

Original Article

MRI assessment of cervical spinal cord cross-sectional area in patients with multiple sclerosis

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ABSTRACT

Objectives: Spinal cord abnormalities including cervical cord atrophy are common in multiple sclerosis (MS). This study aimed to assess the cervical spinal cord cross-sectional area (CSA) using magnetic resonance imaging (MRI) in MS patients.

Materials and Methods: Sixty participants were enrolled in this study (16 male and 44 female), 30 patients with MS, diagnosed according to the revised McDonald criteria, and 30 apparently healthy individuals as the control group. CSA of the spinal cord was measured on axial T2-weighted images of the cervical MRI studies from C2 to C7 vertebral levels.

Results: There was a significant difference between MS patients and the control group in mean CSA at a different level. The mean CSA at C2, in MS cases, was significantly lower than controls ($67.7 \pm 9.4 \text{ mm}^2$ vs. $81.3 \pm 4.6 \text{ mm}^2$). Similarly, the mean CSA at C7 ($64.4 \pm 9.9 \text{ mm}^2$) and average C2–7 ($68 \pm 9.1 \text{ mm}^2$) of MS cases were significantly lower than the control. There was a strong inverse correlation between mean cervical cord CSA and duration of the disease and disability score. The reduction in cervical cord CSA was more prominent in patients with secondary progressive MS. There was no significant difference regarding age, gender, type of treatment, or the number of cervical cord lesions.

Conclusion: The mean CSA was significantly lower in patients with MS than in the control group and was lesser in progressive types. Patients with a longer duration of MS and a high disability score tend to have smaller CSA.

Keywords: Multiple sclerosis, Magnetic resonance imaging, Cervical, Spinal cord

INTRODUCTION

Multiple sclerosis (MS) is considered a progressive demyelinating disease of the central nervous system (CNS),^[1,2] pathologically characterized by chronic inflammation, gliosis, axon loss, and demyelination distributed inside the CNS. MS tends to affect the optic nerves brainstem, periventricular white matter, and spinal cord.^[3] Spinal cord abnormalities are common in MS and involve several pathological processes, including but not limited to gliosis, loss of neuroaxonal and demyelination, eventually causing autonomic dysfunction and sensory and chronic motor.^[4]

Magnetic resonance imaging (MRI) plays an important role in diagnosing and managing MS, including earlier and more assured diagnosis in conjunction with characteristic symptoms, pathophysiology, and monitoring results of MS treatments.^[4-6] Numerous standards have been established to integrate MRI with clinical evaluation and other

diagnostic approaches to reach an initial and more accurate diagnosis, involving the revised McDonald criteria, which is a modification to previous guidelines to help users in the typical practice setting.^[5]

Atrophy of the brain and spinal cord begins early in the process of multiple MS due to early axonal failure and this chronic condition continues, leading to significant loss of parenchymal tissue at later stages of the disease^[7-9] and they are major findings of MRI in the evaluation of MS patients.^[10]

Increased numbers of research articles have concentrated on the value of spinal cord atrophy as a measure of clinical trial outcomes and as a vital predictor of disability progression and monitoring response to treatment.^[11-13] This study was conducted to investigate the correlation between the cervical cord cross-sectional area (CSA) as marker of cord atrophy using conventional MRI and the clinical subtype types of MS, duration of the disease, and clinical disability status.

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MATERIALS AND METHODS

This is a case-control study conducted on 60 cases (30 MS patients and 30 control healthy cases) at Middle Euphrates neuroscience Center - AL-Sadir Medical City (which is a tertiary center in Middle Euphrates area, officially responsible for registration of MS patient in the middle Euphrates at Al Najaf Al Ashraf governorate, located about 160-kilometer southern west capital Baghdad), between January 2020 and February 2021.

Population

Thirty MS patients were included in the study and identified as cases according to McDonald's criteria 2017. Expanded disability status scale (EDSS) was used to evaluate the disability of MS patients. They were referred to the neuroradiology department - MRI unit, for routine MR imaging follow-up.

A second group was identified as a control case and included 30 age- and gender-matched persons who have cervical MRI examinations for other reasons and have no clinical nor radiological evidence of MS.

They were referred to neuroradiology department - MRI unit, for routine MR imaging follow up. A second groups were identified as control cases, included 30 age- and gender-matched persons who have cervical MRI examination for other reasons and have no clinical nor radiological evidence of MS.

