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QUANTITATIVE T2' IMAGING IN PATIENTS WITH CLINICALLY ISOLATED SYNDROME

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Abstract

Objective—T2' imaging has been shown to be sensitive to oxygen saturation changes in normal appearing white and grey matter (NAWM, NAGM) in patients with relapsing-remitting multiple sclerosis (RRMS). We aimed to explore the presence and extent of T2' changes in patients with a clinically isolated syndrome (CIS) and a possible association of T2' with conventional MRI and clinical outcomes.

Material & methods—Quantitative T2- and T2*-weighted images were acquired in 32 treatment-naïve patients with a CIS within 3 months of presentation and 15 age-matched healthy controls (HC). Quantitative T2' values were determined in six regions of interest (ROIs).

Results—T2' values in CIS did not differ significantly from those in HC. Among patients, T2' values correlated positively with the T2 lesion volume (T2LV, $r=0.34$, $p<0.05$). T2' values of the frontal NAWM correlated with the T2LV ($r=0.35$, $p<0.05$) and T2 lesion count ($r=0.4$, $p=0.02$).

Conclusion—As opposed to RRMS, patients with CIS did not show T2' alterations compared to HC. However, the association between the T2LV and higher T2' values suggests that T2' reflects disease evolution. In CIS metabolic changes might be masked by compensatory mechanisms and become overt when disease progresses as has been shown for RRMS patients.

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Introduction

MS is a chronic autoimmune disease of the CNS, which leads to diffuse as well as focal alterations with inflammation, glial proliferation, demyelination and axonal/neuronal damage. The diagnosis of MS is supported by the demonstration of lesions that are disseminated in time and space either clinically or radiologically. Although conventional MRI is well established for detecting white matter lesions and for measuring brain tissue volume, it is unable to detect subtle changes in the so-called normal appearing white- and grey matter (NAWM and NAGM) or to differentiate between inflammation, demyelination, remyelination, axonal loss and gliosis(1;2). Since there is increasing evidence that both focal and diffuse damage appear already at the earliest stages of the disease, there is a great need to develop MRI techniques that reflect the underlying pathomechanisms more specifically. Non-conventional MRI techniques like MR spectroscopy, diffusion tensor imaging (DTI) as well as magnetization transfer imaging (MTR) are capable of detecting NAWM pathology in disease stages as early as CIS⁽²⁻⁶⁾.

Quantification of metabolic activity as an indirect measure of tissue integrity may present an additional tool for the detection of disease pathology. PET studies could show metabolic changes in RRMS patients by measuring the rate of cerebral glucose metabolism(7). T2' imaging is based on blood oxygen level-dependent (BOLD) contrast mechanisms beside other effects and can be used to quantify the oxygen extraction fraction (OEF) by determining the ratio of deoxyhemoglobin over oxyhemoglobin(8;9). Due to its paramagnetic properties low levels of deoxyhaemoglobin are assumed to reflect an increased BOLD signal and by that high T2' values. As such, high T2' values reflect low levels of deoxy-Hb and a lower OEF (= deoxy-Hb/oxy-Hb) corresponding to a state of hypometabolism. In sum, high T2' values appear to be associated with focal hypometabolism in brain regions that might be altered due to diffuse or focal tissue damage by demyelination, gliosis, axonal disintegration or a combination of these. Recently, we have shown that quantitative T2' imaging is feasible and sensitive to detect metabolic changes in frontal NAWM and deep grey matter in RRMS patients(10).

Clinically isolated syndrome (CIS) is considered a pre-stage of MS, and both structural abnormalities on conventional MRI images as well as other paraclinical measures, e.g. intrathecal immunoglobulin synthesis, are associated with a higher likelihood of conversion to clinically definite MS (CDMS). Whereas CIS is defined as a first clinical event (optic neuritis, myelitis, brainstem syndrome and other) suggestive of MS, subtle pathological changes at that stage of the disease are usually undetectable by conventional MRI(2). Detection of such changes by MRI during CIS may increase our understanding of the pathogenetic mechanisms at the earliest stages of disease evolution and furthermore it may guide prognostic estimates as well as treatment decisions. Furthermore, it may help bridging the gap in MS patients where MRI abnormalities do not correlate well with clinical disability(11). The aim of our current study was twofold: i) To investigate whether T2' changes are already detectable during CIS. ii) To explore a potential association of T2' values with conventional MRI measures and clinical outcomes.

