Myelin Water Fraction as a Potential Marker of Progression in Primary Progressive Multiple Sclerosis

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Background

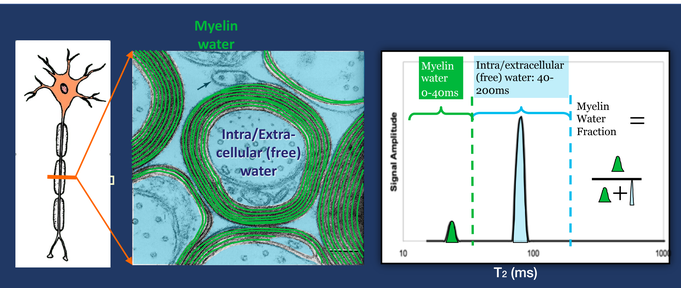
- Progressive Multiple Sclerosis (MS) pathology includes focal lesions and diffuse damage in normal-appearing white matter (NAWM)
- Diffuse damage is difficult to detect with conventional MRI
- Biologically-specific advanced MRI markers that are sensitive to progressive NAWM damage are needed
- Myelin water fraction (MWF) is directly related to myelin levels, making it a potential biomarker candidate

Objectives

To study the variability and natural history of MWF in primary progressive multiple sclerosis (PPMS) patients compared to healthy controls.

Methods

- Data was collected as part of a single-site substudy at the University of British Columbia (Vancouver, Canada) for the double-blinded, placebo-controlled clinical trial with ocrelizumab in PPMS (ORATORIO; NCT01194570)
- Baseline MWF was available on 7 PPMS patients to assess heterogeneity of MWF abnormalities
- Longitudinal MWF was available on 2 PPMS patients treated with placebo for up to 48 months
- Clinical assessment included Expanded Disability Status Scale (EDSS)
- MRI included multi-component driven equilibrium single pulse observation of T1/T2 (mcDESPOT) to calculate MWF
- MWF measures water trapped between myelin bilayers
- MWF was compared to 41 healthy controls



- Voxel-wise MWF Z-score maps (MWFZ) were calculated as:

$$\mathrm{MWFZ} = \frac{\text{patient MWF} - \text{mean of controls' MWF}}{\text{standard deviation of controls' MWF}}$$

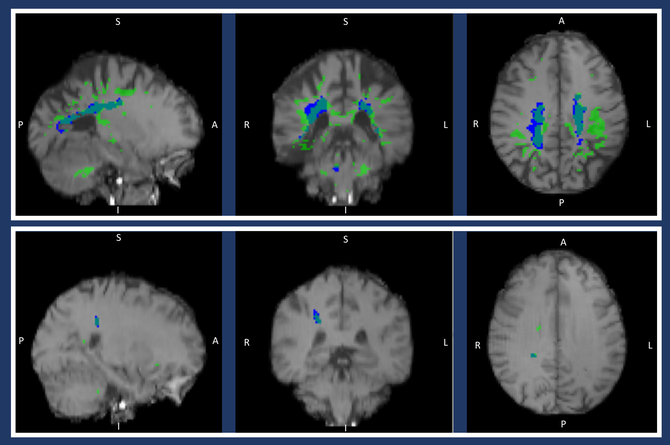
- Significantly reduced MWF was calculated as percentage of white matter voxels with MWFZ < -4 (corresponding to p<0.0001), excluding regions smaller than 25 voxels

Results

Baseline MWF and Lesions (n=7)

PPMS 1:

PPMS 2:



Lesions (baseline)

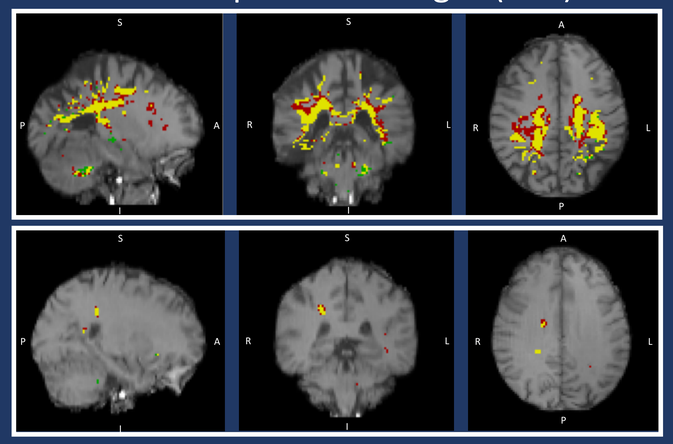
Significantly reduced MWF at baseline

Significantly reduced MWF at baseline and final timepoint

Significantly reduced MWF at final timepoint only

- Volume of significantly reduced MWF in white matter volume (WMV) varied widely between PPMS patients, and was not correlated with EDSS
- Areas of significantly reduced MWF extend far beyond focal lesions
- Two PPMS patients (e.g. PPMS 1) had more than 8% of WMV with significantly reduced MWF
- Five PPMS patients (e.g. PPMS 2) had small (<80 voxels), isolated patches of significantly reduced MWF, affecting <0.25% of WMV

Follow-up MWF Changes (n=2)



PPMS 1:
Baseline (EDSS 6.5) - significantly reduced MWF in 8.9% of WMV
Month 48 (EDSS 6.5) - significantly reduced MWF in 12.6% of WMV

PPMS 2:
Baseline (EDSS 2.5) - no areas of significantly reduced MWF
Month 24 (EDSS 3.5) - significantly reduced MWF in 0.09% of WMV

Conclusions

1. Significant reductions in regional MWF can be deduced for individual PPMS patients relative to a healthy control atlas.
2. PPMS patients vary in the distribution and extent of severe reductions in regional MWF.
3. MWF Z-scores can detect significant changes in individual patients within 1-2 years of follow-up.

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Disclosures

KL Chang, IM Vavasour, and R Tam have nothing to disclose. **D Clayton and V Levesque** are employees of Genentech. **DKB Li** received research funding from the Canadian Institute of Health Research and MS Society of Canada; is Emeritus Director of the UBC MS/MRI Research Group which was contracted to perform central analysis of MRI scans for therapeutic trials with Novartis, Perceptives, Roche and Sanofi-Aventis; received grant support for investigator-initiated independent studies from Genzyme, Merck-Serono, Novartis and Roche; consultant to Vertex Pharmaceuticals; served on the Data and Safety Advisory Board for Opexa Therapeutics and Scientific Advisory Boards for Adelphi Group, Celgene, Novartis and Roche; given lectures supported by non-restricted education grants from Teva, Novartis and Biogen. **AL Traboulsee** did consulting for Biogen, Roche, EMD Serono and Teva Pharmaceuticals, and received research support from Biogen, Chugai, CIHR, Roche, Michael Smith Foundation and the MS Society of Canada. **SH Kolind** received research support from Roche and MS Society of Canada; consulted for Acorda and Genzyme.