Inclusion criteria

Adult patients with MS diagnosis according to McDonald criteria 2017.^[5]

Exclusion criteria

History or presence of cervical spinal surgery, congenital anomaly, infection, or trauma; history of chronic disease (hypertension, diabetes), severe scoliosis or kyphosis, patient refusal, and if MRI study quality was inadequate.

Informed oral agreement to participate in the study was taken from all patients.

Data acquisition

Clinical data

Data collection was including age, weight, height, clinical history, clinical course, type of MS, duration, and drugs taken, were obtained from (record, registry, and history, using a unified research formula [Appendix 1]. Types of MS were secondary progressive MS (SPMS), relapsing-remitting MS (RRMS) and clinically isolated syndrome (CIS). The EDSS was used to assess the clinical disability.

Cervical MRI examination

All cervical examinations were conducted using Philips Achieva 1.5T MRI machine, (Philips Medical Systems, Best, Netherlands). Each examination consisted of multiple sagittal T1-weighted (TR = 560 ms and TE 20 ms) and sagittal and axial T2-weighted sections (TR = 2175 ms and TE = 100 ms). MRI examinations were evaluated on the extended workstation by a specialist radiologist (with 14 years of experience) blinded to the clinical details of the patient, including the initial general evaluation and dedicated assessment of cervical cord.

Measurement of cervical cord CSA

After adjusting contrast, edge sharpness and marking the outline of the cervical cord at each vertebral level between C2 and C7, [Figure 1] the CSA of the cervical cord was measured using free-hand caliber in workstation from C2 to C7 [Figure 2]. An average segmental area of the spinal cord was calculated.

Data was entered, managed, and analyzed using the SPSS, (version 26), with variables presented as mean, standard deviation, frequencies, and percentages accordingly. The Chi-square test used to compare frequencies between cases and control groups, and Student's *t*-test (independent two-sample model) was used to compare mean CSA between cases and controls. Analysis of variances test used to compare mean CSA across the types of MS. Additionally, least significant difference *post hoc* analysis was used for pairwise comparison between the types of MS. Bivariate Spearman's Rho correlation test was used to assess the significance of the correlation between CSA (as scale variable) against categorical variables; spinal cord lesion, treatment, EDSS and gender. Bivariate Pearson's correlation test was used to assess the significance of

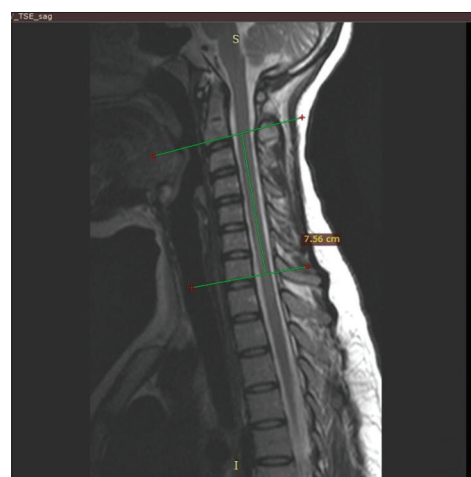


Figure 1: Mid sagittal T2-weighted magnetic resonance image, assigning the levels.

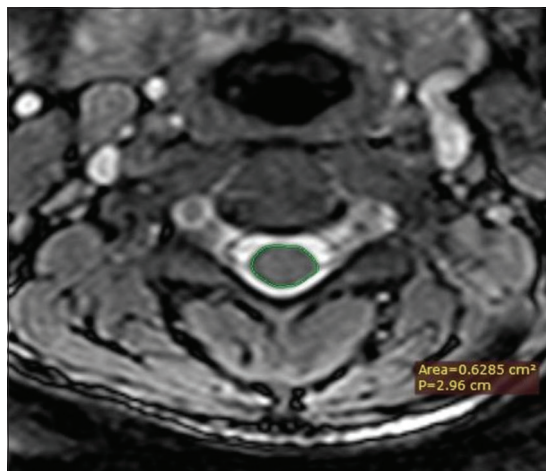


Figure 2: Axial T2-weighted magnetic resonance image, at C2 level showing method of measurement of cervical cord cross-sectional area.

the correlation between CSA (as a scale variable) against other scale variables; age, Body mass index (BMI) and duration of MS. To assess the validity of MRI, CSA in discrimination between types of MS, receiver operating characteristics (ROC) curve analysis was applied. The area under the curve (AUC) was calculated and it is an indicator of the validity and accuracy of a test. $P \leq 0.05$ was set as significant.

RESULTS

There were 60 participants enrolled in this study, 30 with MS (cases group) and 30 healthy individuals (control group), both groups were almost matched for age and gender [Table 1].

