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The impact of cervical spinal cord atrophy on quality of life in multiple sclerosis

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ABSTRACT

Background: Spinal cord demyelination is common in multiple sclerosis (MS) and has been linked to increased disability and progressive clinical course. Spinal cord atrophy shows an especially close relationship to MS-related physical disability, though the relationship between spinal cord lesions/atrophy and health-related quality of life (QOL) has not been explored.

Methods: 62 patients (53 relapsing MS, 7 secondary progressive, 2 clinically isolated syndrome) from our center underwent 3 T MRI within 30 days of clinical examination and QOL assessment. Upper cervical (C1-C3) spinal cord area (UCCA) was obtained from 3D high-resolution MPRAGE sequences (1 mm isotropic voxels). Cervical spinal cord (C1-C7) lesion count, and cervical and brain T2 hyperintense lesion volumes were calculated. Brain parenchymal fraction (BPF) was obtained from an automated segmentation pipeline. Spearman correlations were assessed between MRI and clinical data. Partial Spearman correlations adjusting for age, disease duration, and BPF assessed the independent association between MRI variables and QOL domains.

Results: UCCA showed an inverse relationship with age ($r = -0.330$, $p = .009$), disease duration, ($r = -0.444$, $p < .001$), and nine-hole peg test ($r = -0.353$, $p = .005$). The Upper Extremity Function QOL domain showed the strongest relationship to UCCA ($r = 0.333$, $p = .008$), with Lower Extremity Function QOL ($r = 0.234$, $p = .067$) and Satisfaction with Social Roles and Activities ($r = 0.245$, $p = .055$) correlations bordering significance. The association between UCCA and Upper Extremity QOL remained significant after adjustment for BPF, age, and disease duration. QOL domains reflective of psychological health (Depression, Anxiety, Emotional and Behavioral Dyscontrol, Positive Affect and Wellbeing) showed no relationship to UCCA. Cervical and brain lesion volume related to impairment in Stigma while cervical lesion count was unrelated to NeuroQOL impairment. Brain atrophy correlated with conventional markers of disability and cognition but did not have a significant relationship to QOL.

Conclusion: Cervical spinal cord volume is independently associated with impaired upper extremity-related QOL in patients with MS. These findings suggest specific clinical relevance of MS-related spinal cord atrophy as compared to brain or cervical spinal cord lesions, or whole brain atrophy.

1. Introduction

Spinal cord demyelination and atrophy are common in multiple sclerosis and have been linked to increased MS-related disability [1–6]. Advances in magnetic resonance imaging (MRI) scan acquisition and segmentation techniques have led to improved ability to measure cervical spinal cord atrophy and its relationship to clinical outcomes in MS [6–14]. Spinal cord atrophy is associated with a progressive disease course and has been hypothesized to be an early indicator of imminent disease progression [12–14]. Although spinal cord atrophy is related to MS disability, the link between spinal cord atrophy, lesions and health-related quality-of-life (QOL) has not yet been examined. Prior work has demonstrated association between MS-related MRI brain pathology (lesion volume and atrophy) and QOL, suggesting the potential utility of patient-reported QOL as a clinical outcome in trials [15–17]. The objective of this study was to determine the relative impact of cervical cord atrophy as compared to cord and brain lesions and whole brain atrophy on quality-of-life in MS.

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Table 1
Cohort demographic and clinical characteristics.

Number of MS subjects	62
Age, years	46.3 ± 8.8 (28.4–59.4), 48.1 [40.3, 52.5]
Women, n (%)	42 (68%)
MS disease category, n (%)	
Relapsing-remitting MS	53 (86%)
Secondary progressive MS	7 (11%)
Clinically isolated syndrome	2 (3%)
Disease duration (years)[a]	13.5 ± 7.2 (1.4–41.8), 13.1 [9.2, 15.6]
EDSS score	1.9 ± 1.5 (0–6.5), 1.5 [1, 2]
T25FW (seconds)	5.3 ± 4.0 (3.4–32.4), 4.4 [4, 5.1]
9HPT, dominant (seconds)	23.0 ± 6.0 (15.8–45.5), 23.0 [19.0, 25.0]
BPF	0.83 ± 0.04 (0.73–0.91), 0.83 [0.80, 0.86]
Brain T2LV (mL)	9.3 ± 8.6 (0–34.4), 6.6 [2.7, 13.8]
Cervical spinal cord T2LV (mL)	0.24 ± 0.23 (0–1.4), 0.20 [0.08, 0.34]
Patients with any cervical lesions, n (%)	54/61 (88%)
Cervical lesion number	3.5 ± 2.6 (0–11), 3 [2,5]
UCCA (mm^2)	72.5 ± 9.3 (54.5–92.3), 71.3 [67.0, 77.7]

