Atrophy of the whole cervical cord differs among the major multiple sclerosis clinical phenotypes and is associated with disability: a multicenter study

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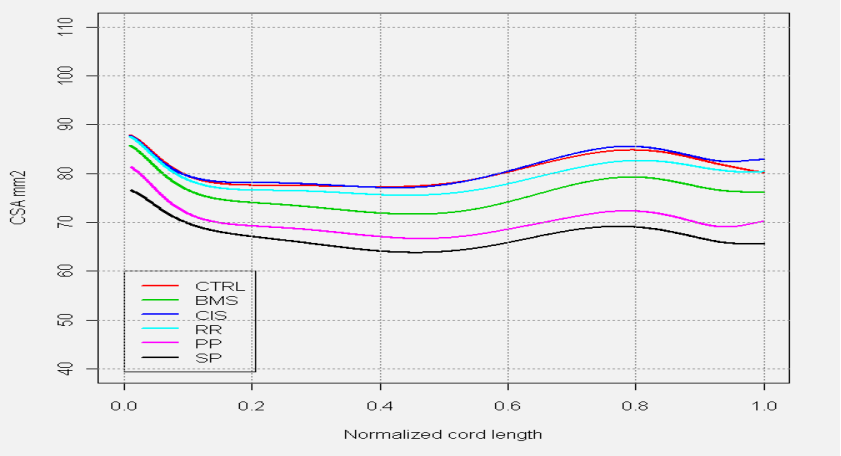
Introduction. An accurate and quantitative assessment of cervical cord damage may be useful for to improving our understanding of the factors leading to irreversible disability caused by demyelinating and neurodegenerative diseases. In multiple sclerosis (MS), magnetic resonance imaging (MRI) is the most sensitive technique for detecting changes in the integrity of tissue with the brain and the spinal cord. Some of the studies assessing the relationship between the extent of cord damage and clinical disability in MS patients found a correlation between atrophy of the cervical cord and disability. To quantify cervical cord atrophy, the previous studies measured the cross-sectional area at a single anatomical level (typically C2 or C5).

Objective. In this multi-center study, we applied a new semi-automatic method [1] which allows the segmentation of the entire cervical cord, to investigate the correlation between cervical cord atrophy and clinical disability in a large sample of MS patients, spanning the major clinical phenotypes, with a wide range of clinical disability.

Methods. Using 1.5 T scanners, dual-echo brain scans and both T2-weighted and 3D T1-weighted cervical cord scans were acquired from 143 healthy controls and 333 patients with MS or suspected MS in three European centers. Twenty patients had clinically isolated syndromes (CIS) suggestive of MS, 101 relapsing remitting (RR) MS, 79 secondary progressive (SP) MS, 58 benign (B) MS and 75 primary progressive (PP) MS. Disability was measured using the expanded disability status scale (EDSS). Brain T2 lesion volumes (LV) were quantified using the Jim software package. Using the same software throughout, cervical cord cross-sectional area (CSA) was measured by an active surface cord model, correcting for cranial cross-sectional area as normalization factor [1]. Between-group comparisons were performed using linear mixed-effects models. Since cervical cord length varies across patients, it was normalized dividing it by patient's neck length: the normalized cord length varies from 0 (most superior axial slice in which the odontoid process of the epistropheus [C2] was still just visible) to 1 (inferior border of C5). A non-parametric kernel estimator was used to obtain smoothing curves of CSA measured along the cervical cord. Pair-wise comparisons were made using a hierarchical linear model with repeated measurements and accounting for potential Center random effect.

Results. Significant between-group differences were found for brain T2LV ($p<0.0001$), number of cervical cord lesions ($p=0.009$) and CSA ($p<0.0001$). CSA was significantly lower in BMS *vs*. RRMS ($p=0.01$), SPMS *vs*. BMS ($p=0.006$), SPMS *vs*. PPMS ($p=0.03$) and PPMS *vs*. healthy controls ($p<0.001$). CSA measures were not different among centers. Figure 1 shows curves of mean CSA along the cervical cord in the different groups of the study.

In the whole group of patients, the only MRI variable showing a significant interaction with EDSS across groups was the CSA ($p<0.0001$). This association showed a differential effect among disease clinical phenotypes: no association in either CIS patients (beta=-0.0297, $p=0.37$) or in BMS (beta=-0.009, $p=0.48$), significant association in RRMS (beta=-0.0491, $p=0.0003$), SPMS (beta=-0.032, $p=0.008$) and PPMS (beta=-0.0348, $p=0.02$).



Normalized length along cord

Figure 1. Smoothed curves of CSA measured along the cervical cord in the different study groups.The curves of RRMS, PPMS and SPMS patients were separated for the entire length of the cervical cord.

Conclusions. The quantification of atrophy of the entire cervical cord provides relevant and useful markers to characterize clinical heterogeneity of MS patients. Our results confirm that the severity of pathology in the cervical cord is one of the factors associated to the accumulation of irreversible disability in MS. The stability of these measures among different centers supports their use as surrogate markers to monitor disease progression in multicenter trials.

References. [1] Horsfield MA, et al. Neuroimage 2010; 50:446-455.