The mean CSA at the C2 level, and C7 level as well as the average of C2–C7 in cases was significantly lower than that in controls, $P < 0.001$ [Table 2].

RRMS was the more frequent MS type contributing to 22/30 (73.4%), with 4 cases (13.3%) for each of the SPMS and CIS types. There were significant differences between all types of MS regarding mean CSA, where the mean CSA of the SPMS group was significantly lower than the other two groups in C2, C7 and average C2–C7, $P < 0.001$ [Table 3].

Bivariate analysis for the correlation between CSA and each of type of MS, spinal cord lesion, treatment and EDSS revealed no significant association except EDSS where a strong inverse correlation was found, $P < 0.001$ as shown in [Table 4].

Furthermore, correlation analysis between CSA and EDSS against independent variables of the MS cases revealed no significant correlation with age, gender, BMI ($P > 0.05$).

No significant difference was found between C2, C7 and average C2–C7 CSA in the prediction of each type, however, the overall AUC was good enough as predictor of MS type

Table 1: Baseline characteristics of the studied group.

Variable	Cases (n=30)		Control (n=30)		P-value
	No.	%	No.	%	
Age (year)					
15–25	4	13.3	6	20.0	0.866
26–30	6	20.0	7	23.3	
31–40	15	50.0	13	43.3	
>40	5	16.7	4	13.3	
Mean (SD*)	34.1±8.3		33.4±7.4		0.717
Gender					
Male	7	23.3	9	30.0	0.569
Female	23	76.7	21	70.0	
BMI category					
Normal	14	46.7	17	56.7	0.69
Overweight	10	33.3	9	30.0	
Obese	6	20.0	4	13.3	
Mean±SD	25.8±3.7		25.1±4.1		0.533

*SD: Standard deviation of mean. BMI: Body mass index

in general [Table 5]. ROC curve analysis revealed that C2, C7 and C2–C7 average CSA were good predictors of RRMS [Figure 3a], and SPMS [Figure 3b], but failed to predict CIS type [Figure 3c].

DISCUSSION

Several studies have studied the significance of spinal cord atrophy as one of the outcomes in clinical trials and as a biomarker of disability progression and it could be an initial sign of MS, developing over time, and specified neuroaxonal loss.^[14,15]

In the current study, the mean CSA of the cervical cord in patients with MS was significantly lower than in the control group. The study found lower values of cervical cord CSA in patients with higher EDSS, so that when the patient is presented with significant disability. We may expect more spinal cord atrophy. This was in consistent with other studies,^[16,17] and especially in PPMS subtype.^[18]

Patients with SPMS in our study were found to have more severe cervical spinal cord atrophy than age-matched RRMS and CIS cases, proposing that cervical spinal cord atrophy could be a potential discriminator between RRMS without progression and patients with CIS and those with early progressive disease. According to these results, any CSA measured at C2, C7 or C2–C7 average can be used as a predictor of RRMS and SPMS, so that this measurement may be a possible imaging marker in the future. The degree of cord atrophy in the RRMS group was more than in the CIS group but less than in the SPMS group, suggesting that early obvious cervical cord atrophy could herald a progressive MS type.

Drugs that delay or prevent atrophy can decrease the progression of disability in the long term. Clinical trials with subcutaneous and intramuscular interferon β -1a,

Table 2: Comparison of C2–C7 CSA by levels between the studied groups.

Level	Cases (n=30)	Control (n=30)	P-value
	Mean±SD*	Mean±SD	
Cross-sectional area of C2 (mm ²)	67.7±9.4	81.3±4.6	<0.001
Cross-sectional area of C7 (mm ²)	64.4±9.9	81.6±3.8	<0.001
Average cross-sectional area C2–C7 (mm ²)	68.0±9.1	81.9±3.9	<0.001

*SD: Standard deviation of the mean. CSA: Cross-sectional area

Table 3: Comparison of the mean cross-sectional area according to the type of MS.

	Type of MS			
	RRMS (n=22)		SPMS (n=4)	CIS (n=4)
	Mean±SD*	Mean±SD	Mean±SD	P-value
Cross-sectional area of C2 (mm ²)	68.9±6.7	51.8±3.9	76.8±7.9	<0.001
Cross-sectional area of C7 (mm ²)	64.0±7.6	52.8±4.8	78.0±9.3	<0.001
Average cross-sectional area of C2–C7 (mm ²)	68.8±6.1	53.3±3.8	78.2±9.4	<0.001

*SD: Standard deviation of the mean. MS: Multiple sclerosis, SPMS: Secondary progressive multiple sclerosis, RRMS: Relapsing-remitting multiple sclerosis

Table 4: Bivariate correlation between CSA at different levels with spinal cord lesions, type of medications, and EDSS results.

