

Primary progressive multiple sclerosis spinal cord volume predicts clinical motor scores

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Introduction: Spinal cord involvement is known to play a large role in disability in multiple sclerosis (MS); changes in the spinal cord are more likely to impact on disability than changes in the brain because the spinal cord contains a greater concentration of tracts (corticospinal) that impact on motor function. However, it is often understudied due to difficulties in spinal cord imaging. This is a particular issue in primary progressive MS (PPMS), which is considered to have greater spinal cord involvement than the more common relapsing remitting MS (RRMS)¹. Spinal cord atrophy (quantitatively defined by MR imaging) has been proposed as a marker of disease severity, degree of neurodegeneration, and neuroprotective therapeutic effects². Correlations between cervical cord volume (CCV) and Expanded Disability Status Scale (EDSS) have been demonstrated³⁻⁶. Significant reductions in CCV have also been demonstrated over one and two years in PPMS with no change in healthy controls⁷, implying that this technique may not only be used to help quantify progressive cord changes in the cervical region of the spinal cord as a result of evolving MS, but also used to monitor neuroprotective therapeutic effects in PPMS patients. Unfortunately, while the EDSS is the most commonly used measure of disability in MS, it is a non-linear measure with limited utility. An alternative is the MS functional composite (MSFC) score⁸, which consists of measures of upper limb motor function (nine-hole peg test (9HPT)), lower limb motor function (timed 25-foot walk (25FTW)) and cognitive function (paced auditory serial addition test (PASAT)). **The goal of this study was to determine whether PPMS CCV is related to the MSFC score, and if so, which of its component tests is the most affected by cord atrophy.**

Methods: A sagittal T₁-weighted SPGR image (pixel size 0.78x0.78x1mm, TE/TR=2.2/4.9ms, flip angle=18°) was collected for 15 PPMS patients (mean age 52y (range: 41-67); median EDSS 5.0 (range: 2.5-6.5)) and 11 healthy controls (mean age 49y (range: 37-64)). The CCV averages were obtained by manually marking the bottom corner of the C2 vertebra sagittally and then segmenting the spine axially (using in-house software) from the 8th slice inferior to the landmark up to the 4th superior slice. The average spine area was calculated across the volume taking into account the axis of rotation and partial volume. The PPMS CCV measurements were compared to the MSFC and its component scores, EDSS, disease duration, age and the control CCV measurements, which were also compared to age. Group comparisons were made using the Mann-Whitney U-test, and relationships between parameters were assessed using Spearman's rank correlation coefficient (R).

Results: The CCV in the PPMS patient group was found to be significantly lower than that of the control group (**p=0.0001**). CCV was found to correlate significantly with 25FTW (**p=0.04**, R=-0.5) (see Figure 1). None of the other clinical scores showed significant correlations with CCV (MSFC (p=0.09, R=0.5), 9HPT (p=0.7, R=0.1), PASAT (p=0.6, R=0.2), EDSS (p=0.08, R=-0.5), disease duration (p=0.7, R=-0.04)). There was a significant relationship between decreasing CCV and increasing age in PPMS (**p=0.01**, R=-0.6) (see Figure 2), which was not found in controls (p=1, R=-0.1).

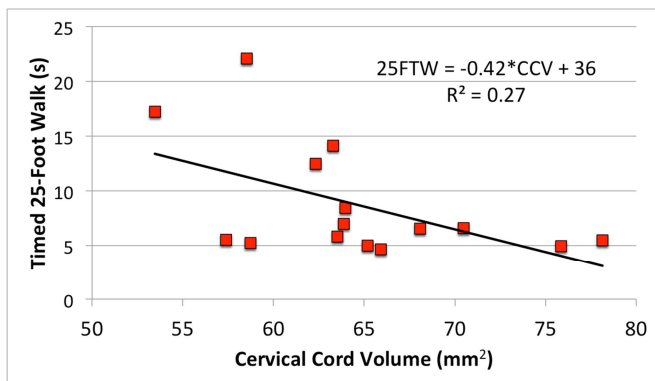


Figure 1: Time to complete a 25-Foot walk was significantly correlated with reduced cervical cord volume.

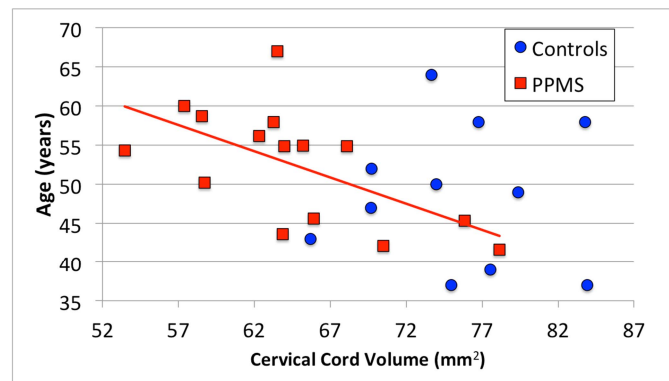


Figure 2: Increased age in PPMS subjects correlated with reduced cervical cord volume; this did not hold in controls.

Discussion and Conclusions: Contrary to previous literature, the correlation between CCV and EDSS was not found to be significant in this cohort although there was a strong trend. Not reaching significance could be a reflection of the small sample size, the small range of values in this particular group, or the restriction to the primary progressive phenotype. The correlation between age and CCV in PPMS that was lacking in controls could reflect a difference in susceptibility to damage over time in PPMS. As CCV did not correlate with disease duration, it is unlikely that disease duration drove the correlation between age and CCV; however, it is difficult to determine the exact onset of disease and there could be variation in diagnosis. The only component of the MSFC score to correlate with CCV was the 25FTW, which highlights the relationship between lower limb motor disability and CCV. Finding the sole significant correlation between CCV and the most motor-related clinical measure supports the utility of quantitative measurement of spinal cord volume/atrophy as a marker of disease severity.

References: 1. Bieniek et al. *J Neurol Neurosurg PS*. 2006;77:1036. 2. Klein et al. *Am J Neuroradiol*. 2011;32:1138. 3. et al. *J Neuroimaging*. 2011;22:122. 4. Nijeholt et al. *Brain*. 1998;121:687. 5. Liu et al. *J Neurol Neurosurg Psychiatry*. 1999;66:323. 6. Losseff et al. *Brain*. 1996;119:701. 7. Laule et al. *Mult Scler*. 2010;16(6):670. 8. Rudick et al. *Mult Scler*. 2002;8:359.