WHITE MATTER MYELIN ALTERATIONS ARE DIFFUSE IN NEUROMYELITIS OPTICA SPECTRUM DISORDERS AND PREVAIL ON AXONAL DAMAGE

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INTRODUCTION and PURPOSE

Cerebrospinal fluid (CSF)-mediated factors are under investigation to explain normal appearing white matter (NAWM) abnormalities in multiple sclerosis (MS). Less is known about CSF influence on regional damage distribution in neuromyelitis optica spectrum disorders (NMOSD). T1/T2-weighted ratio seems to be a promising tool to quantify demyelination.

Aim of this study is to evaluate whether a gradient of NAWM damage is present in NMOSD patients.

METHODS

Study population: 20 aquaporine-4 (AQP4)-IgG positive NMOSD patients (according to Wingerchuk's 2015 criteria [1]), 20 relapsing-remitting MS patients (according to McDonald 2010 criteria [2]) and 20 age-matched healthy controls (HC) were studied. The administration of corticosteroids in the last month, history of head trauma, alcohol or drug abuse and diagnosis of other neurological diseases were considered as exclusion criteria. Within 48 hours from the MRI, all patients underwent a clinical evaluation, with the assessment of the expanded disability status scale (EDSS) [3].

MRI acquisition and analysis: using a 3.0 T Philips Achieva scanner, the following brain MRI sequences were acquired: axial dual-echo fast spin-echo, sagittal 3D T1-weighted magnetization-prepared rapid acquisition gradient echo and diffusion weighted sequences. Using a local thresholding segmentation technique (Jim 7.0, www.xinapse.com), brain T2-hyperintense and T1-hypointense lesion volumes (LV) were measured. The diffusion tensor (DT) was estimated in each voxel by linear regression [4] and fractional anisotropy (FA) and mean diffusivity (MD) maps were derived.

T1/T2-weighted ratio: maps were estimated from 3D T1-weighted and T2-weighted scans using an in-house implemented method (Matlab®) adapted from Ganzetti et al. [5]. T1/T2-weighted ratio measures, FA and MD values were assessed within concentric bands originating from CSF/WM interface and estimated as a function of the geodesic distance of the WM from the CSF (Figure 1).

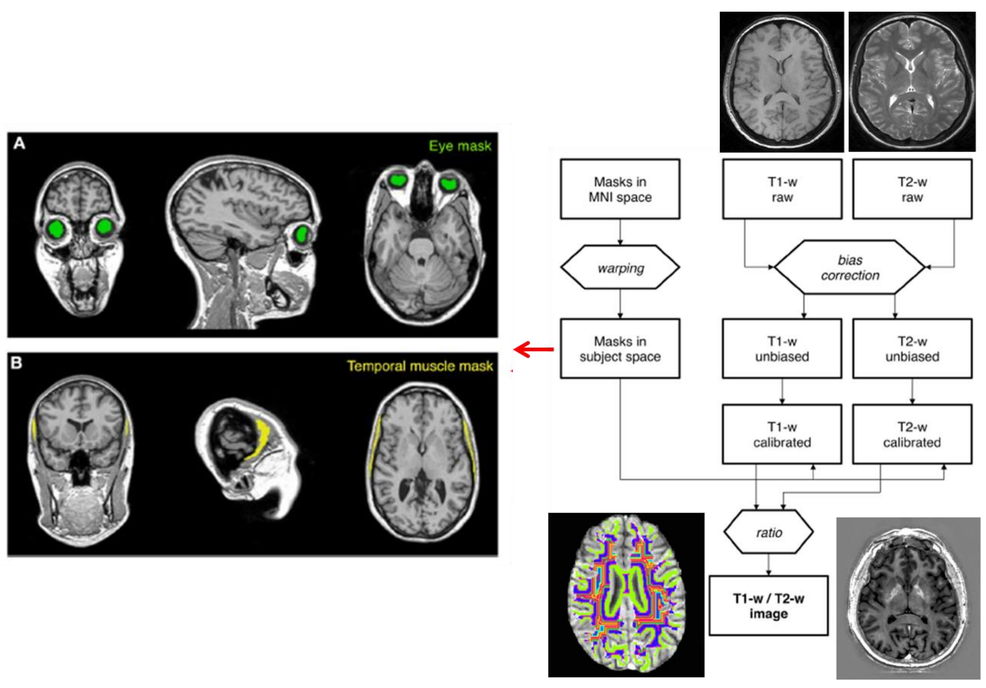

Figure 1. Algorithm to obtain the T1/T2-weighted ratio map (modified from Ganzett et al. [5] applied to a NMOSD patient. The obtainment of concentric bands is also represented.

