Extensive White Matter Dysfunction in Cognitively Impaired Patients with Secondary-Progressive Multiple Sclerosis

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ABSTRACT

BACKGROUND AND PURPOSE: Cognitive impairment is a common, disabling symptom of MS. We investigated the association between cognitive impairment and WM dysfunction in secondary-progressive multiple sclerosis using DTI.

MATERIALS AND METHODS: Cognitive performance was assessed with a standard neuropsychological battery, the Minimal Assessment of Cognitive Function in Multiple Sclerosis. Cognitive impairment was defined as scoring >1.5 standard deviations below healthy controls on ≥2 subtests. Fractional anisotropy maps were compared against cognitive status using tract-based spatial statistics with threshold-free cluster enhancement.

RESULTS: Forty-five patients with secondary-progressive multiple sclerosis (median age: 55 years, female/male: 27/18, median Expanded Disability Status Scale Score: 6.5) were prospectively recruited. Cognitively impaired patients (25/45) displayed significantly less normalized global GM and WM volumes ($P_{corr} < .001$, $P_{corr} = .024$), more normalized T2-weighted and T1-weighted WM lesion volumes ($P = .002$, $P = .006$), and lower WM skeleton fractional anisotropy ($P < .001$) than non-impaired patients. Impaired patients also had significantly lower fractional anisotropy ($P_{corr} < .05$) in over 50% of voxels within every major WM tract. The most extensively impinged tracts were the left posterior thalamic radiation (100.0%), corpus callosum (97.8%), and right sagittal stratum (97.5%). No WM voxels had significantly higher fractional anisotropy in patients with cognitive impairment compared with their non-impaired counterparts ($P_{corr} > .05$). After the inclusion of confounders in a multivariate logistic regression, only fractional anisotropy remained a significant predictor of cognitive status.

CONCLUSIONS: Cognitively impaired patients with secondary-progressive multiple sclerosis exhibited extensive WM dysfunction, though preferential involvement of WM tracts associated with cognition, such as the corpus callosum, was apparent. Multivariate analysis revealed that only WM skeleton fractional anisotropy was a significant predictor of cognitive status.

ABBREVIATIONS: CC = corpus callosum; EDSS = Expanded Disability Status Scale; FA = fractional anisotropy; MNI = Montreal Neurological Institute; RRMS = relapsing-remitting MS; SPMS = secondary-progressive MS; TBSS = tract-based spatial statistics; WML = white matter lesion.
their primary outcome, whereas mean diffusivity has been investigated to a lesser extent. Radial diffusivity and axial diffusivity have been examined as secondary outcomes. Given the recent emphasis on the role of GM pathology both in the etiology of MS and related cognitive dysfunction, FA was considered in the context of GM volume using multivariate regression. Normal-appearing white matter has also been investigated using magnetization transfer ratio.

Tract-based spatial statistics (TBSS) is being increasingly utilized in DTI studies of MS and cognition. TBSS has improved on traditional voxel-based morphometry by thinning WM to invariant tracts common to all patients. The voxel-based morphometry approach suffers from deficiencies related to spatial alignment and smoothing, which are mitigated by TBSS. Several prior TBSS studies have concluded that cognitive impairment in MS is because of the selective disruption of specific WM tracts associated with cognition, such as the cingulum and corpus callosum (CC). It should be noted that this spatial specificity has a physiologic basis and is not mediated by the cognitive nature of these tracts. These studies correlated FA values with performance on individual cognitive tests and examined cohorts primarily or solely comprising patients with relapsing-remitting MS (RRMS). DTI outcomes in patients with SPMS with and without cognitive impairment have not been well investigated, yet 65% of patients with RRMS will progress to SPMS. While WM injury is initially selective for specific tracts associated with impaired cognition in RRMS, DTI abnormalities are expected to become significantly more widespread and generalized with greater impairment and disease severity progression.

We hypothesized that patients with SPMS with impairment spanning multiple cognitive domains should exhibit extensive WM dysfunction not restricted to tracts implicated in cognition, such as the cingulum and CC.