Material & methods

The study was approved by the Ethics Committee of the Board of Physicians in the State of Hamburg.

Patients

32 untreated CIS patients (mean age: 34, range 20–49 years; 22 female, 10 male) were scanned on average 3 months (range: 1–6 months) after their first clinical event regardless of

cerebrospinal fluid (CSF) and MRI abnormalities. 16 patients had optic neuritis, 12 had sensory symptoms suggestive of myelitis and 4 presented with either multifocal CIS (n=3) or brainstem syndrome (n=1). If patients were treated with steroids, the MRI was performed either before or a minimum of 30 days after steroid administration. MRIs were not performed earlier than 1 month after development of clinical symptoms. Patients not meeting these criteria were excluded. For the quantitative MRI measures 15 sex- and age-matched healthy controls (HC) (mean age: 37, range 24–52 years; 8 female, 7 male) served as controls. CIS patients were prospectively recruited from the MS Outpatient- and Day Clinics at the University Medical Center Hamburg Eppendorf, Hamburg, Germany. Written informed consent was obtained from all subjects participating in the study.

Clinical assessment

Neurological disability was assessed by a single experienced neurologist using the Expanded Disability Status Scale (EDSS)(12). In addition, the Hamburg Quality of life Questionnaire (HAQUAMS)(13) including items rating the extent of fatigue and depressive symptoms, respectively, was done. An averaged fatigue score (drawn from 2 index questions) and an averaged depression score (drawn from 2 index questions) were derived from the respective questions in the HAQUAMS questionnaire and used for the final regression analyses. Patients with an average fatigue score of at least 2 were considered fatigued or depressed respectively with an average of 2 in the depression score (category range of 1–5; 1= not at all, 2= little, 3= moderate, 4= much, 5= very much).

MRI acquisition

Brain MRIs were performed on a 1.5 Tesla scanner (Magnetom Sonata, Siemens, Erlangen, Germany) with a standard receive-only head coil and consisted of an axial spin echo proton density-weighted (PDW) and T2-weighted sequence (PD TE: 33 ms, T2 TE: 116 ms, TR 3540 ms, slice thickness: 5 mm, section spacing: 1.5 mm, FOV: 230 mm), a post gadolinium T1-weighted sequences (TE: 10 ms, TR 500 ms, slice thickness: 5 mm, section spacing: 1.5 mm, FOV: 230 mm), and a 3D T1-weighted sequence (MPRAGE, TE: 3.82 ms, TR 1900 ms, slice thickness: 1 mm, section spacing: 0 mm, FOV: 256 mm). Additionally, the MR protocol contained a quantitative T2- and T2*-weighted acquisition. For T2 determination, a fast spin-echo sequence with 15 echoes per shot was used to acquire images at three different TE of 12, 84, and 156 ms within a total acquisition time of 74 s (number of sections: 24; section thickness: 5 mm; section spacing: 0 mm; FOV: 240 mm; matrix: 74×128; TR: 4550 ms; and refocusing flip angle: 150°). T2*-weighted images were obtained with a single-shot gradient-echo echo-planar imaging sequence with TEs of 20, 52, and 88 ms and a TR of 3240 ms, giving a total acquisition time of 19 s (flip angle: 90°; other parameter as for T2).

T2' imaging post-processing

Calculation of T2': Quantitative T2 (qT2), qT2*, and qT2' maps were extracted on-the-fly on the MR system with an extended image reconstruction algorithm custom-made within the manufacturer's image calculation environment. T2 and T2* maps were calculated by fitting the signal intensity decay with TE to $SI(TE) = SI_0 \exp(-TE/T_2)$ and $SI(TE) = SI_0 \exp(-TE/T_2^*)$ for the T2 and T2* sequences, respectively. T2' is equivalent to T2* corrected for spin-spin (T2) effects according to the relationship: $1/T_2' = 1/T_2^* - 1/T_2$. For each voxel, the quantitative T2 and T2* values were used to generate T2' values by applying this relationship. Voxel sizes of the obtained parameter maps were 3.2×1.9×5 mm³.