Parameter	Mean *CSA of C2		Mean CSA of C7		Average CSA C2–C7	
	**R	P-value	R	P-value	R	P-value
Spinal cord lesion	0.039	0.840	−0.164	0.395	0.39	0.840
Medications	0.107	0.574	0.059	0.763	0.110	0.564
***EDSS	−0.794	<0.001	−0.718	<0.001	−0.771	<0.001
Duration of disease (years)	−0.563	0.001	−0.623	<0.001	0.633	<0.001

*CSA: Cross-sectional area, **Correlation coefficient, ***EDSS: Extended disability status-scale

Table 5: Comparison of area under the ROC curve produced by each CSA on ROC analysis for prediction of MS type.

Type	Area under the ROC curve for each level			P-value
	C2	C7	C2–C7	
RRMS	1.000	0.900	1.000	0.921
SPMS	0.845	0.995	0.850	0.681
CIS	0.592	0.503	0.589	0.784
Overall	0.812	0.799	0.813	0.741

P≤0.05 is significant. SPMS: Secondary progressive multiple sclerosis, ROC: Receiver operating characteristics, RRMS: Relapsing-remitting multiple sclerosis, CSA: Cross-sectional area, MS: Multiple sclerosis

subcutaneous interferon β-1b^[19] and glatiramer acetate have shown that these immunomodulatory drugs reduce the inflammatory response of the disease, including clinical relapses and lesion burden^[20] However, in the current study, the type of drug treatment showed no significant association with spinal cord CSA.

Previous studies suggested that patients with longer duration of progressive MS had smaller CSA of cervical cord compared with healthy individuals or patients with

RRMS,^[21,22] which was similar to the finding of our study. However, we did not assess the rate of spinal cord atrophy before the beginning of progressive MS and we think longitudinal studies in RRMS could address whether a prior increase in the rate of cervical cord atrophy during the RRMS phase differentiated the patients who may progress to SPMS. Although there are several technical challenges in multicenter implementation, this study may help clinicians to pay more attention to the advantage of monitoring symptom-free spinal cord involvement as a sign of potentially progressive MS onset.

Although the assessment of CSA at upper cervical cord segments is very reproducible, it does not give a total estimate of the whole cervical spinal cord damage.^[12,23] It was found that the CSA at the C7 level had the highest difference among the SPMS and RRMS patients,^[15] However, the present study found no difference between C2, C7 and other cervical levels of CSA among MS types, so we can measure at any cervical level with preferable measurement on C2 due to the technical possibility of imaging, easier spinal cord segmentation and the less potential for motion artifacts.^[21,24,25]

