé, Genmab A/S, Merck Serono, and Teva Pharmaceutical Industries Ltd.; serves on editorial boards of the *American Journal of Neuroradiology*, *BMC Musculoskeletal Disorders*, *Clinical Neurology and Neurosurgery*, *Erciyes Medical Journal*, *Journal of Neuroimaging*, *Journal of Neurovirology*, *Lancet Neurology, Magnetic Resonance Imaging, Multiple Sclerosis*, and *Neurological Sciences*; serves as a consultant to Bayer Schering Pharma, Biogen-Dompé, Genmab A/S, Merck Serono, Pepgen Corporation, and Teva Pharmaceutical Industries Ltd.; serves on speakers' bureaus for Bayer Schering Pharma, Biogen-Dompé, Genmab A/S, Merck Serono, and Teva Pharmaceutical Industries Ltd.; and receives research support from Bayer Schering Pharma, Biogen-Dompé, Genmab A/S, Merck Serono, Teva Pharmaceutical Industries Ltd., Fondazione Italiana Sclerosi Multipla, and Fondazione Mariani.

Received August 23, 2010. Accepted in final form November 18, 2010.

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