MRI data analysis

All MRI scans were evaluated by one independent and experienced rater. Mean $T2'$ values were measured on $qT2'$ maps with a region of interest (ROI) approach using medical image processing, analysis, and visualization (MIPAV) software (Center for Information Technology, National Institutes of Health, Bethesda, Maryland). ROIs were placed in the following NAWM areas: anterior frontal subcortical (frontWM), occipitoparietal (opWM), superior central subcortical (sWM) and in the following areas of subcortical NAGM: head of the caudate nucleus (caudGM), centre of the thalamus (thalGM) and centre of the lentiform nucleus (lentGM). The ROIs were manually drawn on T2-weighted images (second echo of triple-echo T2 sequences) and then transferred onto the corresponding $qT2'$ images for each subject. ROIs for caudGM, thalGM and lentGM were defined in the same transaxial layer, at their greatest cross-section. ROIs for frontWM were located superior to GM-ROIs avoiding artefacts of paranasal sinuses. sWM ROIs were located one layer beneath the level of the hand knob, avoiding possible lesions present at this level (Figure 1). ROIs were chosen carefully to minimize partial volume effects. No ROIs were chosen in cortical GM because of substantial partial volume effects contributed by CSF. ROIs were placed exclusively in locations without apparent lesions in T2w imaging. In those patients in whom T2 lesions were detectable in the originally planned location, ROIs were located in the nearest region without T2 hyperintensities. ROI sizes could mildly vary depending on the individual lesion distribution and presence of perivascular spaces.

T2/PD-, T1 and T1Gd+ lesion volumes were measured with JIM Version 5.0.

Statistical analysis

Statistical analysis was performed using SPSS 15.0. $T2'$ values were obtained from all 32 patients and all 15 HC within 3 NAWM ROIs (frontWM, opWM, sWM) and 3 NAGM ROIs in each hemisphere (caudGM, thalGM, lentGM). Values from each ROI were first averaged over both hemispheres within each subject. Independent samples t-test was used to compare CIS patients and HC in terms of mean $T2'$ values in each region and as average over the NAWM region and the subcortical GM regions. Additional group comparisons within the CIS cohort were computed between fatigued vs. non-fatigued and depressed vs. non-depressed patients (independent sample t-test). All results underwent Bonferroni correction for multiple testing. Pearson correlation test was used to investigate the association between clinical and imaging parameters. For the association of imaging parameters and the depression score, partial correlation was controlled for age and fatigue, and for the association with fatigue, partial correlation was controlled for age and depression.

Results

Patients and HC

Clinical and conventional MRI characteristics for patients and controls are given in Table 1. There was no significant age difference between patients and controls ($p=0.2$). The median EDSS score in the patient group was 1.0 (range 0–3), and 70% had an EDSS score <2.0 . Results from the HAQUAMS were available from 26 patients out of 32 CIS patients. Fatigue and depression scores were overall low: 80% of the tested CIS patients had a depression score below 2 and 57% of the tested CIS patients had fatigue scores below 2. 87.5% (28/32) of the patients had abnormal MRI scans. According to the 2010 revision of the McDonald criteria 22/32 patients fulfilled the criteria for dissemination in space. Three out of these 22, in addition, met the criteria for dissemination in time. The remaining 10/32 patients fulfilled neither spatial nor temporal dissemination criteria.

MRI/T2'

14 (43%) out of the total of 32 CIS patients had a mean T2 lesion count below 4. Averaged T2' values were compared between groups in a combined analysis. T2' values of the CIS patients did not differ significantly from those in the control group in any of the ROIs examined (see Table 2).

Correlations between conventional MRI, T2' values and clinical scores in CIS

Of note, higher T2' values are assumed to reflect decreased tissue metabolism(9;10). Overall, higher T2' values were positively correlated with the T2 burden of disease (BOD). In detail, frontal T2' values showed a significant positive correlation both with T2 lesion volume ($r=0.35$, $p<0.05$), suggesting a lower oxygen extraction rate, and the number of T2 lesions ($r=0.40$, $p=0.02$). No correlations between T2' values, T1 lesion- and T1Gd+ lesion volumes were found. T2' values did not correlate with any of the clinical measures. No significant differences between the type of CIS (optic neuritis, myelitis, brainstem/multifocal CIS) and T2' values were found ($p>0.05$).