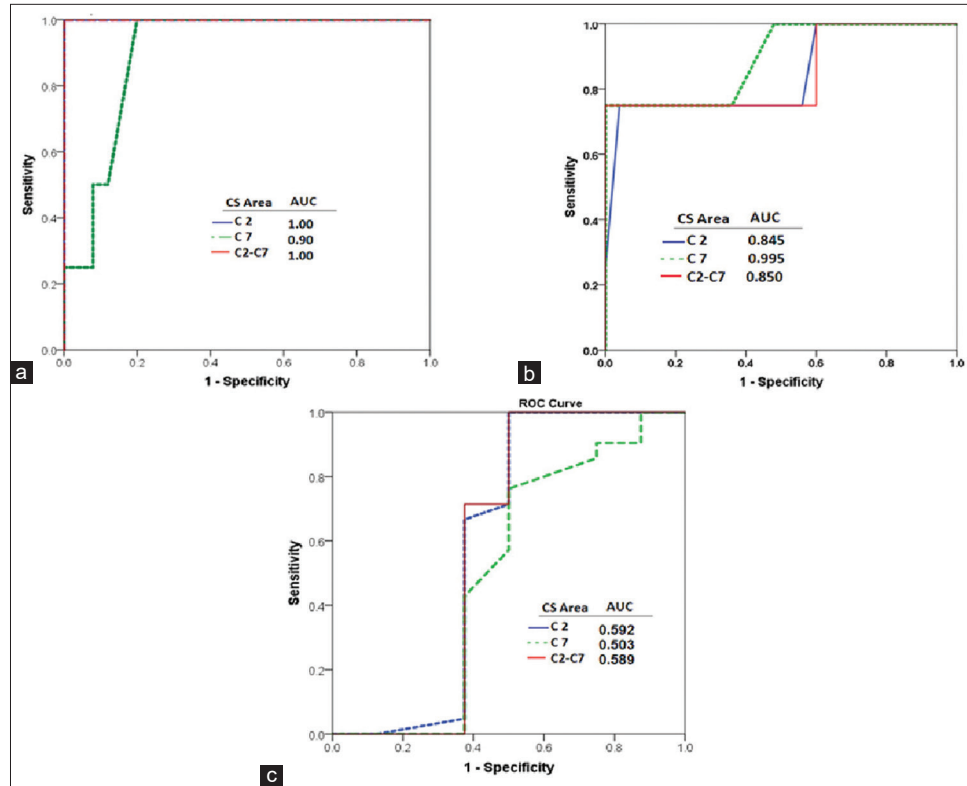


Figure 3: Receiver operating characteristics curve analysis for the validity of cross-sectional area in prediction of relapsing-remitting multiple sclerosis (MS) (a), secondary progressive MS (b) and clinically isolated syndrome types of MS (c).

There is a controversy on the relationship between focal cord lesions and cord atrophy. Cord atrophy is related to a number of cervical spinal cord lesions as reported in a study by Daams *et al.* 2014,^[24] While Rocca *et al.* indicated the independence of the occurrence of cervical lesions.^[26] In our study, the cervical spinal cord lesions were not significantly correlated with CSA, possibly due to a small sample size in comparison with previous studies.^[24,27,28] Generally, earlier pathological studies have confirmed that discrete lesions play a minimal role in local atrophy^[29,30] and investigators have concluded that accumulative mechanisms (Wallerian degeneration) more than focal demyelination could be the main reason for cord atrophy in progressive MS.^[31,32] Moreover, while this spinal cord atrophy happen inside MS plaque, the extended tissue abnormalities are also existing in the usual appearing spinal cord,^[33] and this observation may clarify why cord atrophy happens independent of spinal-cord lesions.

CONCLUSION

In conclusion, the mean cervical spinal cord CSA was significantly lower in patients with MS than in the control group. Among patients with MS, cervical cord CSA was lesser in progressive type than RRMS and CIS types. Patients with longer duration and those with higher disability scores

(EDSS) tend to have lesser mean cervical cord CSA. This study suggests that cervical spinal cord atrophy can be used as a possible prognostic indicator to differentiate between early progressive disease and those with RRMS without progression and patients with CIS.

Furthermore, our recommendation is to conduct a cohort-based study with longer time follow-up and an increase in sample size to evaluate the temporal evolution of cervical atrophy.

Authors contributions

Haider N. AL-Tameemi: Concept and design of the study, performed the clinical evaluation and data collection, performed data analysis, interpretation of data, initial writing of the manuscript, and revised the final draft of the manuscript. Hayder K. Hassoun: Concept and design of the study, performed the clinical evaluation and data collection, acquisition of data, data analysis, and critical revising. Data collection, performed the clinical evaluation, and revised the final draft of the manuscript. Israa Qasim Mohammed: Performed the clinical evaluation and data collection, interpretation, and analyzed the data, participating in writing the initial draft of the manuscript. Performed the clinical evaluation and data collection and revised the final draft of the

manuscript, revised the final draft of the manuscript. Zuhair Allebban: Reviewed the literature, performed the laboratory testing, collected the laboratory data, critical writing of the manuscript, and revised the final draft of the manuscript.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

The authors have no conflict of interest.

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APPENDIX

Patient order: gender: age: Residency:

Bodyweight: height: BMI:

Medical history:

Type of MS:

Relapsing-remitting MS

- Secondary progressive MS
- Primary progressive MS
- Clinically isolated MS
- Radiologically isolated MS

MS associated comorbidities:

EDSS:

Treatment of MS:

Radiological Findings in cervical cord MRI:

Number of lesions location Enhancement:

Cervical cord length from C2-C7 (mm):

Cervical cord cross-sectional area (mm²):

C2	<input style="width: 60px; height: 20px;" type="text"/>
C3	<input style="width: 60px; height: 20px;" type="text"/>
C4	<input style="width: 60px; height: 20px;" type="text"/>
C5	<input style="width: 60px; height: 20px;" type="text"/>
C6	<input style="width: 60px; height: 20px;" type="text"/>
C7	<input style="width: 60px; height: 20px;" type="text"/>
Mean	<input style="width: 60px; height: 20px;" type="text"/>

Appendix 1: The data collection form.