MATERIALS AND METHODS

Patients

This study was approved by the research ethics boards of Sunnybrook Health Sciences Centre and St. Michael’s Hospital. Patients with SPMS were prospectively recruited during a 1-year period from 2 tertiary referral MS clinics. SPMS diagnosis was based on the opinion of a senior neurologist with specialist practice in MS (20 years’ experience). Charts of potential participants were screened by the same senior neurologist before recruitment to ensure eligibility. Exclusion criteria were: history of drug/alcohol abuse, use of disease-modifying drugs or steroids within the past 6 months, pre-morbid (ie, pre-MS) psychiatric history, head injury with loss of consciousness, concurrent medical diseases (eg, cerebrovascular disease), and contraindication to MR imaging. Clinical data included: age, sex, education level, and disease duration. MR imaging acquisition, neurologic examination, and Expanded Disability Status Scale (EDSS) assessment were completed on the same day.

Cognitive Testing

The Minimal Assessment of Cognitive Function in Multiple Sclerosis was administered under the supervision of a senior neuroscientist. This standard MS cognitive battery is a comprehensive assessment tool consisting of 7 neuropsychological tests: Paced Auditory Serial Addition Test (working memory), Symbol Digit Modalities Test (processing speed), California Verbal Learning Test, 2nd Edition (verbal memory), Brief Visuospatial Memory Test, Revised (visuospatial memory), Delis-Kaplan Executive Function System (executive function), Controlled Word Association Test (verbal fluency), and Judgement of Line Orientation (visuospatial perception). Impairment on an individual test was defined as scoring more than 1.5 standard deviations below normative data of healthy controls. Patients with 2 or more test impairments were designated as having cognitive impairment. Beck Depression Inventory scores were also obtained because of the association between depression and cognitive impairment in patients with MS.

MR Imaging Acquisition

MR imaging scanning was performed on a 3T scanner (Philips Healthcare, Best, the Netherlands) with a 16-channel phased array coil. The following sequences were acquired: 1) T1 3D (TR/TE: 9.5 ms/2.3 ms, resolution: 0.71 × 0.71 × 1.4 mm³); 2) proton density/T2 (TR/TE: 2900 ms/10.7 ms, resolution: 0.45 × 0.45 × 3 mm³); 3) DTI (TR/TE: 8966 ms/57 ms, resolution: 2.95 × 2.95 × 3 mm³, 50 sections, b-value: 1000 seconds/mm², single b = 0 scan, 32 gradient directions, 2 sequential scans [co-registered and averaged off-line]).

Image Processing

The structural scans were processed to generate global GM, WM, T2-weighted WML, and T1-weighted WML tissue volumes normalized to total intracranial volume as previously reported. Briefly, regions of GM and WM were delineated algorithmically, and T2-weighted hyperintensities and T1-weighted hypointensities were hand traced using Medical Image Processing, Analysis, and Visualization version 4.0 (National Institutes of Health, Bethesda, Maryland). The FMRIB Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl) processed the DTI scans.

The FSL FLIRT tool co-registered the 2 sequential DTI scans per patient by using a 12-parameter affine transform, and the co-registered scans were averaged using Fslutils (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Fslutils). This approach avoids averaging on the scanner, which is inappropriate because of EPI susceptibility artifacts. The FSL Diffusion Toolbox corrected the co-registered, averaged scans for motion and eddy current distortions before fitting the diffusion tensors and calculating the FA maps. The acquisition space FA maps were normalized to Montreal Neurological Institute (MNI) space using the FSL FNIRT tool. The mean MNI space FA map for all patients was computed and thinned to invariant WM tracts common to every patient. This mean MNI space FA skeleton was thresholded at 0.2 before being applied as a mask to skeletonize the MNI space FA map for each individual patient to exclude non-WM voxels.

Statistical and Image Analysis

Clinical data were compared between patients with and without cognitive impairment using the Wilcoxon rank sum test for continuous variables or Pearson χ² test for dichotomous variables. Results for continuous variables were expressed as median (inter-
The normalized global tissue volumes were analyzed with respect to cognitive status as previously described. The skeletonized FA maps were compared between patients with and without cognitive impairment using FSL’s Randomise tool, which conducts permutation-based nonparametric testing while correcting for multiple comparisons across space. To be conservative and assumption free, voxelwise group analysis was conducted with 5000 permutations and threshold-free cluster enhancement. The results appeared as proportions. The normalized global tissue volumes were analyzed with respect to cognitive status as previously described. The skeletonized FA maps were compared between patients with and without cognitive impairment using FSL’s Randomise tool, which conducts permutation-based nonparametric testing while correcting for multiple comparisons across space. To be conservative and assumption free, voxelwise group analysis was conducted with 5000 permutations and threshold-free cluster enhancement. The results appeared as proportions.