Group comparison

Group comparisons between fatigued and non-fatigued and depressed and non-depressed were measured for all variables. Neither fatigue ($p=0.42$) nor depression ($p=0.82$) were associated with higher T2' values.

Discussion

T2' values reflect tissue oxygen saturation and can be used to quantify the OEF(8;9). They have been shown to be sensitive to tissue metabolism changes that might relate to structural tissue damage in stroke (9). Recently, we described T2' abnormalities in the NAWM of a group of RRMS patients, especially in the frontal white matter(10). Since our findings were consistent with those of PET studies showing a hypometabolism in the frontal NAWM (7), we speculated that T2' changes might be due to a reduction of the OEF secondary to decreased metabolism.

The aim of the present study was to extend our prior analysis to patients with very early disease to examine, whether changes in T2' values are already detectable at the stage of CIS. However, findings in CIS patients did not differ significantly from HC. At first glance this is surprising, since structural and metabolic brain abnormalities have previously been reported in MS patients even during very early disease stages with sophisticated MRI techniques (14). MTR and DTI studies reported subtle tissue abnormalities in the NAWM and NAGM in CIS and early RRMS patients (3–6;15). Further support for the presence of tissue injury in CIS came from studies demonstrating early deep grey matter atrophy and metabolic dysfunction(14;16–19).

The fact that we were unable to demonstrate T2' abnormalities in our group of CIS patients may be explained by a number of factors. First, the majority of our patients (53%) underwent MRI at a very early time-point, i.e. within three months of a first clinical episode. Second, our CIS patients had a relatively benign clinical presentation: 50% of the patients presented with optic neuritis, which might be associated with a better clinical outcome (20;21), and 70% had EDSS scores below 2.0. Third, the overall MRI lesion load was low. 43% of patients showed less than 4 T2- lesions, therefore a lower likelihood to convert to clinically definite MS early as well as to develop higher grades of disability over the long term (20;22–24). The early disease stage, the mild clinical manifestations, and hence the substantial fraction of patients that may not convert early to clinically definite MS, might together explain the lack of significant differences in T2' values between CIS patients and

HC in our study. Further, a possible explanation could be, that, although structural brain damage occurs early as shown by histopathology and DTI studies(25), metabolic abnormalities appear secondary to structural injury and remain compensated until more advanced disease stages. Only then may such metabolic alterations might become evident as shown in our prior study in RRMS patients. This hypothesis is further substantiated by the positive correlation between T2 BOD and T2' values in the current study. This suggests that structural brain damage is associated with regional metabolic decrease. In this scenario, T2' values would be a function of disease progression and become abnormal when measured at more advanced disease stages like clinically definite RRMS. Previous PET studies have not only shown a reduced glucose metabolism in the frontal NAWM, thalamus and whole brain of multiple sclerosis patients with an established diagnosis(7;26;27), but longitudinal observations in RRMS could also demonstrate a decrease in global cortical cerebral glucose metabolism during a 2 year follow up period(27). Furthermore, comparison of regional cerebral metabolic rate of glucose (rCMRglu) between RRMS patients and patients with chronic progressive MS showed worsening of grey matter rCMRglu with disease progression(28). The latter studies examined RRMS or progressive MS patients, and it is therefore difficult to extrapolate to possible alterations in CIS patients. Moreover, gene expression studies in NAWM of RRMS patients documented an upregulation of genes involved in ischemic preconditioning including hypoxia-inducible factor-1(29). These alterations were interpreted as adaptive neuroprotective mechanisms, and it is conceivable that they may, at least for some time during CIS, prevent the detection of T2' alterations. Finally, T2' values are assumed to reflect metabolic changes that are highly dynamic and, in consequence, might mirror rather a disease activity state than fixed tissue damage compared to other non-conventional MRI techniques (e.g. MTR, DTI). To prove this further, T2' imaging should be validated against other non-conventional techniques in future studies. Admittedly, an alternative explanation of our findings could be that metabolic changes do occur in our CIS patients, but they are below the level of sensitivity of the employed T2' imaging technique. Studies employing alternative methods such as ¹H-MRS and perfusion MRI have reported changes in brain metabolites and cerebral blood flow since the earliest stage of the disease(30). For the T2' value calculation, different imaging methods were used for T2 (FSE) and T2* (EPI) quantification which can hamper the T2' calculation due to the different sensitivities to geometric distortions and artefacts. Prior stroke studies using the same T2' mapping protocol clearly showed focal hypometabolism correlating with brain areas which subsequently showed ischemic patterns on MRI(9;31;32). Theoretically, in this early CIS cohort relatively low levels of hypometabolism in the investigated ROIs might well have been below the level of sensitivity of T2' imaging.