Key: Data are mean ± standard deviation (range), median, [25th, 75th percentiles] unless otherwise indicated; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; T25FW = timed 25-ft walk; 9HPT = 9-hole peg test; BPF = brain parenchymal fraction; T2LV = T2 hyperintense lesion volume; UCCA = upper cervical cord area.

[a] Time from first symptom.

2. Methods

2.1. Subjects

We retrospectively studied the MRI scans of 62 patients enrolled in the Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women's Hospital (CLIMB) longitudinal cohort study [18] who met the following inclusion criteria: (1) age 18–60; (2) MS diagnosis of either relapsing-remitting (RR), secondary progressive, (SP) or clinically isolated syndrome (CIS); (3) underwent brain and cervical spine MRI on the same scanner within 30 days of clinical examination and quality-of-life evaluation; (4) had no other severe acute or chronic medical conditions; and (4) had no clinical relapses or corticosteroid usage 4 weeks prior to MRI. Baseline demographic, clinical, and MRI characteristics of all subjects are presented in Table 1. Neurologic examination was conducted by a MS specialist, including assessment of Expanded Disability Status Scale (EDSS) score and timed 25-ft walk (T25FW). All participants were additionally evaluated with nine-hole peg test (9HPT), symbol digit modality test (SDMT), and computerized NeuroQOL testing as part of the Systems Biology Study of Clinical, Radiological, and Molecular Markers in Subjects with Multiple Sclerosis (SysteMS) at a timepoint within 30 days of clinical examination and MRI. The CLIMB and SysteMS studies were approved by the Partners Human Research Committee at the Brigham and Women's Hospital (IRB Protocol #1999-P-010435 and # 2015P001248). Informed consent was obtained from all patients included in the study.

2.2. MRI acquisition

All subjects underwent brain and cervical spine MRI at 3 T using the same scanner and 20-channel craniospinal coil (3 T Skyra, Siemens Medical Solutions, Erlangen, Germany). MRI acquisition protocols were identical among subjects. Head scans covered the whole brain and included 3D high-resolution T1-weighted sagittal magnetization-prepared rapid gradient-echo (MPRAGE) (TR/TE/TI: 2300/2.96/900 ms; voxel size: 1x1x1 mm^3) and axial T2-weighted fluid-attenuated inversion recovery (FLAIR) (TR/TE/TI: 9000/81/2500 ms; voxel size: 1x1x1 mm^3) sequences. Cervical spine MRI covered the whole cervical spinal cord and included 2D axial T2 spin-echo [TR [mean (range)]: 5560.6 (4610–6221.2) ms; TE: 101 ms (4 subjects) and 90 ms (all other subjects) and voxel size: $0.703 \times 0.703 \times 3$ mm^3 (1 subject) and $0.563 \times 0.563 \times 3$ mm^3 (all other subjects)] and sagittal short tau inversion recovery (STIR) (TR/TE/TI: 3000/38/220 ms; voxel size: $0.625 \times 0.625 \times 3$ mm^3) sequences. In addition, the MPRAGE sagittal sequence covered both the whole head and extended to the C5 vertebral level to cover the upper cervical spinal cord. Brain and spinal cord images were repeated five minutes after IV administration of 0.1 mmole/kg of gadolinium.

