Quantification of white matter myo-inositol by 1H-MRS at 3.0 T : Investigations in normal controls and in patients with clinically isolated syndrome (CIS) suggestive of multiple sclerosis

F. Träber[1], M. P. Wattjes[1], W. Block[1], O. Gür[1], M. Harzheim[2], J. Gieseke[3], T. Klockgether[2], H. Schild[1]

[1]Department of Radiology, University of Bonn, Bonn, Germany, [2]Department of Neurology, University of Bonn, Bonn, Germany, [3]Philips Medical Systems, Hamburg, Germany

Introduction: A variety of clinical ^{1}H-MRS studies has already established the role of myo-inositol (mIns) as a potential glial marker for inflammatory disease and cerebral demyelinization. Due to the increased chemical shift dispersion at higher field strength, the signals from the C1/C3 and the C4/C6 protons of mIns at 3.56 ppm appearing as a singlet at 1.5 T are split into a pseudo-doublet separated by 10 Hz at 3.0 T . First purpose of our study was to optimize the MRS acquisition protocol for the in-vivo determination of absolute myo-inositol concentration at 3.0 T in phantom and in volunteer examinations. In a second step, the optimized MRS protocol was applied to investigate possible metabolic alterations in the normal appearing white matter (NAWM) of patients with clinically isolated syndrome (CIS) suggestive of multiple sclerosis (MS).

Methods: On a clinical 3.0 T whole-body MR system (Gyroscan Intera 3.0 T, Philips Medical Systems) equipped with 30mT/m gradients, single-voxel ^{1}H-MRS (PRESS-localized, volume shimming up to second order) in the parietal white matter of the centrum semiovale was performed in 15 healthy controls. Echo time was varied in the range TE 30-140 ms in initial phantom experiments and in-vivo acquisitions to find the optimum TE value for mIns quantification, with respect to the intensity of the spin-coupled mIns multiplets at 3.54 ppm (C1/C3) and 3.62 ppm (C4/C6) and to the separation from adjacent glutamate/glutamine (Glx) signals. Metabolite signal ratios were then obtained from water-suppressed (dual inversion prepulses) measurements with TR/TE 2000/38 ms and TR/TE 2000/140 ms . Absolute concentrations of mIns, of choline compounds (Cho), of total creatine (tCr), and of N-acetyl aspartate (NAA) in the parietal white matter of the controls were determined by relating NAA to the internal water signal from the 8 ml (25 x 20 x 16 mm) MRS voxel in unsuppressed acquisitions with TR/TE 3500/140 ms and correcting for partial CSF volume by water T2 relaxometry (TR 5000 ms, 7 TE 40-750 ms). Additionally, relaxation times T2 of Cho, tCr, and NAA at 3.0 T were measured by mono-exponential fits to a series of 5 water-suppressed spectra with TR/TE 2500/50-400 ms in 11 of the controls. With voxel localization and acquisition parameters held identical to the control investigations, T2 relaxation times and absolute metabolite concentrations were also determined in the NAWM of 30 patients with CIS (5 of them classified as early-stage relapsing-remitting MS according to McDonald's criteria). Postprocessing of all data was performed by time-domain analysis using the AMARES algorithm [1] in the MRUI software package [2].

Results: At TE 35-40 ms, the components of the mIns multiplets at 3.54 and 3.62 ppm appeared as a well-resolved (mean Gaussian linewidth 4.8 ± 0.8 Hz in the patient group) doublet resonance with almost equal intensity of both constituents. TE > 40 ms resulted in spin dephasing of the C1/C3 signal (which is partially rephased at TE 90-110 ms), and at TE < 35 ms the C4/C6 component was influenced by contributions from the adjacent Glx-CH resonances (Fig. 1). T2 relaxation times of Cho and NAA at 3.0 T were slightly prolonged in the NAWM of the CIS patients (257 ± 34 ms and 339 ± 29 ms, respectively, vs. 232 ± 20 ms and 321 ± 16 ms in the controls), while T2 of tCr did not differ between patients and controls (192 ± 17 ms vs. 191 ± 8 ms). Although alterations in metabolite concentrations and signal ratios were less pronounced in the NAWM of the patients with CIS than those typically found in MS lesions (Fig. 2), the preliminary results (Table 1) of our 3.0 T study reveal a 10% increase of [mIns] and mIns/NAA and a significant 10% reduction of [NAA], NAA/Cho, and NAA/tCr in WM volumes appearing completely normal on MRI scans.