The clinical characteristics, including age, sex, education level, disease duration, and EDSS score, were not significantly different between patients with and without cognitive impairment (P > .05) (Table 1). There was a trend toward higher Beck Depression Inventory scores in impaired patients, but this did not reach clinical significance (P = .07). Impaired patients displayed significantly reduced normalized global GM volume (P = .001), significantly lower normalized global WM volume (P = .024), significantly higher normalized T2-weighted WML volume (P = .002), significantly greater normalized T1-weighted WML volume (P = .006), and significantly lower WM skeleton FA (P < .001) than patients without cognitive impairment. No significant difference in normalized global WM volume was found (P > .05) (Table 1). Following multivariate analysis, WM skeleton FA was the only factor that remained a significant predictor of cognitive status (P = .03).

**WM Integrity and Cognition**

Patients with cognitive dysfunction had significantly lower FA values in over 50% of the voxels within every major WM tract compared with those without (Pcorr < .05) (Fig 1, Table 2). The most extensively affected WM tracts were the left posterior thalamic radiation (100.0%), CC (97.8%), right sagittal stratum (includes inferior fronto-occipital fasciculus and inferior longitudinal fasciculus, 97.5%), right posterior thalamic radiation (96.1%), and left sagittal stratum (95.4%). Only 1 other region (right medial lemniscus) had greater than 90% alteration (90.8%). These findings illustrate that although WM dysfunction is predominantly generalized with respect to cognitive status, preferential involvement of specific WM tracts was apparent. No WM voxels had significantly higher FA in patients with cognitive impairment compared with their nonimpaired counterparts (Pcorr > .05).

**DISCUSSION**

Cognitively impaired patients with SPMS in the present series exhibited significantly reduced normalized global GM and WM volumes, significantly increased normalized T2-weighted and T1-weighted WML volumes, and significantly lower WM skeleton FA consistent with the assertion that cognitive impairment is associated with more advanced disease. Multivariate analysis of factors predicting cognitive status demonstrated that only WM skeleton FA was significant. Our results demonstrate that in advanced MS...
disease characterized by SPMS, multiple domain cognitive dysfunction is the result of diffuse WM injury with regional predilections present in the CC, posterior thalamic radiation, and sagittal stratum. Of these 3 regions only the CC is traditionally associated with cognition, though a recent study implicated the posterior thalamic radiation in intellectual performance. Thalamocortical circuit integrity has additionally been found to differentiate normal aging from mild cognitive impairment. This suggests that thalamic radiations are implicated in a wide range of cognitive tasks. Furthermore, significantly reduced FA was recently reported in the inferior longitudinal fasciculus, a component of the sagittal stratum, of patients with mild cognitive impairment. We propose that even though WM dysfunction initially favors tracts associated with cognition, abnormalities become significantly more extensive and generalized as more domains are impaired and disease severity progresses. This suggests that cognitive impairment in patients with MS with progressive disease is a sequela of diffuse, nomenclature specific WM dysfunction. Such a pattern of WM alteration in turn raises the possibility that the underlying disease pathology itself is diffuse and nonspecific during the progressive phase, which aligns with the findings of a landmark postmortem study that investigated a variety of MS subtypes and found diffuse normal-appearing white matter injury to be a characteristic hallmark of progressive phase MS.