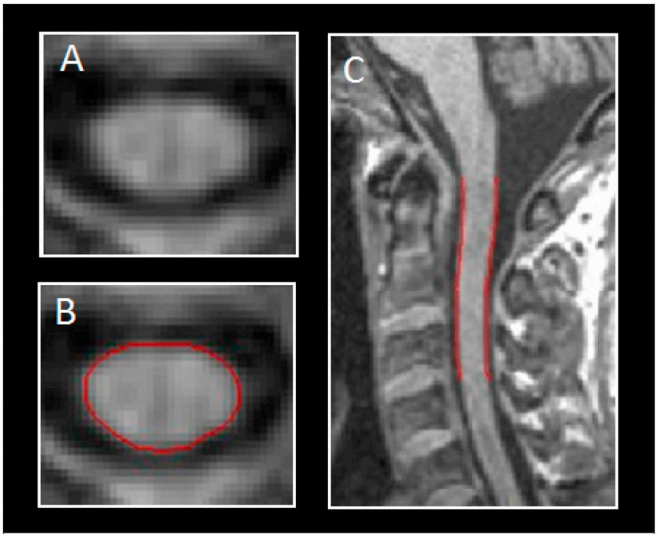

Fig. 1. Upper cervical spinal cord area measurement.
Upper cervical cord area was assessed from C1-C3 on axial T1-weighted magnetization-prepared rapid gradient-echo brain sequence. An example tracing of the axial (A,B) (reconstructed) and sagittal (C) (native) images from a 44-year-old man with relapsing-remitting multiple sclerosis is shown.

2.3. MRI analysis

2.3.1. Upper cervical cord area (UCCA) measurement

Sample images and contouring are illustrated in Fig. 1. Original DICOM images were converted to NIfTI format using Jim 7.0 (Xinapse Systems Ltd., West Bergholt, UK; http://www.xinapse.com). UCCA measurements were obtained at C1–C3 vertebral levels from the MPRAGE images, using a semi-automated active surface contouring pipeline [19]. To calculate cord area, 1-mm-thick reconstructed axial slices perpendicular to the cord axis from C1-C3 were sampled every 5 mm using the semi-automated Jim software "cord finder toolbox" with fixed settings (nominal cord diameter = 8 mm, number of shape coefficients = 24, order of longitudinal variation = 12). Toolkit markers were placed at the center of images and spinal cord contour was determined using a reproducible active surface tool. Sagittal native images were cross-referenced to identify vertebral levels precisely (Fig. 1). Manual adjustments were applied where necessary to assure accurate contours. Mean C1–C3 cross-sectional area was calculated to normalize the cord area by the number of slices sampled [20]. UCCA obtained by this technique shows high intra- and inter-rater reliability [19,21]. Our previous work has shown the effectiveness of using a craniospinal MPRGAGE sequence to derive UCCA measurements [22], which provide equivalent results when compared to direct cervical spinal cord sequences [23].

2.3.2. Brain and cervical cord lesion measurement

Sample images and contouring are illustrated in Fig. 2. Whole-brain T2 hyperintense lesion volume (T2LV) was calculated using a semi-

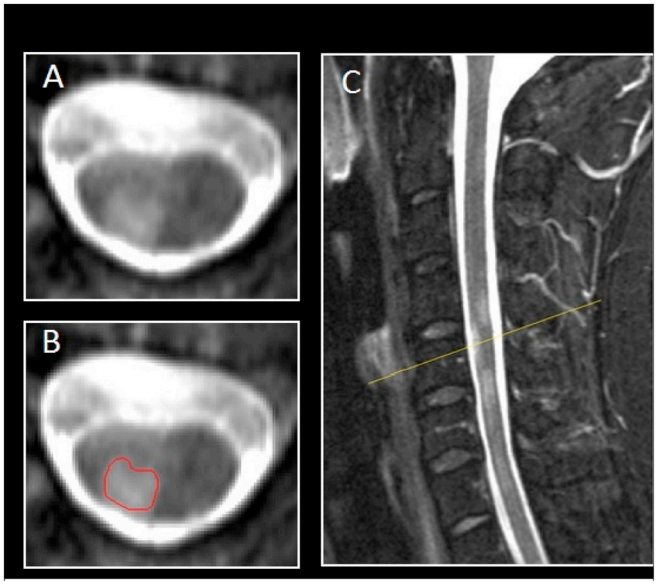

Fig. 2. Cervical spinal cord lesion quantitation.
C1-C7 cervical spinal cord hyperintense lesions were identified on the T2 axial sequence (A, B) and confirmed by corresponding high signal on sagittal short tau inversion recovery images (C, yellow bar indicates the anatomic reference level of the axial image). Lesions were traced (note red contour) on the T2 axial sequence (B). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

automated edge-finding tool in Jim 7.0 software on the axial brain T2 FLAIR sequence. Cervical lesions (C1-C7) were identified on the T2 axial sequence and confirmed by the presence of corresponding high signal on sagittal STIR. Brain and spinal cord lesions were first marked by an experienced observer, and then contoured based on local thresholding (Fig. 2). MRI analysis was blind to demographic characteristics, cervical cord area, and QOL data.

