

Title: “MR T2-relaxation time as an indirect measure of brain water accumulation in Neuromyelitis Optica Spectrum Disorders”

Short title: Brain water and NMOSD

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Background. 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. To provide an estimation of brain water content in NMOSD by measuring T2-relaxation time (T2rt) and to assess whether it differs in patients having a short-term relapse.

Methods. In this multicenter MR study, T2rt was calculated from brain dual echo turbo spin echo images assuming a mono exponential decay. T2rt maps of normal appearing white matter (NAWM), gray matter (GM) and basal ganglia were obtained from 77 AQP4-positive NMOSD and 84 HC. Short-term relapses were defined as occurring within one month before/after MRI scan. 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.

Results. T2rt was increased in the GM (103 vs 97 ms), NAWM (88 vs 84 ms) and putamen (75 vs 72 ms) of NMOSD patients ($p < 0.001$ for all). Short-term relapses occurred in 26% of patients. According to ROC analysis, T2rt cut-offs (ms) of 87 in the NAWM and thalamus and 88 in the

caudatum were able to discriminate between short-term relapsing and stable patients (AUC=0.70, 0.76 and 0.79 respectively, $p \leq 0.027$).

Conclusions. NMOSD patients had increased T2rt values, in line with the hypothesis of subclinical water accumulation in this disorder. The burden of T2rt alterations might be useful for identifying those patients with incipient or recent relapses.