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Short Report

Cognitive impairment in paediatric multiple sclerosis patients is not related to cortical lesions

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Abstract: We investigated the contribution of cortical lesions to cognitive impairment in 41 paediatric MS patients. Thirteen (32%) paediatric MS patients were considered as cognitively impaired. T2-hyperintense and T1-hypointense white matter lesion volumes did not differ between cognitively impaired and cognitively preserved MS patients. Cortical lesions number, cortical lesions volume and grey matter volume did not differ between cognitively impaired and cognitively preserved patients, whereas white matter volume was significantly lower in cognitively impaired versus cognitively preserved MS patients (p=0.01). Contrary to adult MS, cortical lesions do not seem to contribute to cognitive impairment in paediatric MS patients, which is likely driven by white matter damage.

Keywords: Paediatric multiple sclerosis, cortical lesions, grey matter, MRI, double inversion recovery

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Introduction

In adult MS patients, double inversion recovery (DIR) sequences have consistently demonstrated an association between cognitive impairment and the number and volume of cortical lesions[1] as well as a pivotal role of cortical lesions in predicting deterioration of cognitive performance over time.[2]

Cognitive impairment affects a large proportion of paediatric MS patients.[3,4] Studies which have investigated the possible MRI substrates of cognitive deficits in paediatric MS have analysed the contribution of white matter (WM) lesions, atrophy of the WM and/or grey matter (GM) or strategic CNS structures (e.g. the thalamus and corpus callosum)[5] and microstructural damage to the major WM tracts.[4] An aspect that has not been evaluated so far in these patients is the role of cortical lesions in explaining the occurrence of cognitive deficits.

Using DIR, we investigated the contribution of cortical lesions to cognitive impairment in paediatric MS patients. To better characterize the substrates of such an impairment, we also estimated the role of WM lesions as well as that of atrophy of brain WM and GM.

Patients and methods

Subjects

We studied 41 relapsing–remitting (RR) MS paediatric patients relapse- and steroid-free for at least three months and 31 gender- and age-matched healthy controls (Table 1). Within three days from MRI acquisition, all patients underwent a neurological examination with rating of the Expanded Disability Status Scale (EDSS), and a neuropsychological assessment using the Brief Neuropsychological Battery for Children (BNBC), as previously described.[3,4] The fifth or 95th percentile of the corrected scores of the normative data was used as the cut-off for determining failure at a given test. Patients with a failure in ≥2 tests were classified as cognitively impaired.[3,4]

Approval was received from the local ethical standards committee on human experimentation, and

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Table 1. Main demographic, clinical and conventional MRI characteristics of the subjects enrolled in the study.

	Paediatric healthy controls	Paediatric MS patients	*p* value	Paediatric CP MS patients	Paediatric CI MS patients	*p* value
Number of subjects	31	41	–	28	13	–
Girls/boys	19/11	27/14	0.3	21/7	6/7	0.07
Mean age (SD), years	14.9 (3.5)	15.2 (2.5)	1	14.9 (2.3)	15.7 (2.7)	0.2
Median disease duration (range), years	–	1.2 (0.12–8.1)	–	1.05 (0.1–3.1)	3.1 (0.3–8.1)	0.02
Median EDSS score (range)	–	1.0 (0.0–4.0)	–	1.0 (0.0–3.0)	1.0 (0.0–4.0)	0.7
Mean education (SD), years	9.2 (3.7)	8.7 (2.4)	0.5	8.4 (2.3)	9.2 (2.5)	0.2
Therapy: none/interferons/glatiramer acetate/natalizumab/mitoxantrone	–	8/24/4/4/1	–	7/16/3/2/0	1/8/1/2/1	–
Mean T2 LV (SD), ml	–	4.8 (5.6)	–	4.3 (5.7)	6.0 (5.7)	0.2
Mean T1 LV (SD), ml	–	2.9 (3.3)	–	2.5 (2.8)	3.9 (4.2)	0.2
Median number of cortical lesions (range)	–	0 (0–3)	–	0 (0–3)	0 (0–2)	0.9
Mean GM lesion volume (SD), ml	–	0.02 (0.05)	–	0.02 (0.05)	0.01 (0.03)	0.8
Mean NBV (SD), ml	1713 (88)	1646 (79)	0.003	1665 (69)	1608 (87)	0.06
Mean GMV (SD), ml	860 (70)	825 (57)	0.03	832 (57)	811 (58)	0.3
Mean WMV (SD), ml	853 (49)	821 (47)	0.04	832 (46)	805 (47)	0.01

MS: multiple sclerosis; CI: cognitively impaired; CP: cognitively preserved; EDSS: Expanded Disability Status Scale; LV: lesion volume; SD: standard deviation; GM: grey matter; NBV: normalized brain volume; GMV: grey matter volume; WMV: white matter volume

written informed consent was obtained from all subjects' parents.