2.3.3. Brain parenchymal volume measurement

Brain parenchymal fraction (BPF), a surrogate for whole brain atrophy, was obtained via fully automated quantitative analysis pipeline [24]. Key steps were co-registration of MR sequences, anatomical parcellation with heuristic misclassification correction, and an expectation-maximization algorithm. This pipeline for measuring BPF has shown high accuracy and reliability in prior work, with intraclass correlation coefficient of 0.86 and scan-rescan reliability coefficient of variation of 0.4% [24].

2.4. Quality-of-life evaluation

The NeuroQOL survey, which has been previously validated in MS cohorts [25], was administered to all subjects in computerized-adaptive format within 30 days of MRI and clinical examination. NeuroQOL assesses 11 QOL domains: Ability to Participate in Social Roles and Activities, Anxiety, Depression, Emotional and Behavioral Dyscontrol, Fatigue, Lower Extremity Function, Positive Affect and Wellbeing, Satisfaction with Social Roles and Activities, Stigma, Cognitive Function and Upper Extremity Function. Higher absolute NeuroQOL test scores indicate better (i.e. wellbeing, extremity function) or worse function (i.e. depression, fatigue) depending on the specific domain. T-scores were calculated for each QOL domain based on a standardized reference population. Clinical reference populations were used for Stigma, Fatigue and Emotional and Behavioral Dyscontrol domains, while all other domains used a general population reference sample for comparison.

2.5. Statistical analysis

Statistical correlations between MRI metrics, clinical variables, and QOL domains were assessed by Spearman correlation coefficients. Partial Spearman correlation coefficients were calculated adjusting for age, disease duration, and BPF to assess the independent association between MRI variables and QOL domains. Partial Spearman correlation coefficients were calculated using the ppcor library in R (www.r-package.org). A $p < .05$ was considered statistically significant.

3. Results

3.1. Upper cervical cord area: clinical outcomes & QOL

UCCA showed inverse correlations with age ($r = -0.330$, $p = .009$) and disease duration ($r = -0.444$, $p = .001$). UCCA showed statistically significant correlations with traditional measures of MS-related disability [EDSS ($r = -0.326$, p = .009), T25FW ($r = -0.278$, $p = .029$), 9HPT ($r = -0.353$, p = .009)] (Table 2). The relationship between UCCA and NeuroQOL is shown in Table 2. UCCA correlated strongest with the NeuroQOL Upper Extremity Function domain ($r = 0.333$, $p = .008$). Borderline significant correlations between UCCA and Lower Extremity Function ($r = 0.234$, $p = .067$) and Satisfaction with Social Roles and Activities ($r = 0.245$, $p = .055$) were also noted. Mental health NeuroQOL domains (Depression, Anxiety, Positive Affect and Wellbeing, etc.) showed no relationship to UCCA. The association between UCCA and Upper Extremity Function QOL remained significant after adjustment for age, disease duration, and brain atrophy (BPF) ($p < .05$ for all analyses) (Supplementary Table 1).

3.2. Differential impact of cervical atrophy vs. lesions

Cervical T2LV showed no significant relationship to age or disease duration and correlated poorly with NeuroQOL (Table 2). Only a weakly significant relationship to increased Stigma ($r = 0.258$, $p = .045$) was observed. The correlation was similar after adjustment for age, disease duration, and whole brain atrophy, though statistical significance was decreased (Supplementary Table 1). The significant inverse relationship between UCCA and Upper Extremity Function QOL was not seen between cervical T2LV and Upper Extremity Function QOL (Table 2). A mean 3.5 ± 2.6 (0−11) cervical lesions were identified in this cohort, though cervical lesion number was not related to any QOL domain (data not shown). The relative impact of UCCA versus cervical T2LV on QOL was not different after removing CIS subjects ($n = 2$) or African American subjects ($n = 3$) (data not shown).

