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Spinal cord atrophy in multiple sclerosis and relationship with disability across clinical phenotypes

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Abstract
Background: Several studies have shown a relationship between spinal cord atrophy and clinical disability in patients with multiple sclerosis (MS).
Objectives: We examined the correlation between cervical cord cross-sectional area at the C2 vertebral level (CSA-C2) and the expanded disability status scale (EDSS) in patients with relapsing-remitting and progressive forms of MS. The latter included both secondary and primary progressive MS patients.
Methods: A total of 150 patients with MS were recruited from the Wayne State University MS clinic. Ninety-three had relapsing-remitting MS and 57 patients had progressive MS. MRI scan of the cervical cord was obtained for each patient. Correlation studies and multivariate regression analysis was performed, blinded to clinical status.
Results: The mean age was 41.3 year old, 64.6% were women, mean disease duration was 11.2 years, CSA-C2 was 80.2 mm^2 and mean EDSS was 3.8. There was significant correlation between CSA-C2 and EDSS (r −0.75, $p<0.0001$). Sub-group analysis showed CSA-C2 was 68.6 mm^2 and 87.3 mm^2 in the progressive and relapsing-remitting groups, respectively ($p<0.0001$). Multivariable regression showed that CSA-C2 was a significant predictor of disability independent of disease duration, and phenotype.

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Conclusions: Our study demonstrates that CSA-C2 has a strong correlation with clinical disability in both RRMS and progressive MS. Greater spinal cord atrophy was seen in patients with progressive than relapsing-remitting MS. CSA-C2, disease duration, and phenotype are independent predictors of disability.

1. Introduction

Multiple sclerosis (MS) is one of the leading causes of disability in young adults (Noseworthy et al., 2000). Involvement of the spinal cord in MS is considered to be a major reason of clinical disability (Evangelou et al., 2005; Kidd et al., 1993). Clinical manifestations of spinal cord pathology often include sensory symptoms, lower extremity weakness, ambulation difficulties and sphincter dysfunction among other symptoms, leading to disability. Loss of independent ambulation and activities of daily living remain a significant concern for all MS patients (Yamout et al., 2013).

Focal structural abnormalities in the spinal cord can significantly affect the functional outcome of patients. However, several reports have demonstrated ambiguity in the relationship between focal spinal cord lesions and disability (Kidd et al., 1993; Lukas et al., 2013; Weier et al., 2012). In contrast, volumetric studies of spinal cord in MS have shown strong correlation with clinical disability (Kidd et al., 1996; Zivadinov et al., 2008; Losseff et al., 1996; Bonati et al., 2011). Furthermore, spinal cord atrophy has been shown to have better correlation with disability than with focal spinal cord lesion load (Kidd et al., 1993; Lukas et al., 2013; Oh et al., 2013; Cohen et al., 2011). Similarly, quantitative MRI studies of the spinal cord atrophy in MS using advanced imaging techniques, capture clinically relevant microstructural changes and demonstrate a strong relationship with disability (Oh et al., 2013). The correlation between spinal cord atrophy and disability, however, has not been explored in the context of disease phenotype.

The aim of this study was to examine how the clinical phenotype in patients with MS affects the correlation between disability and the upper cervical cord area by measuring the cervical cord cross-sectional area at the C2 vertebral level (CSA-C2).

2. Patient and methods

2.1. Study participants

This was a cross-sectional study in which patients with clinically definite MS (CDMS) from our MS Clinic were enrolled. All patients had confirmed CDMS using established diagnostic criteria (Polman et al., 2005) and were clinically well characterized. Detailed demographics and clinical features including expanded disability status scale (EDSS) were obtained for all patients. For the purpose of this study, patients were divided into two categories: relapsing-remitting and progressive MS. The latter included both primary and secondary progressive forms of MS. Phenotype classification of each patient was obtained from the medical charts. All patients underwent cervical spinal cord imaging as described below. Whenever a patient was administered corticosteroids, the MRI scan was deferred for at least 6 weeks until after the administration of the corticosteroids. The local IRB approved the study and written informed consent was obtained from every patient.

2.2. Magnetic resonance imaging

The MRI scan of the cervical spine without contrast was performed on a 3.0 T Siemens Verio System (Erlangen, Germany). All subjects underwent imaging of the spinal cord with an axial MPRage 3D-T1W image of the cervical cord (TR 1680; TE 3.52; FA 9; in plane resolution $0.8 \times 0.8\ mm^2$; matrix 384×384; 1 mm slice thickness with 176 total number of slices). From this, five contiguous 3 mm pseudo axial slices were reformatted using the center of the C2/C3 intra-vertebral disc as a caudal landmark, with the slices perpendicular to the spinal cord. The images were transferred to a Sun workstation (Sun Microsystems Inc., Mountain View, CA, USA) and uniformity corrected. With the use of an automated program, the mean CSA-C2 was calculated from the axial cervical cord images using a previously described technique by Losseff et al. (1996). All image analyses were conducted blinded to the clinical status of the patient. Spinal cord lesions were not counted.

2.3. Statistical analysis

Statistical analyses were performed using the SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Comparisons of the clinical and demographic data between the disease subtypes were conducted by using the Mann–Whitney *U* test or Pearson chi-squared test. Spearman rank correlation analysis was used to investigate associations between EDSS and CSA-C2 in all patients. Sub-analysis was also performed to examine this relationship in the relapsing-remitting and progressive MS groups, separately. Because of the exploratory nature of this study, adjustment for multiple comparisons was not performed. Multiple regression analysis was performed between EDSS scores as the dependent variable and CSA-C2, age, disease duration, gender, and phenotype (RRMS coded as 1, progressive MS coded as 2) as the predictor variables. We used the widely used semi-partial correlation coefficient (SP-r) (Kleinbaum et al., 2013) to report the unique contribution of each predictor variable to the total variance of the dependent variable. Statistical significance was defined as $p < 0.05$.