MR T2-RELAXATION TIME AS AN INDIRECT MEASURE OF BRAIN WATER ACCUMULATION IN NEUROMYELITIS OPTICA SPECTRUM DISORDERS

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INTRODUCTION and PURPOSE

In neuromyelitis optica spectrum disorders (NMOSD) no biomarkers predicting short-term relapses are available. The blood brain barrier protects brain from water unbalance, with aquaporin-4 (AQP4) water channel on astrocytes being the main regulator of water influx and efflux. In NMOSD, its integrity might be threatened by anti-AQP4 antibodies, which trigger complement-mediated astrocytes damage. Accordingly, increased T2-signal in acute lesions ("bright spotty lesions") is considered specific for NMOSD, but it is unknown whether these patients present a chronic water unbalance.

Aim of this study to provide an estimation of brain water content in NMOSD by measuring T2-relaxation time (T2rt) and to assess whether it differs between clinically stable patients and patients having a short-term relapse.

METHODS

Study population: 77 aquaporine-4 (AQP4)-IgG positive NMOSD patients (according to Wingerchuk's 2015 criteria [1]) and 84 age-matched healthy controls (HC) were recruited at two European Centers (Milan and Belgrade). 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) [2]. Patients having a relapse within one month before or after the MRI acquisition were defined as short-term relapsing, whereas the other were considered clinically stable.

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 sequences. Using a local thresholding segmentation technique (Jim 7.0, www.xinapse.com), brain T2-hyperintense lesion volumes (LV) were measured.
After 3D-T1 weighted images lesion refilling, masks of the entire brain, grey matter, white matter and deep grey matter nuclei (caudate, pallidum, putamen, thalamus and hippocampus) were segmented and by using FSL SIENAx software and FMRIB's Integrated Registration and Segmentation Tool (FIRST) pipeline (FMRIB, Oxford, UK).

T2 relaxation time (T2rt): T2rt was calculated from brain dual echo turbo spin echo images assuming a mono exponential decay and T2rt maps of intra-lesional, normal appearing white matter (NAWM), gray matter (GM) and basal ganglia were derived (Figure 1).

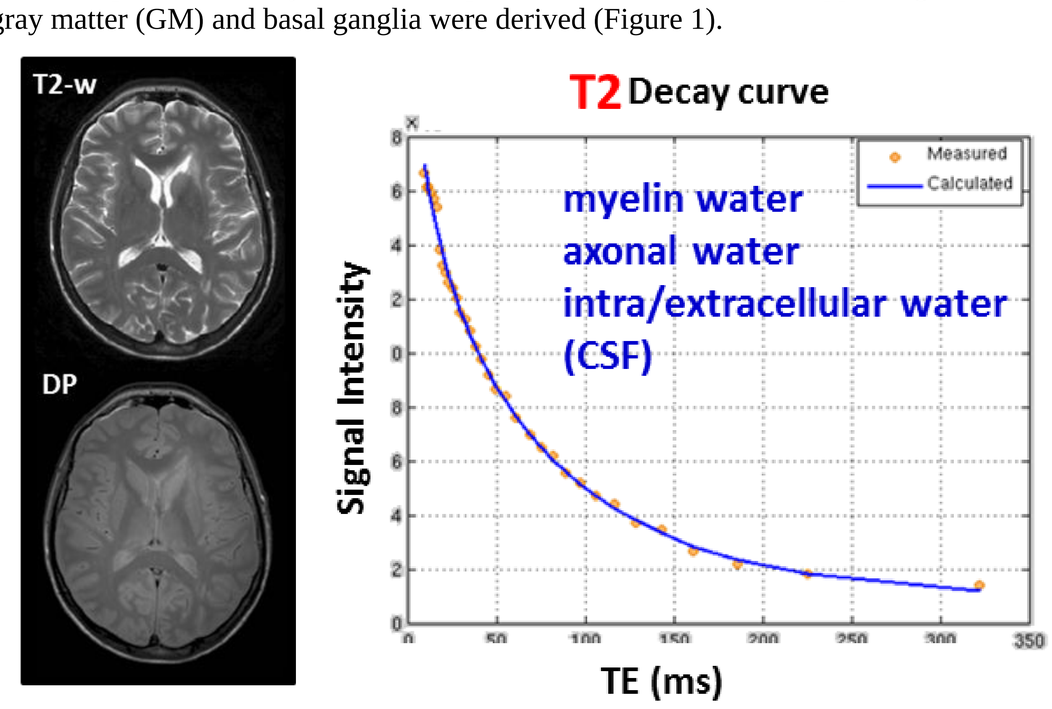

Figure 1. Calculation of T2rt from dual echo turbo spin echo images by assuming a mono exponential decay.

Statistical Analysis: Differences between NMOSD and HC were assessed with age-, sex- and site-adjusted linear models. ROC analyses were run to identify discriminators between stable and short-term relapsing patients. (SPSS software, version 23.0).

RESULTS

Clinical and conventional MRI measures are reported in Table 1.