3.3. Brain T2 lesions and atrophy: clinical outcomes & QOL

Brain T2LV strongly inversely correlated with cognitive Cognitive Function as assessed by SDMT ($r = -0.576$, $p < .001$) but had no relationship to other disability outcomes or demographic characteristics (Table 3). Stigma ($r = -0.271$ $p = .033$) was the only NeuroQOL domain to show a significant pathological relationship with Brain T2LV; a borderline significant association with Cognition domain impairment was also noted (Table 3). A statistical correlation with Emotional and Behavioral Dyscontrol QOL was noted though the directionality was not consistent with a pathological correlation (Table 3). None of these correlations persisted in adjusted analyses accounting for whole brain atrophy (Supplementary Table 1). BPF showed an inverse correlation with age ($r = -0.268$, $p = .037$) and disease duration ($r = -0.302$, $p = .018$), as well as traditional measures of MS-related disability [EDSS ($r = -0.449$, $p \leq .001$), T25FW ($r = -0.240$, $p = .063$), 9HPT ($r = -0.315$, $p = .014$), SDMT Sum Score ($r = 0.488$, p ≤.001)], however there was only a weak borderline significant association with Emotional and Behavioral Dyscontrol QOL ($r = 0.238$, $p = .065$) and

Table 2
Cervical spinal cord atrophy and T2 lesions vs. clinical and QOL variables.

	UCCA		Cervical T2LV	
	r_s value	*p*-Value	r_s value	p-Value
Clinical variables				
Age	−0.330	.009*	−0.207	.110
Disease duration	−0.444	< .001*	−0.094	.470
EDSS score	−0.326	.010*	0.051	.694
9HPT	−0.353	.005*	0.190	.142
T25FW	−0.278	.029*	0.116	.374
SDMT	0.279	.028*	−0.136	.296
NeuroQOL domains:				
Upper Extremity Function	0.333	.008*	−0.167	.199
Lower Extremity Function	0.234	.067	−0.142	.277
Depression	0.164	.203	−0.028	.828
Anxiety	−0.032	.803	−0.098	.454
Fatigue	−0.108	.403	0.025	.850
Emotional and Behavioral Dyscontrol	0.153	.236	−0.026	.845
Positive Affect and Wellbeing	−0.073	.571	−0.092	.481
Ability to Participate in Social Roles and Activities	0.210	.102	−0.096	.460
Satisfaction with Social Roles and Activities	0.245	.055	−0.165	.204
Stigma	−0.150	.243	0.258	.045*
Cognitive Function	0.044	.736	−0.070	.594

Key: UCCA = upper cervical cord area; T2LV = T2 hyperintense lesion volume; EDSS = Expanded Disability Status Scale; QOL = quality-of-life; T25FW = timed 25-ft walk; 9HPT = 9-hole peg test; SDMT = symbol digit modalities test (sum score); r_s = Spearman correlation.
* $p < .05$.

no significant relationship with other QOL domains (Table 3).

3.4. Other MRI results

Table 4 shows the relationship among MRI variables investigated in this study. UCCA showed no relationship to cervical T2LV or cervical lesion number, though cervical T2LV and cervical lesion number showed strong positive correlations with each other ($r = 0.849$, p ≤.001) (Table 4). UCCA also showed a stronger association with brain atrophy ($r = 0.451$, $p < .001$) than with brain T2LV ($r = -0.271$, $p = .033$) (Table 4). Weaker associations, but with similar magnitude, were noted between brain T2LV, cervical lesion number, T2LV and UCCA (Table 4). No subjects had gadolinium contrast-enhancing lesions in the brain or spinal cord.

Table 3
Whole brain atrophy and T2 lesions vs. clinical and QOL variables.

	BPF		Brain T2LV	
	r_s value	p-Value	r_s value	p-Value
Clinical variables				
Age	−0.268	.037*	−0.047	.717
Disease duration	−0.302	.018*	0.173	.179
EDSS score	−0.449	< .001*	0.296	.020*
9HPT	−0.315	.014*	0.206	.108
T25FW	−0.240	.063	0.212’	.099
SDMT sum score	0.488	< .001*	−0.576	< .001*
NeuroQOL domains				
Upper Extremity Function	0.196	.131	−0.247	.053
Lower Extremity Function	0.204	.115	−0.176	.171
Depression	0.157	.227	−0.089	.491
Anxiety	0.063	.627	−0.018	.890
Fatigue	0.055	.675	−0.040	.760
Emotional and Behavioral Dyscontrol	0.238	.065	−0.266	.037*
Positive Affect and Wellbeing	0.054	.680	0.025	.847
Ability to Participate in Social Roles and Activities	0.195	.132	−0.210	.101
Satisfaction with Social Roles and Activities	0.206	.111	−0.145	.260
Stigma	−0.187	.149	0.271	.033*
Cognitive Function	0.138	.289	−0.242	.058

Key: T2LV = T2 hyperintense lesion volume; BPF = brain parenchymal fraction; EDSS = Expanded Disability Status Scale; QOL = quality-of-life; T25FW = timed 25-ft walk; 9HPT = 9-hole peg test; SDMT = symbol digit modalities test; r_s = Spearman correlation.
* p < .05.