Statistical Analysis: between-group comparisons of demographic, clinical and MRI variables were performed using two-sample t-test/Mann-Whitney U- test or general linear regression models age, sex and head-size corrected (SPSS software, version 23.0).

RESULTS

Clinical and conventional MRI measures: the three groups had similar demographic features (see Table 1).

Clinical variables				
	HC (n=20)	**NMOSD (n=20)**	**MS (n=20)**	**p**
Mean age (SD) [years]	43.6 (9.6)	43.5 (11.8)	43.1 (8.5)	0.989*
Males/Females	8/12	3/17	10/10	0.06^
Median disease duration (IQR) [years]	-	5.3 (2.9-11.2)	7.6 (4.4-7.3)	0.25+
Median EDSS (IQR)	-	3.75 (1.5-6.0)	2.0 (1.5-3.0)	0.11+
Global brain MRI variables				
Median T2 LV (IQR) [ml]	0.00 (0.00-0.02)	0.16 (0.03-0.41)	5.54 (2.96-8.38)	**<0.001+**
Median T1 LV (IQR) [ml]	0.00 (0.00-0.00)	0.10 (0.01-0.19)	3.59 (2.15-6.61)	**<0.001+**
Mean NBV (SD) [ml]	1581 (82)	1548 (59)	1510 (106)	**0.037***
Mean NWMV (SD) [ml]	851 (48)	842 (39)	837 (44)	0.062*
Mean NGMV (SD) [ml]	730 (43)	706 (39)	672 (75)	**0.007***
Mean NAWM FA (SD)	0.27 (0.015)	0.26 (0.06)	0.20 (0.10)	**0.003***
Mean NAWM MD (SD)	0.716 (0.30)	0.832 (0.19)	0.852 (0.27)	0.209*
Mean NAWM AD (SD)	0.969 (0.37)	0.998 (0.30)	1.091 (0.26)	0.443*
Mean NAWM RD (SD)	0.668 (0.27)	0.694 (0.22)	0.678 (0.31)	0.955*
Mean NAWM T1/T2-w ratio (SD)	1.328 (0.29)	1.153 (0.45)	1.237 (0.38)	0.359*

* ANOVA test; ^ $\chi 2$ test; +Kruskal-Wallis test.

Table 1. Main demographic, clinical and brain MRI features of HC, NMOSD and MS. Significant p values are shown in bold.

NAWM microstructural damage: FA values were similar between NMOSD patients and HC, whereas they were significantly reduced in the MS population, especially in the bands nearer to the CSF, compared to HC (p=0.01) and NMOSD (p=0.01). MD was significantly higher in the bands near the CSF interface in MS and NMOSD compared to HC (p=0.01, p=0.04 respectively), with NMOSD patients showing intermediate values. NMOSD patients had a severe reduction of the T1/T2-weighted ratio among all concentric bands compared to the other groups (p<0.001). MS patients had a milder T1/T2-weighted ratio reduction (Figure 2).

