NeuroImage: Clinical 9 (2015) 574–580

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Brain and cord myelin water imaging: a progressive multiple sclerosis biomarker

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ARTICLE INFO

Article history:
Received 13 July 2015
Received in revised form 9 September 2015
Accepted 1 October 2015
Available online 3 October 2015

Keywords:
Myelin water imaging
Primary progressive multiple sclerosis
Spinal cord
Atrophy
Myelin

ABSTRACT

Objectives: Conventional magnetic resonance imaging (MRI) is used to diagnose and monitor inflammatory disease in relapsing remitting (RR) multiple sclerosis (MS). In the less common primary progressive (PP) form of MS, in which focal inflammation is less evident, biomarkers are still needed to enable evaluation of novel therapies in clinical trials. Our objective was to characterize the association — across the brain and cervical spinal cord — between clinical disability measures in PPMS and two potential biomarkers (one for myelin, and one for atrophy, both resulting from the same imaging technique).

Methods: Multi-component driven equilibrium single pulse observation of T1 and T2 (mcDESPOT) MRI of the brain and cervical spinal cord were obtained for 15 PPMS patients and 11 matched controls. Data were analysed to estimate the signal related to myelin water (VF_M), as well as volume measurements. MS disability was assessed using the Multiple Sclerosis Functional Composite score, which includes measures of cognitive processing (Paced Auditory Serial Addition Test), manual dexterity (9-Hole Peg Test) and ambulatory function (Timed 25-Foot Walk); and the Expanded Disability Status Scale.

Results: Brain and spinal cord volumes were different in PPMS compared to controls, particularly ventricular (+46%, $p = 0.0006$) and cervical spinal cord volume (−16%, $p = 0.0001$). Brain and spinal cord myelin (VF_M) were also reduced in PPMS (brain: −11%, $p = 0.01$; spine: −19%, $p = 0.000004$). Cognitive processing correlated with brain ventricular volume ($p = 0.009$). Manual dexterity correlated with brain ventricular volume ($p = 0.007$), and both brain and spinal cord VF_M ($p = 0.01$ and 0.06, respectively). Ambulation correlated with spinal cord volume ($p = 0.04$) and spinal cord VF_M ($p = 0.04$).

Interpretation: In this study we demonstrated that mcDESPOT can be used to measure myelin and atrophy in the brain and spinal cord. Results correlate well with clinical disability scores in PPMS representing cognitive, fine motor and ambulatory disability.

1. Introduction

In 10–20% of cases, multiple sclerosis (MS) presents with progressive development of disability from onset (primary progressive (PP) MS), differentiating it from the more common relapsing–remitting (RR) form of the disease. Although it is not believed to be a separate disorder (Antel et al., 2012), none of the current therapies used to treat RRMS have been found to be effective in PPMS (Kantarci, 2013). The identification of an effective therapy for PPMS has been hindered by the lack of a sufficiently sensitive biomarker to evaluate a therapeutic effect in early phase clinical trials. There is therefore an urgent need

Abbreviations: CCV, cervical cord volume; CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; FOV, field of view; mcDESPOT, Multi-component driven equilibrium single pulse observation of T1 & T2; MR, magnetic resonance; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, Multiple Sclerosis Functional Composite; PASAT, Paced Auditory Serial Addition Test; PP, primary progressive; RR, relapsing remitting; SPGR, spoiled gradient echo; SSFP, steady state free precession; TE, echo time; TR, repetition time; T25FW, Timed 25-Foot Walk; vCSF, ventricular cerebrospinal fluid; VF_M, myelin water volume fraction; 9HPT, 9-Hole Peg Test.

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http://dx.doi.org/10.1016/j.nicl.2015.10.002

for methods that can better monitor PPMS disease progression to assist in the development of disease modifying drugs and for incorporation into clinical trials (Rice et al., 2013).

Atrophy occurs early in MS (De Stefano et al., 2001; Sastre-Garriga et al., 2005a; Tiberio et al., 2005) and has been measured in all MS phenotypes (De Stefano et al., 2010; Grassiot et al., 2009; Pagani et al., 2005; Tedeschi et al., 2005), with PPMS showing greater and earlier spinal cord atrophy than RRMS (Bieniek et al., 2006; Lukas et al., 2013). Atrophy of the brain and cervical spinal cord correlate with clinical scores and appear to be good biomarkers for disability; they have also been demonstrated to be reliable measures for assessing disease progression (Bieniek et al., 2006; Chard et al., 2004; Grassiot et al., 2009; Lukas et al., 2013; Sastre-Garriga et al., 2005b; Tiberio et al., 2005). Cervical cord volume (CCV) has been shown to decrease significantly over two years in PPMS, demonstrating potential utility within the timeframe of most clinical trials (Laule et al., 2010).

While atrophy measurements are clearly sensitive and relevant to MS progression, they are unspecific. It is also important to differentiate between contributing pathological processes, including inflammation, axonal damage, and particularly, myelin damage, as these may distinguish between different MS subtypes and provide a greater understanding of disease pathogenesis and treatment effect.

Multi-component relaxation imaging is a sensitive and specific MRI technique for measuring changes in myelin. This approach separates MR (magnetic resonance) signal into that originating from different water environments, based on relaxation characteristics; water in intra/extracellular spaces relaxes more slowly than water trapped between myelin sheaths (MacKay et al., 1994). Multi-component driven equilibrium single pulse observation of T1 & T2 (mcDESPOT) consists of a series of spoiled gradient echo (SPGR) and balanced steady state free precession (SSFP) images, each acquired over a range of flip angles. The various flip angles provide an assortment of different contrasts with varying degrees of T1- and T2-weighting. It can be used to estimate the fraction of signal from each water pool, in particular, the fraction of faster-relaxing signal of water associated with myelin, the myelin water volume fraction (VF_M) (Deoni, 2011; Deoni et al., 2008). Previous studies have demonstrated reduced VF_M in PPMS brain (Kolind et al., 2012), and robust results in healthy cervical spinal cord (Kolind and Deoni, 2011). Beneficially, the images that make up the mcDESPOT acquisition can also be assessed as standard structural images. An SPGR scan with a flip angle of 18° provides excellent contrast for assessment of brain and spinal cord volume. Thus our protocol can be used to simultaneously assess atrophy and VF_M, both of which appear to be important in PPMS.

