Comparative Study of Quantitative MRI Markers of Disease Progression in Primary Progressive Multiple Sclerosis

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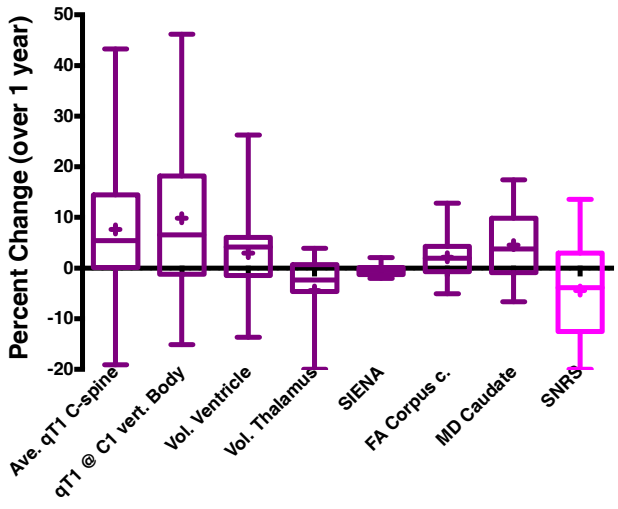
Target Audience: Researchers and clinicians interested in using quantitative MRI as end points in clinical trials.

Purpose: Various quantitative MRI (qMRI) parameters have been shown to be both sensitive to the disease process in neurodegenerative diseases and independent of imaging session-specific biases such as radiofrequency (RF) transmit and receive-coil profiles and gains. Such qualities make them attractive candidates for use as endpoints in clinical trials of disease progression or treatment. Here, we compare volumes, DTI, and quantitative T_1 (qT_1) from various CNS structures for their relative ability to track clinical progression over 1 year in primary progressive multiple sclerosis (PPMS).

Methods: Thirty-one patients (age: 55 ± 8 years, 15 male) clinically diagnosed with PPMS were recruited for this study. Clinical and MRI data from two visits 1 ± 0.05 years apart are analyzed here. Subjects underwent a complete clinical evaluation including clinical scoring using Expanded Disability Status Scale (EDSS), Scripps Neurologic Rating Scale (SNRS), Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modality Test (SDMT), 9-hole peg test (9HP), and a 25 foot walk. MRI of the brain and cervical spinal cord were performed on one of two 3T scanners (Siemens Skyra or GE HDx), with longitudinal scans from each patient being maintained on the same scanner. Brain images from the two longitudinal time-points were registered to each other to create an average for each patient in the MNI space. qMRI measures included volumetric analysis (using LesionTOADS[1] and SIENA[2] for brain, and ROI analysis for c-spine), brain DTI from 2 mm isotropic scans acquired with b=0, 1000 s/mm^2 registered to 1mm isotropic T2 images (using TORTOISE[3]), and qT_1 (using DESPOT1-HIFI[4] on the GE or Bloch-Siegert[5] method on the Siemens scanners). ROIs for the volumetric analysis were derived from the brain segmentation algorithm (TOADS-CRUISE[6]); ROIs for qT_1 and DTI as well as all spinal cord scans were drawn manually on anatomical images to avoid errors due to misregistration. Statistical analysis included paired t-test between the longitudinal time points, and correlation of percentage changes in qMRI to clinical parameters after adjusting for age and sex.



Results: After careful QA across the 31 patients, longitudinal analysis was successful for volume in 28, and for DTI and qT_1 in 26, in the brain; spinal cord qT1 analysis was successful in 24 patients. Amongst the clinical parameters investigated SNRS decreased (4.4%, p=0.007) indicating clinical progression, whereas the median EDSS was unchanged at 6.0 between the two visits. Thalamic (lesionTOADS) and brain (SIENA) volumes decreased by 4.4% (p=0.02) and 0.5% (p=0.02) respectively, while ventricular volume increased by 2.9% (p=0.04). Among all the DTI parameters explored, changes were observed from only the FA from corpus callosum (2.1% increase, p=0.02) and mean diffusivity of the caudate (4.6% increase, p=0.002). Average qT_1 from the cervical cord and dens increased by 7.6% (p=0.04) and 9.8% (p=0.006) respectively over one year. However, none of the ROIs in the brain showed any changes in qT_1.

Discussion: Less than 20% of the qMRI and clinical parameters tested in the patient cohort showed any change over one year in this patient cohort. Most of the qMRI parameters that showed changes were correlated with disease progression in the direction that would be expected for a neurodegenerative disease, such as a decrease in volume and anisotropy and an increase in qT1 with progression. The notable exception was an increase in FA from the corpus callosum, showing moderate negative correlation with SNRS (r=-0.42, p=0.04). An increase in FA has been reported in neurodegenerative diseases such as mild Alzheimer's Disease[7], this highlights the need for a better understanding of the specificity of qMRI signal in PPMS. qMRI parameters from the cervical cord were among the parameters that showed the largest change as well as variability in this longitudinal study. This is in line with the prevalent observation that spinal cord may be more involved in the disease process in PPMS. Further analysis such as test-retest in healthy volunteers, tests for normality of data are being done, along with similar analysis in a cohort of secondary progressive MS subjects.

Conclusion: While quantitative imaging of the spinal cord was more challenging due to motion artifacts and its small cross-section, qT_1 from c-spine seem to have the largest change in this longitudinal study. The study highlights the need for improving the specificity of qMRI signal as well as the need for developing spinal cord imaging techniques to fully understand progression in PPMS. This cohort is being followed longitudinally for further data collection and analysis.

References: 1. Shiee et. Al Neuroimage. Jan 15, 2010; 49(2): 1524; 2. Smith et. al. Journal of Computer Assisted Tomography, 25(3):466; 3. Pierpaoli et. al. ISMRM 18th annual meeting; 4. Deoni et. al. J Magn Reson Imaging. 26(4):1106; 5. Duan et. al. NMR in Biomedicine 26(9):1070; 6. JIST tool http://www.nitrc.org/projects/toads-cruise/ 7. Douaud et. al. NeuroImage 55(3):880.