MRI acquisition and analysis

As previously described,[6] using a 3.0 Tesla scanner, the following sequences were collected: a) DIR; b) dual-echo turbo spin-echo (TSE); and c) 3D T1-weighted fast field echo (FFE).

T2 WM lesions (including those located juxtacortically) were identified on dual-echo images, and T1 hypointense lesions on 3D FFE images, which were previously co-registered to the dual-echo scans. GM and WM hyperintense lesion volumes and WM T1 hypointense lesion volumes were measured using a local thresholding segmentation technique (Jim 5). Normalized brain volumes (NBVs), GM (GMVs) and WM (WMVs) volumes were measured on 3D FFE scans using SIENAx software.

Statistical analysis

Between-group comparisons were performed using the Pearson chi-square test or Fisher exact test for categorical variables, and the nonparametric Mann–Whitney *U* test for continuous variables. The number of cortical lesions was compared using negative binomial regression model (SAS Release 9.3).

Results

GM lesions were found in five (12%) paediatric MS patients. Compared with healthy controls, paediatric MS patients had significantly lower NBV, WMV and GMV (Table 1).

Thirteen (32%) paediatric MS patients were classified as cognitively impaired. Supplementary Table 1 (online) summarizes the performance of paediatric MS patients in individual neuropsychological tests. One patient showed a low IQ (total IQ score <70). The cognitive domains most frequently involved were: spatial and verbal memory, language abilities and attention.

Table 1 summarizes the main demographic, clinical and neuroimaging findings from cognitively preserved and cognitively impaired paediatric MS patients. Compared with cognitively preserved patients, cognitively impaired MS patients had significantly longer disease duration and lower WMV, whilst they did not differ in age, EDSS, education, T2 lesion volume, T1 lesion volume, NBV and GMV. In paediatric MS patients, WMV was significantly correlated with the number of abnormal neuropsychological tests ($r = -0.51$, $p=0.001$).

Cortical lesions were found in three (11%) cognitively preserved and two (15%) cognitively impaired MS patients ($p=0.6$). The number and volume of cortical lesions did not differ between cognitively preserved and cognitively impaired MS patients.

Discussion

This study shows that cortical lesions do not contribute to explaining the occurrence of cognitive impairment in paediatric MS patients. To quantify cortical lesions we used a DIR sequence, which, at present, is the technique with the highest sensitivity in detecting cortical lesions on commonly available MR scanners.[7] Albeit we cannot rule out that our negative results might be due to technical limitations leading to an inability of DIR sequences to visualize the full burden of such lesions (compared with pathological assessment around 18% of cortical lesions are detected with DIR);[8] this would have influenced lesion detection in both patient groups.

We also confirmed, on a larger sample of patients with respect to our previous investigation,[6] that the frequency of cortical lesions in paediatric MS patients is much lower than that reported in adult patients, including those with clinically isolated syndromes[1] or radiologically isolated syndromes,[9] who showed cortical lesions in nearly 40% of the cases.[1,9] Several factors could explain the lower number of cortical lesions in paediatric versus adult MS patients, including a different immunological profile, the level of GM maturation and the closeness to the biological onset of the disease (with consequently less involvement of the GM, as suggested by pathological studies).[10]

Atrophy of the WM was the only MRI measure capable of distinguishing cognitively impaired from cognitively preserved paediatric MS patients. Similarly to previous studies,[3,4] we found that our patients had a prominent involvement of spatial and verbal memory abilities, language, attention and concentration, suggesting that our sample is representative of the more general population of paediatric MS patients. Using a voxel-wise approach to define the contribution of damage to the different brain compartments,[4] we recently found that damage to the WM of the posterior cingulum and corpus callosum is one of the most important substrates of cognitive deficits in paediatric MS,[4] thus supporting the notion that WM involvement is likely to be one of

the main substrates of cognitive impairment in paediatric MS. Other investigators found an association between thalamic atrophy and cognitive impairment in these patients.[5] As a consequence, we cannot exclude that the assessment of regional WM/GM damage might be useful to understand cognitive decline in paediatric MS. Future studies should evaluate the relative contributions of regional versus global damage as well as that of strategic regions, such as the cerebellum, to cognitive deficits in these patients. Longitudinal studies should also define whether the contribution of WM damage to cognitive impairment reflects a deficit of maturation and myelination of CNS structures.

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Conflict of interest

The authors declare no conflict of interest.

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