

## Characterization of the perivascular distribution of white matter lesions in multiple sclerosis phenotypes by 7T MRI

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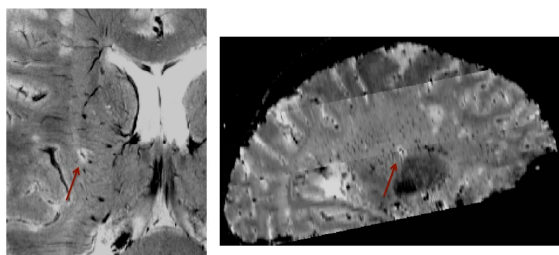
**Introduction.** Multiple sclerosis (MS) is a disease with profound heterogeneity in clinical course, and neuroradiological appearance of lesions both in white and gray matter (WM, GM). Histological data demonstrate that heterogeneous pathogenic mechanisms underlie the formation of MS-like demyelinating plaques, at least in WM, and identify four major patterns of demyelination (1). This pathogenic heterogeneity is thought to have fundamental implications for diagnosis, and monitoring MS course. Two patterns (type I and type II) are WM demyelinated plaques typically centered on small veins and venules, showing close similarities to T-cell mediated autoimmune encephalomyelitis, in contrast to the other patterns of WM lesions (III, IV), which are more suggestive of an oligodendrocyte dystrophy rather than autoimmunity. Recent studies show that T<sub>2</sub>\*-weighted images at ultra-high field MRI can be used to identify small parenchymal veins within MS lesions (2), with a detection rate significantly higher than lower field strength MR systems, thus representing a useful tool to investigate the pathogenesis of WM lesions in MS. Here, we used 7T high-resolution T<sub>2</sub>\* imaging in a large cohort of 47 subjects with MS to assess the presence of a central vein in WM plaques in different disease phenotypes, and investigate the clinical relevance of the perivascular distribution WM lesions in MS.

**Methods.** Seven patients with clinically isolated syndrome (CIS, mean±SD Expanded Disability Status Scale, EDSS, score=1.5±0.2, range=0-2; mean±SD disease duration=1.1±0.9 years), 22 patients with relapsing-remitting (RR) MS (mean±SD EDSS score=2.3±1.3, range 1-6 ; mean±SD disease duration=7.5±4.3 years), and 18 patients with secondary-progressive (SP) MS (mean±SD EDSS score=6±1.4, range=3-8; mean±SD disease duration=15.7±6.8 years), were scanned on a 7 T scanner (Siemens, Erlangen, Germany) with 40mT/m maximum gradient amplitude using either an in-house developed 8-channel (six patients) or a 32-channel phased array coil (all remaining patient). In each subject we collected 2D Flash, T<sub>2</sub>\* spoiled gradient-echo weighted images (TR/TE=1000/21, flip angle=55°, FOV=800x1724, bandwidth=30 Hz, 1.0-1.5 mm thick slices with an in-plane resolution of 330 x 330 μm<sup>2</sup>, 2-3 slabs allowing coverage of the whole supratentorial brain).

An experienced neuroradiologist and a neurologist interpreted the images by consensus. FLASH T<sub>2</sub>\*-weighted images were viewed in axial and sagittal planes for identification of WM lesions with a visible central vessel. Vessels were hypointense on T<sub>2</sub>\*-weighted images, and WM lesions with a central vessel were included in the analysis if a vessel: 1) could be identified in at least two perpendicular planes, 2) appeared linear in at least one plane, 3) was completely surrounded by hyperintense signal in at least two planes. An example of a WM plaque with a central vessel is shown in Fig.1. The lesion loads of WM lesions with an identifiable central vessel (WMLLwCV) and of lesions without a central vein (WMLLwoCV) were calculated using a semi-automated contouring technique (Alice, Hayden Solutions) (3). Furthermore WMLLwCV was classified into a) periventricular (PV), b) subcortical (SC), c) callosal (CC), for lesions located in the corpus callosum, d) other WM, (oWM) for lesions located in other white matter regions. The loads of these different lesional subtypes were also calculated using the same contouring technique. Differences between MS subgroups were performed pair-wise using Mann-Whitney U test. Correlations between neurological disability and measures of WM lesion loads were assessed using Spearman's Rank Correlation Coefficient (SRCC).