Table 4
Relationships among MRI variables.

	BPF	Brain T2LV	UCCA	Cervical T2LV
BPF		−0.672*	0.451*	−0.065
		p < .001	p < .001	p = .620
Brain T2LV	−0.672*		−0.271*	0.298*
	p < .001		p = .033	p = .020
UCCA	0.451*	−0.271*		0.030
	p < .001	p = .033		p = .819
Cervical T2LV	−0.065	0.298*	0.030	
	p = .620	p = .020	p = .819	

Key: Values in each cell are Spearman correlation r_s (above) and *p*-values (below); BPF = brain parenchymal fraction; T2LV = T2 hyperintense lesion volume; UCCA = upper cervical cord area.
* $p < .05$.

4. Discussion

The purpose of this study was to investigate relative impact of cervical cord atrophy as compared to lesions in the spinal cord and both brain lesions and atrophy on QOL in MS. Our results showed that cervical spinal cord atrophy had a significant independent association with NeuroQOL impairment related to Upper Extremity Function and borderline significant relationship to Lower Extremity Function and Satisfaction with Social Roles and Activities. Cervical T2 lesion burden, by comparison, correlated poorly with extremity QOL, and showed only a modest relationship to Stigma. Brain T2LV was related to impaired cognition and increased Stigma, which was distinct from the effect on QOL observed with either UCCA or cervical T2LV. Whole brain atrophy related to conventional measures of disease severity, though did not strongly impact QOL. Our findings underscore the complementary roles of brain and spinal cord lesions in characterizing MS severity.

In this work, we demonstrated relationships between cervical cord volume and clinical disability that extend upon the findings of previously published clinical-MRI correlation studies. At 1.5 T, our lab has used similar methods to show that cervical spinal cord area correlates with EDSS score ($r_s = -0.383$, $p = .03$) [21]. The same study found a statistically significant inverse relationship between UCCA and cervical T2LV ($r_s = -0.330$, $p = .07$) [21]. In the present study, we found a significant correlation between UCCA and Upper Extremity Function QOL ($r_s = -0.330$, $p = .009$) which approximates the moderate effect seen between EDSS and UCCA in the current study ($r_s = -0.325$, $p = .010$) and in our prior work at 1.5 T. The current study, however, shows dissociation between UCCA and cervical T2LV, which may be due technical differences in spinal cord lesions/atrophy at 3 T vs. 1.5 T and cohort differences (our cohort being larger, $n = 62$ vs. 31 patients, with slightly different demographic characteristics). Technical factors may also affect the observed trends, as spinal cord lesions may become less apparent on MRI over time and thus the effect on QOL could be underestimated. Clinical-MRI correlation studies at 3 T have shown a stronger inverse relationship between UCCA and EDSS score ($r_s = -0.515$, $p = .020$) but not between brain or cervical T2LV and EDSS score [26]. In our study, UCCA, but not cervical T2LV, showed correlation with many standard clinical variables (EDSS, ambulation time, 9HPT) (Table 2) supporting findings form prior work implicating higher clinical relevance of cervical atrophy as compared to cervical T2

lesions to physical disability [26]. Lastly, prior work also showed a poor relationship between spinal cord and brain MRI involvement in MS, with respect to both lesions and atrophy [26], suggesting that these topographic specific aspects of the disease progress somewhat independently. These findings are consistent with our data.