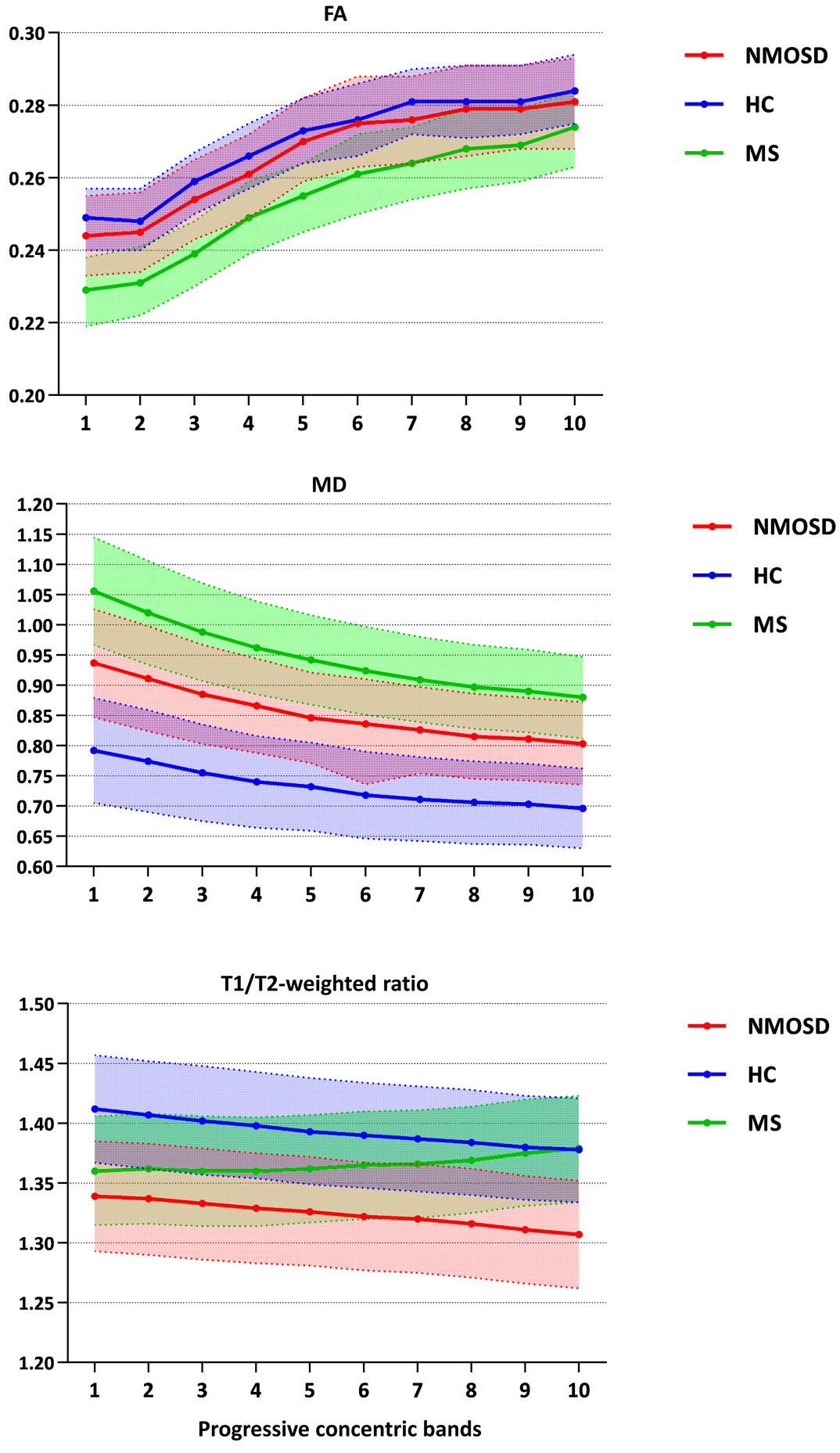

Figure 2. NAWM structural measures of damage in progressive concentric bands, starting from the CSF.

CONCLUSIONS

- **NAWM abnormalities occur in NMOSD, with a prominence of diffuse myelin alteration instead of axonal damage.**
- **Such alterations are not influenced by CSF distance, confirming the serological origin of the pathogenetic element in this condition.**
- **A gradient of microstructural damage can be observed in MS patients, with more severe alterations occurring in the bands nearer to the CSF interface**
- **The discrepancy between DTI measures and T1/T2-weighted ratio in NMOSD could mirror an increase of tissue extracellular water which could be specific for a channelopathy.**

LITERATURE

1) Wingerchuk, Neurology 2015; 2) Polman, Ann Neurol 2011; 3) Kurtzke, Neurology 1983; 4) Basser, J Magn Reson B 1994; 5) Ganzetti et al., Front Hum Neurosci. 2014.