Clinical and MRI features			
	NMOSD (n=77)	**HC (n=84)**	**p**
Mean age (SD) [years]	44.0 (13)	41.0 (13)	0.14*
Sex [F/M]	62/15	50/34	**0.004**^
Median disease duration (IQR) [years]	4.9 (2-11)	-	-
Median EDSS (IQR)	4.25 (2.5-6.5)	-	-
Global brain MRI variables			
Median T2 LV (IQR) [ml]	0.36 (0.11-1.48)	0.00 (0.00-0.75)	**0.002***
Mean NBV (SD) [ml]	1482 (93)	1582 (77)	**<0.001***
Mean NWMV (SD) [ml]	747 (80)	780 (86)	**0.007***
Mean NGMV (SD) [ml]	732 (64)	803 (81)	**<0.001***

*two-sample t test and ^Chi squared test.

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

NMOSD *vs* HC: Compared to HC, NMOSD patients had higher T2rt in the GM (103 vs 97 ms), NAWM (88 vs 84 ms) and putamen (75 vs 72 ms, p<0.001 for all).
Results are reported in Table 2 and Figure 2.

T2rt			
Structure	**NMOSD (n=77)**	**HC (n=84)**	**p**
GM	103 (102-105)	97 (96-100)	**<0.001**
NAWM	88 (87-89)	84 (84-86)	**<0.001**
Thalamus	96 (92-100)	90 (86-95)	0.07
Caudate	90 (84-96)	86 (78-93)	0.40
Putamen	75 (75-76)	72 (72-74)	**<0.001**
Pallidum	65 (65-66)	65 (64-66)	0.71

Data are reported as mean (95% CI); Age-, sex- and site-adjusted linear models
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Table 2. T2rt in NMOSD patients and HC. Significant p values are shown in bold.

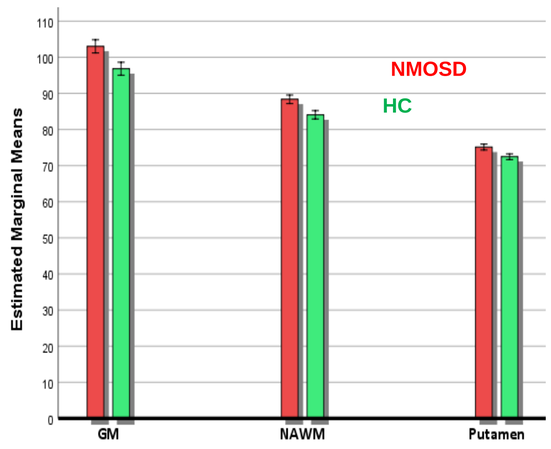

Figure 2. Box-plots of T2rt values in NMOSD and HC (significant results only).

T2rt in NMOSD patients having a short-term relapse: Short-term relapses occurred in 20/77 NMOSD patients (26%). According to ROC analysis, T2rt cut-offs of 87 ms in the NAWM, 87 ms in the thalamus and 88 ms in the caudatum were able to discriminate between short-term relapsing and stable patients (AUC=0.70, 0.76 and 0.79 respectively, p≤ 0.027).Results are reported in Figure 3 and Table 3.

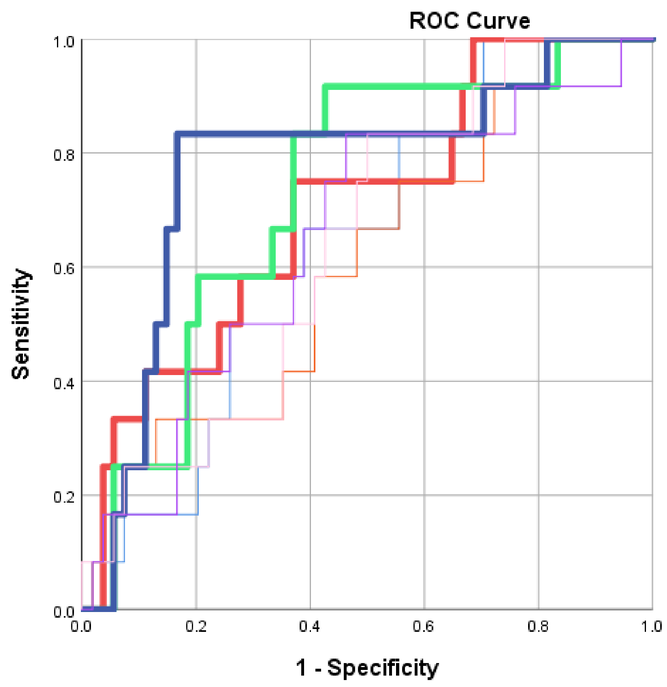

Figure 3. ROC curve of T2rt in GM (light blue), NAWM (red), thalamus (green), caudate (blue), putamen (light pink), pallidum (violet) and intra-lesional (pink). Bold lines represent significant results.

	Structure	T2rt (ms)	AUC	p
	GM	102	0.65	1.1
	NAWM	**87**	**0.70**	**0.027**
	Thalamus	**87**	**0.76**	**0.014**
	Caudate	**88**	**0.79**	**0.003**
	Putamen	76	0.64	0.13
	Pallidum	62	0.65	0.10
	Intra-lesional	122	0.61	0.24

Table 2. Results of the ROC analysis, reporting T2rt cut-offs, corresponding area under the curve (AUC) and p values.

CONCLUSIONS

- **NMOSD patients had increased T2rt values compared to HC**
- **These findings are in line with the hypothesis of subclinical brain water accumulation in this disorder.**
- **The burden of this alteration was higher in patients having a short-term relapse, hence potentially being useful in NMOSD disease monitoring**

LITERATURE

1) Wingerchuk, Neurology 2015; 2) Kurtzke, Neurology 1983.