Discussion: The increased chemical shift dispersion at 3.0 T strongly alters the ^{1}H-MRS pattern of the mIns multiplets compared to lower field strengths, and an appropriate echo time has to be selected for optimum component resolution and quantification accuracy. First results of our clinical study indicate higher mIns concentration already in lesion-free NAWM during the very early stages of MS. These observations are in line with the results from a larger patient study recently obtained at 1.5 T [3]. With an increased number of cases, the significance of our findings and the sensitivity at 3.0 T compared to 1.5 T may be assessed.

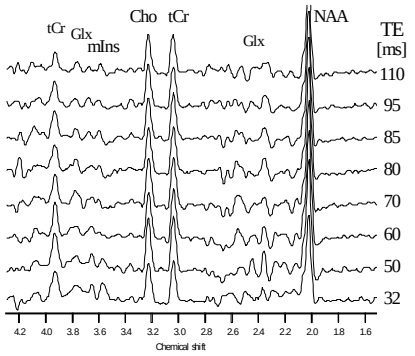

Fig. 1 : Variation of TE in healthy control

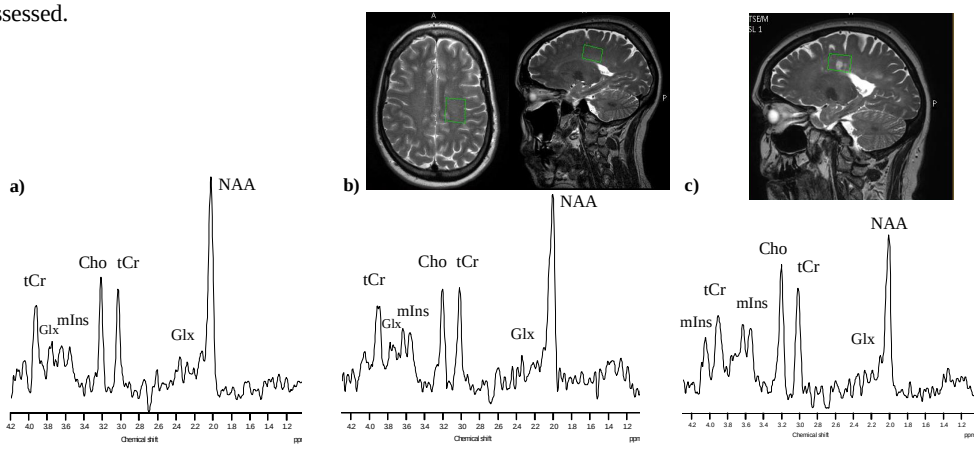

Fig. 2 : TR/TE 2000/38 ms, VOI 8 ml in **a)** healthy control, **b)** NAWM of CIS patient, **c)** lesion of MS patient (vertical scale normalized to identical signal intensity for tCr methyl resonance)

Table 1 : Absolute metabolite concentrations (mmol/l brain tissue) and signal ratios (at TE 140 ms for NAA ratios, at TE 38 ms for mIns ratios) in the parietal WM of the centrum semiovale, measured by ^{1}H-MRS at 3.0 T (SD = standard deviation, p-values from unpaired t-test)

	n		[mIns] *(mM)*	[Cho] *(mM)*	[tCr] *(mM)*	[NAA] *(mM)*	NAA/Cho	NAA/tCr	mIns/tCr	mIns/NAA
CIS patients	30	Mean	**4.27**	**2.12**	**7.30**	**13.3**	**2.29**	**2.56**	**0.58**	**0.31**
		SD	0.92	0.31	1.00	1.5	0.32	0.31	0.14	0.08
controls	15	Mean	**3.89**	**2.12**	**7.07**	**14.7**	**2.55**	**2.78**	**0.56**	**0.26**
		SD	0.72	0.40	0.88	1.6	0.41	0.24	0.09	0.04
						p < 0.01	*p < 0.05*	*p < 0.05*		*p < 0.05*

References

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