The relationship between axonal loss and demyelination in the MS spinal cord

Background

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease affecting the whole central nervous system (CNS). Limb dysfunction due to damage and loss of cortico-spinal tracts (CSTs) axons is common among people with MS (pwMS). The relationship between demyelination and CST axon remains unclear, possibly due to variation in sampling techniques.

Objectives

To accurately quantify the loss of CST axons in the MS spinal cord and assess its relationship with demyelination.

Methods

Formalin fixed spinal cords of nine people with secondary progressive MS (5 women and 4 men, age = 62 ± 3 years, disease duration= 24 ± 3 years) and three reference cases (2 women and 1 man, age= 84 ± 8 years) with no known neurological disease were studied. Spinal cords were dissected into ≈0.5 cm thick axial tissue blocks across the entire length (total n blocks = …). Sequential 10μm-thick sections were stained for myelin basic protein (MBP) to identify demyelinated areas and SMI-31 to identify axons using established protocols. Images of axons in four microscopic fields (40x), randomly cast on each lateral CST area, were acquired and then quantified using ImageJ software. The density of axons in each CST was estimated bilaterally as the density of axons inside the counting fields multiplied by the corresponding cross-sectional CST area in μm^2.

Results

Reduction in CST axonal density in pwMS was 62% ($p < 0.0001$), 49% ($p < 0.0001$), and 50% ($p = 0.0018$) at cervical, thoracic and lumbar level respectively. The percentage of demyelinated grey matter (GM) was significantly higher than in white matter (WM): 26% and 11% ($p = 0.012$), 47% and 12% ($p < 0.0001$), 13% and 3% ($p = 0.032$) at cervical, thoracic and lumbar level, respectively. A moderate negative correlation was detected the density of axons and the extent of demyelination at cervical level only (r= -0.2456, p= 0.05).

Conclusions

Comprehensive sampling is required to draw more definitive conclusions about the relationship between major components of pathology in the MS spinal cord. We observed axonal loss of at least 49% throughout the spinal cord, however only at the cervical level was with loss – moderately – associated with demyelination. Wallerian or tract specific degeneration may explain lack of

association at lower cord levels. Further work is underway to explore these mechanisms and to correlate these findings in the spinal cord with in cortical demyelination and neuronal loss in the brain.