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Cervical cord myelin water imaging shows degenerative changes over one year in multiple sclerosis but not neuromyelitis optica spectrum disorder

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ABSTRACT

Spinal cord pathology is a feature of both neuromyelitis optica spectrum disorder (NMOSD) and relapsing-remitting multiple sclerosis (MS). While subclinical disease activity has been described in MS using quantitative magnetic resonance imaging measures, current evidence suggests that neurodegeneration is absent between relapses in NMOSD, although most evidence comes from brain studies. We aimed to assess cross-sectional differences and longitudinal changes in myelin integrity in relapse-free MS and NMOSD subjects over one year. 15 NMOSD, 15 MS subjects, and 17 healthy controls were scanned at 3 T using a cervical cord mcDESPOT protocol. A subset of 8 NMOSD, 11 MS subjects and 14 controls completed follow-up. Measures of the myelin water fraction (f_M) within lesioned and non-lesioned cord segments were collected. At baseline, f_M in lesioned and non-lesioned segments was significantly reduced in MS (lesioned: $p = 0.002$; non-lesioned: $p = 0.03$) and NMOSD (lesioned: $p = 0.0007$; non-lesioned: $p = 0.002$) compared to controls. Longitudinally, f_M decreased within non-lesioned cord segments in the MS group (-7.3%, $p = 0.02$), but not in NMOSD ($+5.8\%$, $p = 0.1$), while change in lesioned segments f_M did not differ from controls' in either patient group. These results suggest that degenerative changes outside of lesioned areas can be observed over a short time frame in MS, but not NMOSD, and support the use of longitudinal myelin water imaging for the assessment of pathological changes in the cervical cord in demyelinating diseases.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing autoimmune disease of the central nervous system that, due to similar clinical and neurological features, was long thought to be a rare variant of multiple sclerosis (MS) (Wingerchuk et al., 2015). Since the discovery of a highly specific antibody (Jarius and Wildemann, 2010), and the advent of serum testing to aid differential diagnosis, it is now considered a separate entity (Weinshenker, 2007). Serum antibodies to the aquaporin-4 water channel protein (AQP4-Ab), found on astrocytic foot processes, are detectable in a high proportion of patients (Pandit et al., 2015). AQP4 is expressed throughout the brain, and is found in particularly high concentration in the optic nerve and spinal cord, in line with the observed frequency of pathology in these regions in NMOSD (Pittock et al., 2006).

Unlike in MS, which can present as a relapsing-remitting disease with secondary conversion to a progressive phase, or as progressive from onset (Compston and Coles, 2008), conversion to a progressive phase is extremely rare in NMOSD (Aboul-Enein et al., 2013; Cabre et al., 2009; Collongues et al., 2010, 2014). Clinical disability is accrued as a consequence of damage sustained during relapses, whereas clinical disability scores in MS increase more steadily during the progressive phase (Collongues et al., 2011; Wingerchuk et al., 2007a). Current clinical and neuroimaging evidence suggests that subclinical disease activity does not occur between attacks in NMOSD (Wingerchuk et al., 2007b), contrary to what is observed in MS (Filippi and Agosta, 2010; Matthews et al., 2015). However, it has been suggested that NMOSD attacks are so severe that the resulting sequelae hide the subtler changes that may accrue over time as a result of progressive axonal deterioration following inflammation (Wingerchuk et al., 1999).

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The cervical spinal cord is a frequent target of disease activity in both NMOSD and MS. The main feature of cord pathology in NMOSD is the presence of longitudinally extensive lesions, spanning three or more vertebral segments. These favour the grey matter (Krampla et al., 2009; Nakamura et al., 2008) and are characterised by abnormal magnetic resonance imaging (MRI) diffusion metrics, reflecting greater tissue injury compared with MS lesions (Klawiter et al., 2012; Rivero et al., 2014). Abnormal magnetization transfer (Benedetti et al., 2006; Filippi et al., 1999; Rocca et al., 2004) and diffusion parameters (Jeantroux et al., 2012; Pessôa et al., 2012; Qian et al., 2011; Rivero et al., 2014) have been observed in the cervical cord in NMOSD, suggesting the presence of inflammatory processes, demyelination and axonal pathology. Abnormally low myo-inositol (normalized to creatine) levels have been measured in the upper cervical cord, thought to reflect astrocytic dysfunction within lesions, a process thought to play a major role in the pathogenesis of the disease by contributing to oligodendrocyte dysfunction and eventually secondary demyelination (Ciccarelli et al., 2013).

Overall, focal cord pathology is considered more aggressive in NMOSD; diffuse damage of the type seen in MS has only been shown inconsistently, while secondary degenerative processes in white matter tracts may be common to both diseases (Klawiter et al., 2012). However, the majority of studies do not differentiate between lesional and normal-appearing spinal cord tissue (NASCT); to date, no longitudinal advanced imaging study has assessed whether changes in NASCT occur in NMOSD outside of clinical relapses.

