LONGITUDINAL ASSESSMENT OF CERVICAL CORD ATROPHY ACROSS MS CLINICAL PHENOTYPES: A MULTICENTER STUDY

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INTRODUCTION and PURPOSE

The spinal cord is an eloquent site of the CNS that is frequently involved in multiple sclerosis (MS). Atrophy of the spinal cord (especially in the cervical segment) is a well-known feature of MS, which is more severe and correlates with disability in the progressive forms of the disease [1]. The relative small size of the spinal cord makes an adequate quantification of cord area a demanding task, especially in a longitudinal, multicenter context. Previous multicenter studies showed global atrophy of the cervical cord of MS patients, with a differential involvement across disease clinical phenotypes. Cord atrophy was more pronounced in progressive than relapsing MS phenotypes [2, 3] and correlated with clinical disability [2]. Large, multicenter studies assessing cord atrophy over time are still scanty. One preliminary study assessed the upper portion of the cervical cord over two years of follow-up, and found the highest rate of atrophy in progressive MS patients and in patients with disability progression [4]. A semi-automatic method based on active surface (AS) has been developed, allowing the segmentation of large portions of the spinal cord [5]. Such a method was reliable and reproducible in detecting changes of cord atrophy over time [6].

Aims of this multicenter study were:
- to characterize baseline cervical cord atrophy in MS compared with healthy controls and among the main MS clinical phenotypes;
- to evaluate the modification of cervical cord cross-sectional area (CSA) over one-year of follow-up in MS compared with healthy controls and in the main MS clinical phenotypes;
- to assess the effect of cervical cord atrophy development on disability progression.

METHODS

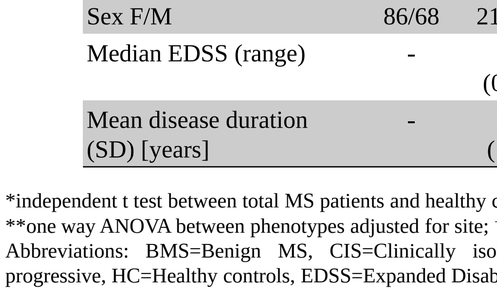
Subjects. The study design includes two MRI visits; the baseline scan has been already performed at all study sites, while follow-up visits (scheduled one year after baseline) are still ongoing. Patients were enrolled at eight European centers part of the MAGNIMS network (**www.magnims.eu**):
(a) VU Medical Centre, Amsterdam, The Netherlands. Baseline: 91 MS patients and 47 healthy controls (HC); (b) Universitari Vall d'Hebron, Barcelona, Spain. Baseline: 28 MS patients and 10 HC; follow-up: 18 MS patients and 7 HC; (c) St. Josef Hospital Ruhr University, Bochum, Germany. Baseline: 13 MS patients and 6 HC; follow-up: 4 MS patients; (d) UCL Institute of Neurology, London, UK. Baseline: 25 MS patients and 10 HC; follow-up: 22 MS patients and 10 HC; (e) Universitaetmedizin Mannheim, University of Heidelberg, Germany. Baseline: 19 MS patients and 6 HC; (f) San Raffaele Scientific Institute Milan, Italy. Baseline: 140 MS patients and 47 HC; follow-up: 34 MS patients and 16 HC; (g) Second University of Naples, Naples, Italy. Baseline: 22 MS patients and 11 HC; follow-up: 13 MS patients and 5 HC; (h) University of Oxford Hospitals Trust, Oxford, UK. Baseline: 15 MS patients and 17 HC; follow-up: 11 MS patients and 9 HC.
Table 1 summarizes the main baseline demographic and clinical characteristics of the subjects enrolled.

	HC	All MS	CIS	RRMS	SPMS	BMS	PPMS	p*	p**
Number	154	353	36	145	89	45	38		
Mean age (SD) [years]	39.9 (13.3)	46.5 (12.6)	34.1 (8.6)	41.2 (11.7)	54.5 (8.0)	49.2 (9.3)	56.3 (11.0)	0.001	0.001
Sex F/M	86/68	216/137	21/15	99/46	53/36	29/16	14/24	0.26+	0.012++
Median EDSS (range)	-	3.5 (0-8.0)	1.5 (0-4.0)	2.5 (0-7.5)	6.0 (2.5-8.0)	2.5 (1.0-3.0)	6.0 (3.0-8.0)		0.001
Mean disease duration (SD) [years]	-	15.8 (10.0)	1.05 (0.9)	10.3 (7.8)	22.2 (9.3)	20.7 (4.9)	16.2 (9.7)		0.001

*independent t test between total MS patients and healthy controls, adjusted for site; +Mann-Whitney U test.
**one way ANOVA between phenotypes adjusted for site; ++Kruskall and Wallis test.
Abbreviations: BMS=Benign MS, CIS=Clinically isolated syndrome, RR=relapsing-remitting, PP=Primary progressive, SP=Secondary progressive, HC=Healthy controls, EDSS=Expanded Disability Status Scale.