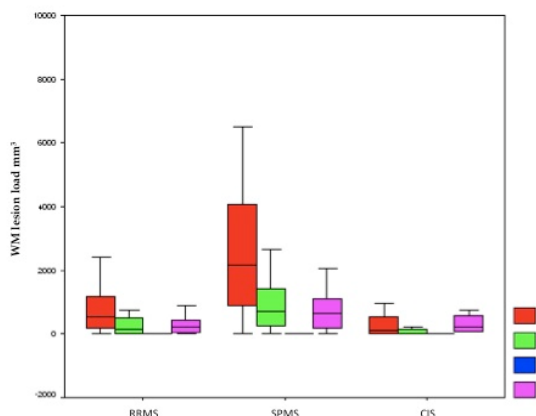
**Results.** White matter lesions with a central vessel were detected in all MS phenotypes, and at all disease stages. WMLLwCV was 87% of the total lesion load in CIS, 78% and 77% of the total WM lesion load in RRMS and SPMS respectively. Despite having significantly greater disability (p<0.04 by Mann-Whitney U test) and longer disease duration (p<0.0001 by Mann-Whitney U test), patients with RRMS did not differ significantly to CIS patients in either WMLLwCV or WMLLwoCV. This finding was confirmed even after dividing all CIS and RRMS patients into two subgroups based on disease duration (early MS≤3 years; late MS≥4 years). Patients with SPMS showed instead significantly greater WMLLwCV (<0.0001 by Mann-Whitney U test), and WMLLwoCV (<0.005 by Mann-Whitney U test) compared to RRMS patients. White matter plaques with a central vessel had more frequently a periventricular location in all MS phenotypes, followed by a subcortical location in RRMS and SPMS, but not in CIS (Fig.2.). WMLLwCV was less commonly located in the corpus callosum. In the group of 47 MS patients, disability as measured by EDSS positively correlated with disease duration (p<0.001, SRCC=0.741), total WMLL (p<0.01, SRCC=0.37), WMLLwCV (p<0.01, SRCC=0.36), WMLLwoCV (p<0.02, SRCC=0.33), and more strongly with PV WMLLwCV (p<0.002, SRCC=0.45) but also with SC WMLLwCV (p<0.02, SRCC=0.35). A multivariate analysis revealed that, out of all the variables, only PV WMLLwCV was positively related to EDSS (p<0.007).

**Conclusions.** Our results show that most but not all MS lesions in the WM are characterized by the presence of a central vessel, as shown by post-mortem studies. The percentage of such lesions compared to the overall WM lesion load is in line with previous reports that used 7T T<sub>2</sub>\* imaging in a small sample of patients with MS (2). Although WMLLwCV can be detected in different MS phenotypes and at all disease stages, the finding that WMLLwCV does not differ significantly between CIS and RRMS, despite longer disease duration and different clinical status, while being significantly higher in SPMS compared to the other MS groups, suggests that the presence and the extent of WMLLwCV might underlie specific pathogenesis mechanisms that operate in the transition to a chronic form of MS. WMLLwCV, however, particularly periventricular is also related to greater disability, independently of disease type, probably due to its vicinity to the internal capsule and possible involvement of the



**Fig 1.** Magnified axial (left) and sagittal (right) views of 7T high-resolution FLASH-T<sub>2</sub>\* images (330x330 μm<sup>2</sup> in plane resolution) showing a WM lesion containing a central blood vessel in a patient with MS.

cortical spinal tract by Wallerian degeneration. Further studies are needed to elucidate the in vivo pathological substrates of WMLLwCV, its changes over time in relation to clinical outcome to clarify whether it can be used as a simple clinical marker for monitoring disease progression as well as the effects of therapeutic agents.



**Fig. 2.** Distribution of WMwCV lesion loads according to the periventricular (PV, red), subcortical (SC, green), corpus callosum (CC, blue), and other WM regions (O, purple) locations in different MS phenotypes. SPMS patients (middle) had significantly higher (p ranging from 0.001 to 0.02) PV, SC, O lesion loads than both RRMS (left) and CIS (right).

**References.** 1. Lucchinetti C. et al, Ann Neurol, 2000. 2. Tallantyre EC et al, Invest Radiol, 2009. 3. Mainero C. et al, Neurology, 2009.

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