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Title of Presentation: Cortico-spinal tract integrity measured using transcranial magnetic stimulation and magnetic resonance imaging in neuromyelitis optica and multiple sclerosis.

Abstract

Background: Multiple sclerosis (MS) is a neurological disease affecting mainly the myelin sheath. Neuromyelitis optica (NMO) is a rare, aggressive disorder, characterized by damage to astrocytes that results in the development of optic nerve damage and spinal cord lesions. NMO usually presents with severe axonal degeneration while MS characteristically presents with focal demyelination.¹ Both diseases show similar clinical and radiological features but treatment and prognosis differ significantly. Thus, identification of biomarkers that are sensitive to differences in pathology between MS and NMO would have important clinical implications. Myelin water imaging is an advanced MRI technique that can distinguish between water compartments within a single voxel based on differences in T₂ relaxation.² Single pulse transcranial magnetic stimulation (TMS) is a non-invasive approach to index corticospinal excitability when applied over the primary motor cortex.³ Paired pulse TMS can evaluate intracortical excitability of inhibitory (ICI) and excitatory (ICF) pathways. In this study, we aimed to characterize differences in cortical excitability and myelin status of descending motor output pathways and evaluate the relationships between these measures in individuals with MS and NMO compared to healthy controls.

Method: Ten MS participants (mean age 42, EDSS range 0.0 - 6.0) were age and gender matched to ten NMO participants (mean age 43, EDSS range 2.0 - 6.0), and ten healthy controls (mean age 42). The MRI protocol was performed on a Philips 3.0T Achieva system and consisted of a 3DT₂ 32 echo GRASE sequence as well as a 3DT₁-weighted image for identification of the cortico-spinal tract (CST).⁴ The 3DT₂ echo sequence was fit via multiple exponential components and T₂ relaxation was calculated using non-negative least squares with an extended phase graph algorithm.^{5,6} Myelin water fraction (MWF) was computed as the ratio of area under the T₂ distribution from 10-40ms to the total area.² TMS was performed using a figure-of-eight coil attached to a Magstim 200 stimulator targeting the motor cortex.⁷ Motor evoked potentials (MEPs) were recorded through surface electromyography of the extensor carpi radialis bilaterally and peak-to-peak amplitudes were determined. For paired pulse assessment, a subthreshold conditioning pulse was delivered either 2 or 12ms prior to a suprathreshold test pulse to assess ICI and ICF respectively. Paired pulse delivered with a short interstimulus interval results in a decrease in amplitude (ICI) of conditioned MEP and a long interval results in an increase in amplitude (ICF) of conditioned MEP. Paired-pulse MEP amplitudes were normalized to unconditioned single-pulse MEP values (Paired-pulse ratio: conditioned MEP/unconditioned mean MEP).⁷

Results: The ANOVA showed a significant effect of CST MWF over the 3 groups ($p = 0.003$) and post-hoc analysis revealed that there was a significant decrease in MWF in NMO (mean = 0.165, SD = 0.02) participants compared to MS (mean = 0.193, SD = 0.02, $p = 0.01$) and healthy controls (mean = 0.199, SD = 0.02, $p = 0.003$). ICI differences across groups were significant (ANOVA $p = 0.009$) and post-hoc analysis indicated that individuals with MS (mean = 0.60, SD = 0.2) had significantly greater ICI compared to NMO (mean = 0.88, SD = 0.3, $p = 0.01$) and controls (mean = 0.83, SD = 0.2, $p = 0.004$). ICF was not statistically different across groups (ANOVA $p = 0.1$). No significant correlations were found between MWF and ICI or ICF in any of the 3 study groups.

Discussion: In this preliminary study, structural changes were found in the descending motor output pathway white matter of individuals with NMO and cortical excitability changes in MS that are specific to intracortical inhibitory pathways in comparison to one another and also compared to healthy controls. However, these metrics are not related to one another suggesting that inhibition in the CST is not directly linked to myelination. These results suggest that there are both neurophysiological and neuroanatomical changes that may potentially offer novel biomarkers to distinguish individuals with MS from those with NMO.

References: ¹Love J Clin Pathol 2006; 11:1151. ²Mackay MRM 1994; 37:34. ³Siebner Exp Brain Res 2003; 148:1. ⁴Prasloski Neuroimage 2012; 61:533. ⁵Prasloski MRM 2012; 67:1803. ⁶Whittall JMR 1989; 84:134. ⁷Edwards Stroke 2011; 42:728.