Clinical evaluation. Rating of EDSS score at baseline and follow-up. Clinical progression at follow-up was defined according to baseline EDSS: if a patient had an EDSS score increase ≥1.0 when baseline EDSS was <6.0, or an EDSS score increase ≥0.5 when baseline EDSS was ≥6.0.
MRI Acquisition. Cervical cord and brain MRI scans were obtained using 3.0 Tesla scanners (Barcelona: Siemens Trio; Mannheim: Siemens Skyra; Oxford: Siemens Prisma; Bochum, London and Milan: Philips Achieva; Amsterdam and Naples: GE Signa HDxt).
The Following cervical cord sequences were obtained from all study subjects:
1) dual-echo turbo-spin-echo (TSE) (Amsterdam, London, Mannheim, Oxford);
2) sagittal short tau inversion recovery (STIR) (Barcelona, Bochum, Milan, Naples);
3) sagittal 3D T1-weighted magnetization-prepared rapid acquisition gradient echo (MP-RAGE) (all sites).
In addition, brain dual-echo or fluid-attenuated inversion recovery (FLAIR) sequences were acquired from all study subjects for T2 lesion quantification.
MRI Analysis.
Lesion count: hyperintense lesions in the cervical cord were counted on dual-echo or STIR scans (Jim 6.0 software).
Cervical cord atrophy quantification:
•reformatting of 3D T1-weighted image into the axial plane and resampling to 1x1x1 mm^3 of spatial resolution.
•Cord cross-sectional area (CSA) outlined between C1 (upper extremity of the odontoid of the epistropheus) and C7 (inferior border of C7/T1 disk) using the AS method, both at baseline and at follow-up.
•Average cord CSA = total cord volume/cord length [5] (**Figure 1**).

Figure 1. Cord outlines estimated with the AS method.



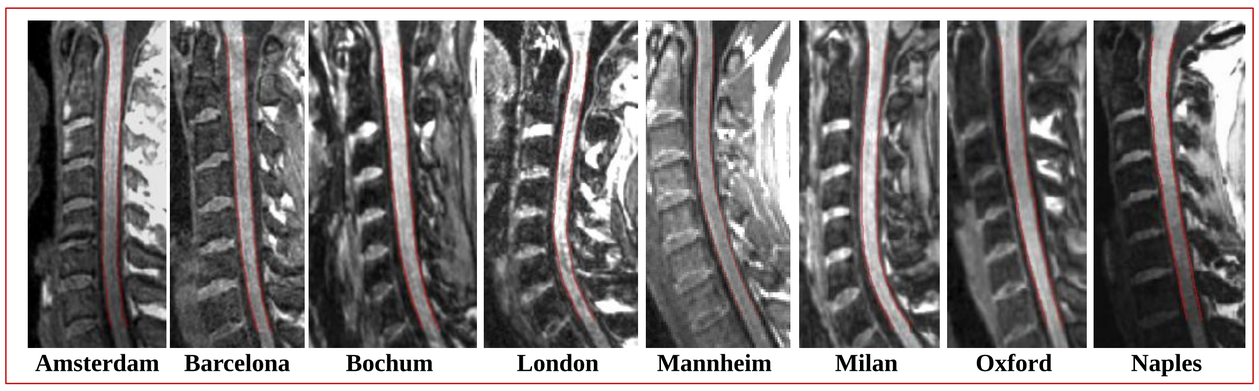
Horsfield et al., 2010 [5]

Statistical Analysis. Demographic, clinical and conventional MRI measures compared between groups using ANOVA models and Kruskall and Wallis tests, as appropriate.
• Baseline between-group comparison of cord CSA: independent sample t test or ANOVA models adjusted for site, age and sex.
• Post hoc comparisons chosen *a priori* based on the natural history of disease: HC *vs* CIS, HC *vs* PPMS, CIS *vs* RRMS, RRMS *vs* SPMS, RRMS *vs* BMS, SPMS *vs* BMS, CIS *vs* PPMS, SPMS *vs* PPMS.
• Longitudinal changes of cord CSA: t test for paired samples (within-group comparisons); repeated-measures ANOVA models adjusted for site, age, and sex (between-group comparisons).