In this study, we applied a mcDESPOT protocol to measure atrophy and VF_M in PPMS brain and spinal cord, comparing results with those from matched healthy controls as well as with clinical measures of disability. The goal was to demonstrate the applicability of mcDESPOT to the study of PPMS and its potential for use in future clinical trials of disease modifying therapies.

2. Materials and methods

2.1. Subject information

The study was ethically reviewed and given a favourable opinion, under the UK's Health Research Authority, by the South East Coast—Surrey Research Ethics Committee (REC reference: 11/LO/0739). Appropriate approvals were also obtained from the King's College NHS Foundation Trust, through which patients were recruited. Informed consent was obtained from all participants. Fifteen subjects with clinically defined PPMS fulfilling the 2005 revised McDonald criteria for diagnosis (Polman et al., 2005): 11 males, mean age 52 (range 41–67) years; median Expanded Disability Status Scale (EDSS) = 5.0 (2.5–6.5); mean disease duration = 6 (2-17) years; mean brain lesion volume = 19 (0–61) cm^3; mean number of spinal cord lesions = 4 (2-6) were recruited and compared to 11 age and gender-matched healthy controls (9 males, mean age 49 (range 37–64) years).

Disability was assessed for the MS subjects using EDSS (Kurtzke, 1983) and the Multiple Sclerosis Functional Composite (MSFC) score (Fischer et al., 1999), which includes measures of cognitive processing (Paced Auditory Serial Addition Test; PASAT), manual dexterity (9-Hole Peg Test; 9HPT) and ambulatory function (Timed 25-Foot Walk; T25FW).

2.2. Image acquisition

Brain: MR image acquisition was performed on a 1.5 T GE Signa system (General Electric, Waukesha, USA). mcDESPOT data were acquired sagittally over the whole brain, with a 1.7 mm isotropic voxel size; SPGR: TE/TR = 1.9/5 ms, 8 optimised flip angles up to 18°; SSFP: TE/TR = 1.8/3.6 ms, 8 optimised flip angles up to 70°, phase-cycling pattern = 0° and 180° (for correction of off-resonance effects); *total scan time 10 min* (Deoni et al., 2008). Axial FLAIR and PD/T2-weighted images were also collected for lesion identification (*total 7 min*).

Spinal Cord: mcDESPOT data were acquired sagittally over the entire cervical spinal cord (field of view (FOV) = 20 cm) with 0.78(A/P) × 0.78(A/P) × 1 mm(S/I) voxel size; SPGR: TE/TR = 2.2/4.9 ms, 8 optimised flip angles up to 18°; inversion recovery prepared SPGR (IRSPGR): TE/TR = 2.05/4.9 ms, $\alpha = 5°$, TI = 350 ms (for correction of B1 inhomogeneity effects (Deoni, 2011)); SSFP: TE/TR = 1.6 ms/3.2 ms, 8 optimised flip angles up to 70°, phase-cycling pattern = 0° and 180°; *total scan time 24 min* (Kolind and Deoni, 2011). Sagittal T1-weighted and T2-weighted and axial multiple-echo recombined gradient echo ("MERGE") images were also collected for lesion identification (*total 15.5 min*).

2.3. Image analysis

Volume measurements: Both brain and cervical spinal cord volume measurements were calculated using one of the 3D T1-weighted SPGR scans from the mcDESPOT data (flip angle = 18°).

Brain volume measurements: Whole-brain, peripheral and total grey matter, white matter and ventricular cerebrospinal fluid (vCSF) volume were calculated using the FSL tool Structural Image Evaluation using Normalisation of Atrophy (SIENAX) (Smith et al., 2002). First, lesions were manually delineated by an experienced neuroradiologist on the PD images and linearly registered to the SPGR. Within SIENAX, brain and skull images are extracted and affine registered to the Montreal Neurological Institute 152 standard image. Tissue-type segmentation is then carried out, taking the lesion masks as input to ensure correct classification of white matter voxels with altered intensities. A back-normalised standard space mask is used to isolate peripheral (i.e. cortical) from total GM, which also includes subcortical structures. Finally, SIENAX produces tissue-class-specific volumes normalised for head size, using a scaling factor derived from the registration.

Spinal cord volume measurements: Cervical cord area was computed from 13 slices at the C2/C3 intervertebral disc using a modified version of the semi-automatic method by Tench et al. (Tench et al., 2005). The algorithm is a region-growing technique that uses edge detection, partial volume estimation and cord angle correction to ensure accuracy.

VF_M measurements: VF_M maps were calculated voxelwise using a three-pool mcDESPOT analysis approach (Deoni et al., 2013). White matter was extracted using FSL-FAST. Regions of interest in the corpus callosum and minor forceps were selected based on previous results showing correlation between VF_M and the mental functional system EDSS score in these regions (Kolind et al., 2012). These regions of interest were generated from the JHU atlases in FSL, manually edited to remove regions of partial volume, and analysed in native space. Spinal cord tissue was extracted (over the whole cervical cord from C1 to C7) using FSL-FAST, and manually edited to remove regions of partial