Volumetric cervical spinal cord atrophy differs between younger and older onset relapsing-remitting multiple sclerosis (RRMS) and correlates with disability

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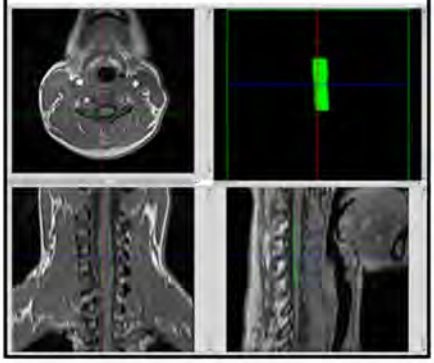
INTRODUCTION Multiple Sclerosis (MS) is a chronic degenerative disease of the CNS, characterized by inflammation, demyelination, and axonal loss. Clinical diagnosis categorizes patients into one of three sub-types: relapsing-remitting (RRMS), primary- or secondary-progressive (PPMS, SPMS). Magnetic resonance imaging (MRI) has been used to study the spinal cord in MS, but many studies have failed to show a relationship between spinal lesion load and disability, and there are mixed results relating to atrophy [1]. Longitudinal studies of people with MS have determined a rate of atrophy around 1-2% per year in the upper cervical spinal cord [2]. No studies, however, have explored differences in cervical spine (c-spine) atrophy using age of onset as primary criteria, and most studies use a single short segment of the spinal cord, often the C2-C3 interface owing to technical difficulties in imaging lower regions of the c-spine.

PURPOSE OF STUDY Primarily (i) to establish the extent of c-spine atrophy over the C2-C5 span with age as the primary difference as well as replicate and confirm (ii) the correlation of c-spine atrophy and disability measures in RRMS patients using MRI.

METHODS A total of 162 RRMS patients were involved in this study, sub-divided into two age groups: young (n=86, 69F/17M, aged 31.4±3.9yrs) and older (n=76, 58F/18M, aged 45.2±5.5yrs). All MRI data was obtained using a Siemens 3T Verio scanner using a 12-channel phased array head coil and an 8-channel neck coil. T1-weighted axial 3D MPRAGE volumes were acquired with a 0.6x0.6x2mm resolution. Spinal masks were defined using Analyze 11.0 and an intensity-based approach similar to [1], spanning the c-spine from the top of C2 to the top of C5 (Figure 1). Analysis of variance (ANOVA) was used for group comparisons of age and clinical measures (EDSS, number of years of MS, number of relapses within the last year), and analysis of covariance (ANCOVA) facilitated comparison of the c-spine mean cross-sectional area (CSA) in the young and older MS patients whilst accounting for clinical covariates.

Figure 1: Sample C-spine mask



RESULTS There was a significant main effect of age (P<0.001), number of years of MS (young: 3.6±3.3yrs; older: 5.2±4.4yrs; P=0.009), and EDSS (young: 3.0±1.1; older: 4.0±1.5; P<0.001) between the young and older RRMS groups, but no variation in the number of relapses within the last year (P=0.128). Including the clinical measures as covariates in the ANCOVA, a significant main effect of group was observed for the measures of mean CSA (Figure 2): the older RRMS patients having significantly reduced mean CSA compared to the young group (young: 82.3±9.4; older: 78.5±8.0; P=0.007). The group difference in mean CSA of 3.8mm^2, spread over the 13.77 years of age change, and assuming a linear atrophy rate, predicts a reduction in c-spine mean CSA of 0.34% per year. Figure 3 shows that the correlation between c-spine atrophy and disability measures is fairly moderate but nevertheless significant (EDSS: R=-0.37, P<0.001; Number of years of MS: R=-0.38, P<0.001).

Figure 2: Group difference in mean CSA

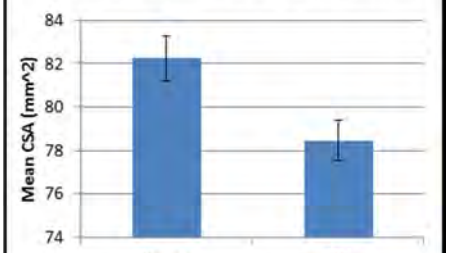
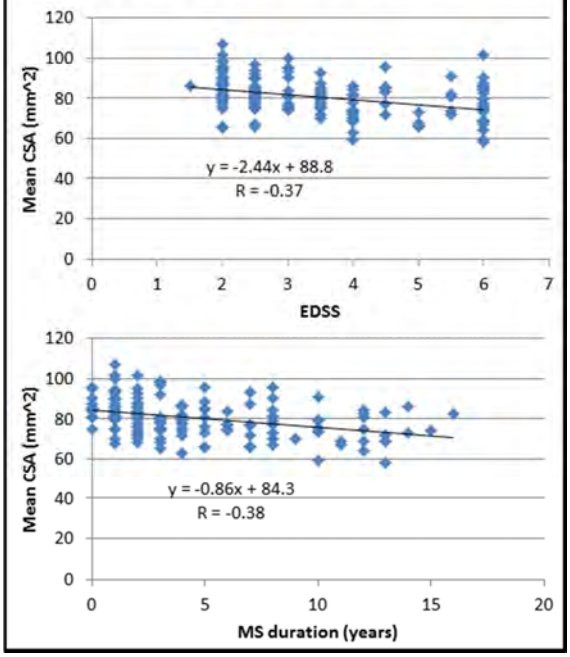


Figure 3: C-spine atrophy versus disability



DISCUSSION The cord CSA of a normal, healthy individual at C2 is approximately 80mm^2, so the values reported here for the young and older RRMS patients straddle this. Since the c-spine masks defined here include both WM and GM tissue, and WM is highly prone to inflammation, it is possible that WM inflammation in the young RRMS group (i.e., patients typically in the first 3 years of disease) is contributing to a relatively enlarged c-spine cord area. The cord atrophy rate of -0.34% per year before diagnosis of MS, approximated from this cross-sectional study, is much lower than the reduction of 1-2%/year previously reported after diagnosis of MS [2]. Correlation strengths with respect to disability scores are on a par with those reported for brain parenchymal fraction/volume in RRMS [1, 3], suggesting that both brain and c-spine atrophy measures established from MRI are suitable imaging biomarkers of neurological impairment and disability in the early years of RRMS.

References: [1] Losseff NA et al., Brain (1996), 119, 701-708 [2] Lukas C et al. J Neurol Neurosurg Psychiatry 2014;0:1–9 [3] Bermel et al., J Neurol Sci, vol. 208.