RESULTS

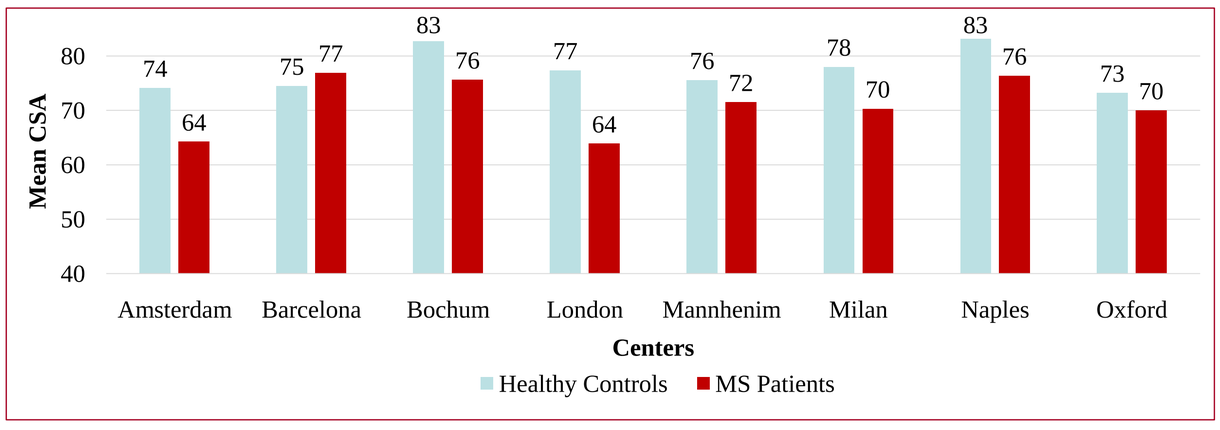
The median number of hyperintense cord lesions in MS patients was 1 (range= 0-10) and the average brain T2 lesion volume was = 12.6 ml (SD=14.1 ml).
Eight HC and 16 MS patients were excluded from the analysis because of inadequate cord images (mainly related to movement artefacts or positioning problems).
In all remaining study subjects, the AS method produced reliable estimates of cervical cord outlines, also when T1 hypointense lesions were present (**Figure 2**).

Figure 2. **Illustrative examples of cord contours outlined on cervical cord 3D T1-weighted scan at each study site.**



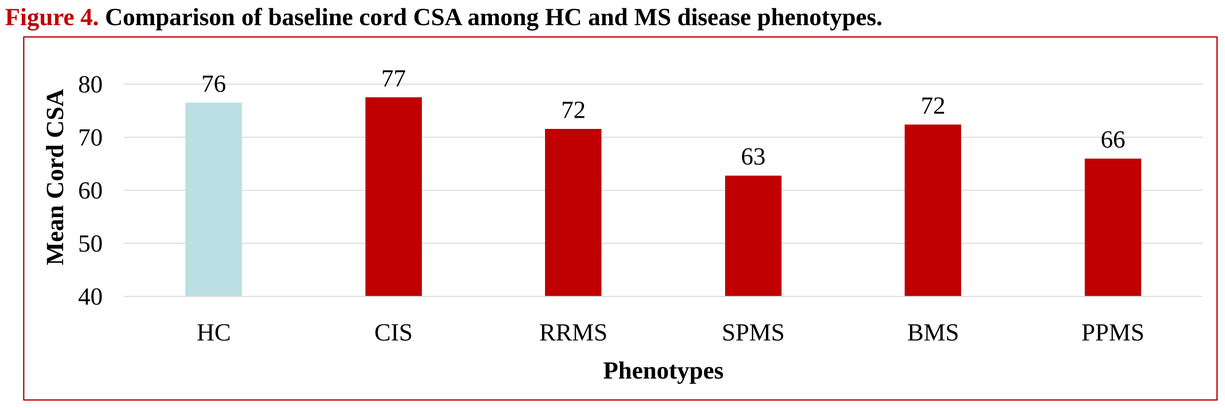
Baseline analysis of cervical cord atrophy
Average values of cord CSA in the HC and MS patients acquired at the different sites are reported in **Figure 3**.
•Significant heterogeneity of cord CSA was found among study sites (p<0.001);
•A significant decrease of cord CSA was found in HC *vs* MS (average CSA in HC=76.46 mm^2, SD=7.39 mm^2; MS patients=69.42 mm^2, SD=9.57 mm^2; p<0.001).