Studies validating the use of the NeuroQOL short forms have shown that MS-related QOL impairment occurs frequently, most commonly in domains of Upper Extremity Function and Lower Extremity Function, and Satisfaction with Social Roles and Activities, among other areas [25]. There are limited prior studies investigating the relationship between brain MRI and MS patient QOL, however. The largest study used the Functional Assessment in Multiple Sclerosis (FAMS) Emotional Wellbeing and Thinking/Fatigue subscales to characterize QOL, demonstrating that increased brain T2 lesion load and decreased grey matter volume was linked to worse FAMS Emotional Wellbeing and Thinking/Fatigue scores [16]. Spinal cord MRI was not investigated in that study. Though we show novel relationships between QOL and UCCA, in this work, we did not find a strong relationship between brain T2LV or whole brain atrophy and NeuroQOL Fatigue or Positive Affect and Wellbeing (NeuroQOL domains arguably comparable to the FAMS subscales). QOL assessment of FAMS and NeuroQOL may differ intrinsically, though the Mowry et al. cohort [16] was significantly larger and included more progressive MS patients, which may have increased ability to detect brain T2LV/atrophy-QOL associations. Previous MRI-QOL correlation studies at 1.5 T MRI have shown an increased likelihood of QOL impairment and stronger QOL-MRI correlations in people with secondary progressive as compared to RRMS [15]. Lastly, we did find an association between brain T2LV and increased Stigma ("Perceptions of self and publicly enacted negativity, prejudice and discrimination as a result of disease-related manifestations") and worse SDMT score as well as a weak association between brain atrophy and Emotional and Behavioral Dyscontrol, and these outcomes overlap with QOL assessed by FAMS Emotional Wellbeing and Thinking/Fatigue subscales.

Our study has several limitations that warrant discussion. First, the generalizability of our results is limited by cohort clinical/demographic characteristics. Patients in this study were generally mildly disabled, predominantly of RRMS subtype, and had a low mean cervical lesion number and volume, which may have limited the power to detect correlations with QOL. Our study was not powered to evaluate group differences between RRMS and SP/PPMS subgroups, and prior work has demonstrated that cervical atrophy may have less clinical impact in RRMS [27]; thus, larger studies are needed to interpret how the MRI-QOL correlations observed in our cohort apply to specific disease stages. Secondly, the stability of MRI-QOL associations we identified and their relationship to disease progression is unclear as longitudinal change was not analyzed. Recent work indicates that decline in UCCA is related to impending disease progression and disability [8,12–14], though the impact on health-related QOL has not been investigated. We are currently in the process of collecting longitudinal clinical and QOL data at our center. In future studies, we plan to evaluate serial relationships between MRI and QOL to assess how early spinal cord involvement may predict QOL impairment and progression. Thirdly, there are limitations in the use of NeuroQOL for the evaluation of health related QOL. In this work we used a computer-adapted version of NeuroQOL that differs slightly from the short form version that was formally validated in MS. Self-report/recall of QOL can be limited in patients with MS as a result of cognitive impairment. Furthermore, QOL "appraisal"—the way individuals think about their QOL—impacts measurement, and for example, may lead to underestimation of QOL burden related to long-standing deficits [28]. This may help account for the observation that MRI correlates with Upper Extremity Function QOL, though in MS patients, lower extremity symptoms tend to present earlier. Though we focus discussion primarily on strongest correlations between MRI and QOL, weaker correlations may still be clinically meaningful, as would longitudinal trends within an individual patient which we do not report. Validation of our preliminary observations with long-term assessment and alternative QOL assessment tools is needed. Extension of this work to the thoracic cord would be informative, as prior studies have shown association between thoracic atrophy and MS disability [29], and the relationship to QOL is not known. Further studies are needed to investigate how other MRI measurements linked to disease progression (e.g. deep grey matter [30], brainstem [31], and cortical [32] involvement) correlate with patient QOL. We did not explore the effect of treatment on MRI-QOL relationships as this study was not powered to assess this, though treatment effects (presumably leading to milder MRI and improved QOL) should be investigated in larger cohorts. Nonetheless, this study adds to the growing understanding that spinal cord involvement can often help to bridge the gap between brain involvement and disability (clinical-MRI dissociation) in MS [33].

5. Conclusions

Cervical spinal cord atrophy is independently related to impairment in Upper Extremity Function QOL, whereas cervical lesions correlate poorly with NeuroQOL. Cervical cord atrophy better correlates with traditional markers of clinical disability as compared to total cervical or brain lesion load, which has a distinct effect on Stigma QOL and cognition. These findings highlight the complementary information provided by brain and spinal cord lesion volume and atrophy in the assessment of MS severity.

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