Table 2: Tract-based spatial statistics group analysis identifying WM tracts with significantly lower FA values in patients with cognitive impairment compared with patients without cognitive impairment

| Total Voxels | Significant Voxels | % Significant |
|--------------|--------------------|--------------|
| Middle cerebellar peduncle | 2608 | 2068 | 79.3% |
| Corpus callosum | 7044 | 6891 | 97.8% |
| R corticospinal tract | 134 | 72 | 53.7% |
| L corticospinal tract | 208 | 154 | 74.0% |
| R medial lemniscus | 174 | 158 | 90.8% |
| L medial lemniscus | 209 | 171 | 83.8% |
| R cerebellar peduncle | 476 | 331 | 69.5% |
| L cerebellar peduncle | 414 | 294 | 71.0% |
| R cerebral peduncle | 575 | 502 | 87.3% |
| L cerebral peduncle | 600 | 415 | 69.2% |
| R internal capsule | 2219 | 1728 | 77.9% |
| L internal capsule | 1659 | 1308 | 78.8% |
| R corona radiata | 3935 | 3267 | 83.0% |
| L corona radiata | 3142 | 2486 | 79.1% |
| R posterior thalamic radiation | 1086 | 1044 | 96.1% |
| L posterior thalamic radiation | 554 | 554 | 100.0% |
| R sagittal stratum | 652 | 636 | 97.5% |
| L sagittal stratum | 345 | 329 | 95.4% |
| R external capsule | 1115 | 993 | 89.1% |
| L external capsule | 565 | 437 | 77.3% |
| R cingulum | 526 | 397 | 75.5% |
| L cingulum | 319 | 220 | 69.0% |
| R superior longitudinal fasciculus | 1614 | 1363 | 84.4% |
| L superior longitudinal fasciculus | 1338 | 840 | 62.8% |

Note: R indicates right; L, left. a Regions with greater than 95% WM impingement.

Yu et al highlighted the significant correlations between reduced FA values and lower cognitive test scores in cognitively relevant tracts. However, significant correlations also occurred within all association fibers, commissural fibers, and projection fibers. This suggests that while WM abnormalities were principally tract selective, they appeared on a background of generalized WM alteration. Strikingly, the most extensively impaired WM regions in that study were the posterior thalamic radiation, CC, and sagittal stratum. Those results mirror our findings of diffuse WM dysfunction with residua of tract selectivity in the presence of greater disease severity.

Possible limitations of this study include sample size. The present cohort of patients with SPMS is relatively well populated (n = 45), but larger DTI studies of cognition in MS have been performed using different analytic approaches (n = 82). It is also possible that fatigue may have impacted the cognitive testing as it was not assessed. In addition, TBSS is a semi-automated technique that relies on a somewhat arbitrary FA threshold of 0.2 to define WM. In terms of cognition, we chose to solely focus on global cognitive impairment dichotomized based on the findings of a standard neuropsychological battery, instead of investigating individual subtests. This decision was motivated by the dearth of MS neuroimaging studies examining cognition as a multidomain entity, though this method is not without its own inherent limitations. Without the use of individual subtests, we were not able to fully establish a damage-response relationship where incremental changes in cognition can be correlated with incremental neuronal dysfunction.

Another potential limitation is our choice of SPMS as a disease subtype to investigate. RRMS is an earlier form of the disease and has been investigated much more frequently than SPMS. Our decision to examine patients with SPMS with cognitive impair-
ment means that our results are therefore not directly comparable with previous DTI studies of MS and cognition. 8,11,13,34 However, our data do demonstrate structural differences between patients with SPMS with and without cognitive impairment and provide insight into the diffuse WM tract disturbances that occur with disease progression. Differences between impaired and non-impaired patients with SPMS may also provide a potential surrogate marker for new therapeutic interventions to forestall the onset of cognitive impairment even in advanced disease.

CONCLUSIONS

This study sought to examine MR imaging correlates of multiple domain cognitive impairment in patients with SPMS with an emphasis on WM integrity. Impaired patients exhibited extensive WM dysfunction that severely disrupted every major tract in the brain while retaining prediction for pathways associated with cognition, such as the CC. These findings strongly suggest that cognitive impairment in patients with MS with advanced disease progression is predominantly the result of diffuse WM injury superimposed on a background of cognition-specific tract damage sustained during earlier stages of the disease. While impaired patients with SPMS also displayed significantly reduced global GM and WM volumes and significantly increased T2-weighted and T1-weighted WML loads, multivariate analysis revealed that only WM skeleton FA was a significant predictor of cognitive status.

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