Figure 3. Baseline average cervical cord CSA in HC and MS patients, according to site.



•At baseline, there was a significant heterogeneity of cord CSA also among phenotypes, after correcting for age, sex and acquisition site (p<0.001, **Figure 4**). In particular:
- no difference of cord CSA was found between CIS and HC (p=0.4), or PPMS *vs* SPMS (p=0.4);
- cord CSA was significantly lower in PPMS *vs* HC and CIS (p<0.001), RRMS *vs* CIS (p<0.001) and SPMS *vs* RRMS (p<0.001) (**Figure 4**).

Figure 4. Comparison of baseline cord CSA among HC and MS disease phenotypes.



Longitudinal changes of cervical cord atrophy
Table 2 shows the results of longitudinal analysis of cervical cord atrophy:
•Cord CSA measurements remained stable in HC;
•A significant decrease of cord CSA over time was detected in MS patients *vs* HC (time *x* group effect: p=0.02);
•When looking at disease phenotypes, separately, a significant cord tissue loss could be detected in RRMS and PPMS patients only (**Table 2**);
•Clinically worsened MS patients had a significant reduction of CSA compared to clinically stable ones (time *x* group effect: p=0.03).

Table 2. Results of longitudinal analysis of cord CSA.

	Mean CSA Baseline (SD)	Mean CSA Follow-up (SD)	Mean CSA percentage change	p*	p**	p***	p§
HC	77.1 (6.5)	77.1 (6.4)	+0.01 (1.66)	0.9	0.08	0.02	0.02
All MS	72.2 (9.5)	71.4 (9.7)	-1.12 (2.71)	0.001			
CIS	77.1 (1.2)	77.0 (7.1)	-0.06 (2.11)	0.8			
RRMS	73.5 (8.1)	72.3 (8.1)	-1.51 (2.83)	0.001			
SPMS	63.0 (8.8)	62.4 (8.9)	-1.03 (2.54)	0.1	0.17	0.001	0.10
BMS	83.5 (7.0)	83.8 (7.4)	+0.36 (1.29)	0.5			
PPMS	67.7 (9.3)	66.4 (9.3)	-1.97 (3.29)	0.05			
No EDSS worsening	70.7 (9.6)	70.2 (9.7)	-0.67 (2.81)	0.06	0.40	0.50	0.03
EDSS worsening	70.1 (8.3)	68.6 (8.3)	-2.17 (2.03)	0.001			

p*= paired sample t test; Repeated measure ANOVA: **main effect of time, **main effect of group, §= time *x* group interaction.

CONCLUSIONS

• The application of the AS method in a multicenter context allowed a reliable measurement of whole cervical cord atrophy at high field, both cross-sectionally and longitudinally. As previously demonstrated in a single center study [6], the AS provided very consistent values of cord CSA in HC over time, thus ensuring reliability of cord measurements. In line with previous investigations [7], AS cord outlines were not influenced by the presence of T1 hypointense lesions.
• The baseline results confirm that cervical cord atrophy contributes to a better characterization of the clinical heterogeneity of MS. While CIS patients showed a trend towards an increased of cord CSA, possibly related to inflammation or edema-related cord expansion [8], cord tissue loss was significant in RRMS, and more severe in progressive than in relapsing MS phenotypes [2, 3]. Conversely, BMS patients showed a relative sparing of cervical cord tissue, which might contribute to explain their favorable disease course [2].
• The longitudinal analysis showed a significant decrease over time of cord CSA in RRMS and PPMS patients, as well as in patients with disability progression. This is in line with previous studies [4, 6] and confirms the clinical relevance of cord atrophy and its ability to explain clinical worsening.
• The completion of follow-up scans will allow us to further expand our analysis, with a more accurate investigation of the temporal trends of cord atrophy in the different phenotypes, the correlations between cord atrophy and clinical impairment (both in terms of global disability and impairment at specific functional systems), and the predictive value of cord atrophy on the subsequent clinical course.

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