MS diagnosis is predicted at initial clinical presentation by venocentric lesions detected with 3T SWI

Matthew P Quinn[1,2], Marcelo Kremechutzky[3], and Ravi S Menon[1,2]

[1]*Centre for Functional and Metabolic Mapping, Robarts Research Institute, London, Ontario, Canada,* [2]*Medical Biophysics, Western University, London, Ontario, Canada,* [3]*Clinical Neurological Sciences, Western University, London, Ontario, Canada*

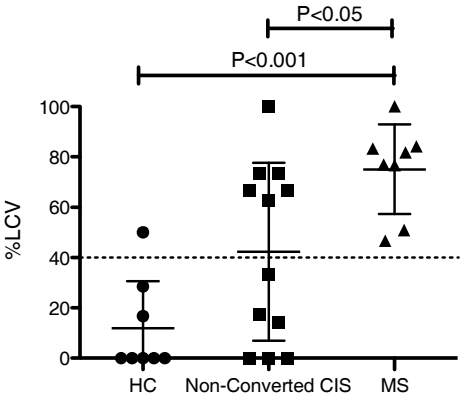
TARGET AUDIENCE: Clinicians, researchers interested in MR biomarkers that will allow earlier multiple sclerosis (MS) diagnosis.

INTRODUCTION: Demonstration of white matter hyperintensities (WMHs) with MRI is central to MS diagnosis; however, WMHs are present in other disease. There is growing interest in identifying biomarkers to discriminate between MS and non-MS *at clinical presentation*. One biomarker may be a MRI-detectable WMH-penetrating vein. MS lesions were reported to be venocentric – that is, centered along a vein – in the earliest descriptions of the disease. This feature has been consistently demonstrated *in vivo* with ultra-high field MRI (7T). In one study, *all* patients who converted from suspected MS to confirmed MS had >40% WMHs with central veins at baseline (1). The visibility of small veins at clinical field strengths (1.5T, 3T) is diminished and the utility of this biomarker is unestablished. Our objectives are (i) to determine if central veins in WMHs can be detected using multi-echo susceptibility weighted imaging (SWI) at 3T; and (ii) to investigate the value of this marker for predicting MS diagnosis in patients with clinically isolated syndromes (CIS) suggestive of MS.

METHODS: Twenty-two CIS patients and 16 age- and sex-matched healthy controls (HC) were recruited. At study baseline, participants were imaged on a 3T MR system [2D axial FLAIR (1x1x3 mm^3) and 3D multi-echo GRE (0.5x0.5x1.0 mm^3)]. SWI was produced from multi-echo data as described in (2). From a mean clinical follow-up of 11.2 months, updated statuses for all patients were available. No imaging was performed at this follow-up. Images from all volunteers were rated in a random order and the rater was blinded to the status of the volunteer. FLAIR and SWI were co-registered. WMHs were first visualized on FLAIR. The FLAIR image was then toggled off to reveal the SWI image. The presence of a central vein was then rated (yes or no) using criteria proposed in (1). For each subject, the %LCV (percentage lesions with central vein) was calculated as: (number of WMHs with central vein)/(total number of WMHs)x100%. This metric was compared between HCs, CIS patients who had not converted to MS at clinical follow-up, and CIS patients who *had* converted to MS at follow-up.

	HC	ncCIS	MS
Venocentric WMHs	7	65	106
Non-venocentric WMHs	22	64	53

RESULTS: By follow-up, 8 patients had been diagnosed with MS; the remaining 14 patients are referred to as the non-converted CIS (ncCIS) group. Group totals of WMHs with and without central veins are presented (Table). 67% of WMHs were venocentric in the MS group, 50% in ncCIS, and 24% in HC. Chi-square comparison between these groups yielded a highly significant $P<0.0001$. Pair-wise comparisons were: between HC and ncCIS, $P=0.013$; between HC and MS, $P<0.001$; and between ncCIS and MS, $P=0.011$. %LCV for each volunteer is shown (Figure), where we see that *all* CIS patients who were diagnosed with MS at follow up had %LCV>40 at study baseline. All subjects with no WMHs (8 HC, 2 ncCIS) were excluded from this plot.



DISCUSSION: Studies at 7T have reported that the fraction of WMHs in MS with central veins ranges from 59% to 92%. Using 3T multi-echo SWI, the incidence of central veins within MS lesions (67%) was at the lower end of this range.

There was a significantly larger fraction of venocentric lesions in the ncCIS compared to HC group (50% versus 24%). This suggests that (i) several patients remain in the ncCIS group who will eventually be diagnosed with MS, or (ii) venocentric WMHs are a feature of other diseases that might be indistinguishable from MS at early clinical presentations, or (iii) both. WMHs in individuals in the HC cohort may be associated with relatively benign pathology such as high blood pressure or headache. Healthy controls included in this study had relatively few WMHs (median: 2, min: 1, max: 7). The occasional association of these foci with veins may be due to chance.

We reproduced the 7T finding (1) that all patients eventually diagnosed with MS had %LCV>40 at baseline. Due to the relatively short study window, it is likely that some CIS patients who have not yet received an MS diagnosis will eventually receive one. In fact, the ncCIS group shows a bi-modal tendency, with one cluster of patients (%LCV>40) having %LCV distinctly larger than the other cluster (%LCV<40) (see figure). An interesting hypothesis that awaits confirmation following future clinical follow-up is that those ncCIS patients in the upper cluster will eventually be diagnosed with MS, and those in the lower cluster will not.

As implemented here, multi-echo SWI requires approximately 32 minutes for full brain coverage. This is prohibitively long for clinical use. We did not investigate the ability of SWI with reduced echoes/coverage to visualize intra-lesional veins. Moreover, the prospective value of this biomarker might be diminished if large values of %LCV are also detected in common MS mimics.

CONCLUSION: Results in CIS patients are consistent with previous reports that the presence of veins within WMHs is *highly predictive* of a subsequent MS diagnosis. ***REFERENCES:***(1) Tallantyre et al. Neurology 2011; 76. (2) Quinn et al. AJNR 2013; ePub.