Multicomponent Driven Equilibrium Single Pulse Observation of T_1 and T_2 (mcDESPOT) is a quantitative myelin water imaging method with great sensitivity for the estimation of myelin content (Deoni et al., 2008), and has been suggested as a possible marker of disease progression in primary progressive MS (Kolind et al., 2015). Matthews et al. (2015) previously found no evidence of disease progression in a group of clinically stable NMOSD subjects, while several quantitative imaging brain metrics, including the mcDESPOT-derived myelin water fraction (f_M) in major white matter tracts, showed widespread differences and changes over one year in a group of relapsing-remitting MS subjects. In the present study, we report cross-sectional and longitudinal evaluations of the cervical spinal cord in a subset of the same NMOSD, MS subjects and healthy controls using mcDESPOT. We aimed to characterise normal-appearing and lesional cervical cord pathology at baseline, and to assess whether evidence of degenerative changes could be detected over one year in either patient group.

2. Methods

2.1. Population characteristics and study design

2.1.1. Ethics

This study was approved by the South East Hampshire NHS Research Ethics Committee. All participants gave written informed consent before taking part.

2.1.2. Subjects

15 AQP4-Ab NMOSD patients, 15 relapsing-remitting MS patients, and 17 sex and age-matched healthy controls were recruited from the NHS Neuromyelitis Optica Highly Specialized Service in Oxford, UK – a subset of the groups previously reported on in Matthews et al. (2015). All NMOSD subjects were receiving immunosuppressant medication (7 on azathioprine, 2 on methotrexate, 1 on prednisone, and 5 on combinations thereof), while the majority of MS subjects were on disease-modifying therapies (6 on Copaxone, 3 on beta-interferons, and 1 on low-dose naltrexone; 5 were not receiving treatment). A subset of 8 NMOSD, 11 MS and 14 controls completed a follow-up scan after one year. All patients had been relapse-free for at least 6 months prior to the baseline scan, and none experienced a relapse between baseline and follow-up.

2.1.3. MRI acquisition

Participants were scanned on a 3 Tesla MRI scanner (Siemens MAGNETOM Verio, Erlangen, Germany) with a mcDESPOT protocol (Kolind and Deoni, 2011) which covered the whole cervical cord with $0.9 \times 0.9 \times 1.8$ mm voxels, reconstructed to 0.9 mm^3 isotropic (scan time 22 min). The mcDESPOT data consisted of series of spoiled gradient echo (SPGR) scans over a range of 8 optimized flip angles (α) (TE/TR = 2.7/6.1 milliseconds (ms); α = [2.25, 4.5, 6.75, 9, 11.25, 13.5, 15.75, 18]°), 8 balanced steady state free precession scans (TE/TR = 2.3/4.6 ms; α = [5.625, 11.25, 16.875, 22.5, 28.125, 33.75, 39.375, 45]°) acquired over two phase-cycling patterns (0° and 180°) to correct for off-resonance effects (Deoni, 2009), and an inversion recovery-prepared SPGR scan for correction of B_1 inhomogeneity (Deoni, 2011) (TE/TR = 2.7/6.3 ms, TI = 450 ms, α = 5°). An axial T_2-weighted multi-echo gradient echo sequence, sagittal T_1-weighted magnetization-prepared rapid gradient echo, and a sagittal T_2-weighted turbo spin echo sequence were acquired for lesion assessment.

2.2. Image analysis

2.2.1. Lesion identification

Lesions were identified on the patients' anatomical scans by an experienced radiologist (J.S.L.) blinded to diagnosis, primarily based on the sagittal T_2-weighted scan with additional information gleaned from the sagittal T_1 and axial T_2-weighted scans. The assessment was done for both baseline and follow-up concurrently. Spinal levels (heretofore referred to as segments) were identified as normal-appearing or lesioned. For small lesions located at a disc level, both adjoining segments were considered lesioned.

2.2.2. Segmentation

For each subject, an SPGR image from the mcDESPOT protocol with good contrast between tissue and cerebrospinal fluid (α = 9°) was used for preprocessing. The spinal cord was segmented using *PropSeg* (De Leener et al., 2014), a semi-automated propagation-based method from the Spinal Cord Toolbox (De Leener et al., 2016) (SCT; http://sourceforge.net/projects/spinalcordtoolbox/). Each subject's SPGR was warped to the MNI-Poly-AMU template (Fonov et al., 2014). The inverse transform was then applied to the template in order to obtain vertebral level segmentation in subject space. We considered the region from C1 to C7 for whole cervical cord measures. Using the lesion assessment described above, separate masks were created by considering only segments marked as either normal-appearing or lesioned. An example of a lesioned tissue mask is shown in Fig. 1.

2.2.3. f_M measurement

Images from the mcDESPOT protocol were linearly registered within-subject to the reference SPGR scan with FSL-FLIRT (Jenkinson et al., 2002), using trilinear interpolation. f_M maps were calculated with a three-pool model (Deoni et al., 2013), and manually edited (by an observer blinded to group and time point (A.J.E.C.)) to exclude voxels where partial volume effect in the acquired images led to artificially very low computed values. Visual inspection was performed for all images to ensure the quality of co-registration. Median f_M values were collected within the whole cervical cord, and within NASCT and lesioned tissue separately using the masks described above.

2.3. Statistics

Non-parametric tests were chosen due to small sample sizes, and after visual inspection showed that MRI variables were not normally distributed. Percent changes between baseline and follow-up metrics were calculated for each subject. Differences between patient groups were evaluated using the Mann-Whitney *U* test, and between the three groups using the Kruskal-Wallis test. Post hoc comparisons following a significant omnibus test (alpha = 0.05) were conducted with the Mann-