Nonetheless, future studies with a larger sample of CIS patients and longitudinal T2' imaging will shed further light on the dynamics of T2' changes across disease stages and during disease evolution. A combined approach with high- field MRI could probably further improve correlations between focal tissue changes and T2' abnormalities(33).

Finally, we did not find any associations between T2' values and the fatigue and depression scores, which may again be due to the relative mild clinical phenotype of our cohort. It has previously been shown that MS patients with fatigue show reduced metabolism (rCMRglu) in prefrontal cortex, the adjacent white matter and basal ganglia as assessed by PET(7;34). Moreover, cognitive impairment has also been shown from the earliest stages of the disease(35). The majority of our patients, however, were not significantly fatigued nor depressed when examined with the HAQUAMS. In the future, the assessment of fatigue, depression and cognition with i.e. elaborated questionnaires will enable a more comprehensive evaluation of these symptoms.

Conclusion

Regional brain T2' values did not differ significantly between CIS patients and HC. We suggest that metabolic alterations appear as a function of disease progression as shown by the significant positive correlation between T2 BOD and T2', indicating a reduction in metabolism with an increase of T2 lesion number and volume. Longitudinal studies are warranted to elucidate the dynamics of T2' abnormalities and the relationship with disease progression.

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Figure 1. Regions of interest (ROIs) displayed on a T2' map
(frontal NAWM= frontWM, occipitoparietal NAWM = opWM, subcortical NAWM= sWM, the caudate nucleus= caudGM, thalamus= thalGM and lentiiform nucleus= lentGM).

Table 1

Demographics, clinical and conventional MRI findings of CIS patients

Clinical presentation	
- Optic Neuritis	16 (50%)
- Myelitis	12 (37.5%)
- Multifocal CIS/Brainstem syndrome	4 (12.5%)
Disease duration [months]	
Mean (range)	3 (0–6)
EDSS	
Median (range)	1 (0–3)
Depression [score]	
- Depressed/	1.2 (21)/
- Non-Depressed *	3.4 (5)
Mean score (n)	
Fatigue [score]	
- Fatigued/	1.1 (15)/
- Non-Fatigued †	2.5 (11)
Mean score (n)	
T2 lesions [n]	8 (0–33)/
T2 lesion volume [ml]	1.4 (0–6.1)
Mean (range)	
T1 lesion volume [ml]	0.8 (0–2.1)
Mean (range)	
T1 Gd+ lesion volume [ml]	0.03 (0–0.6)
Mean (range)	

CIS, clinically isolated syndrome; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging.

* Depressed (any score ≥ 2)/non-depressed (any score < 2); as assessed by the HAQUAMS

† Fatigued (any score ≥ 2)/non-fatigued (any score < 2); as assessed by the HAQUAMS

Table 2

T2' values from different brain regions in CIS patients and HC

	caudGM	lentGM	thalGM	frontWM	sWM	opWM
HC	120,74 (32,03)	116,90 (21,33)	144,95 (16,34)	187,12 (26,76)	185,93 (25,15)	184,51 (12,41)
CIS	121,93 (29,30)	123,38 (20,10)	144,18 (18,80)	184,51 (31,83)	176,44 (33,89)	181,59 (20,85)

HC, healthy controls (n = 15); CIS, CIS patients (n = 32); frontWM, frontal NAWM; opWM, occipitoparietal NAWM; sWM, subcortical NAWM; caudGM, caudate nucleus grey matter; thalGM, thalamic grey matter; lentGM, lentiform nucleus grey matter. Values are mean (SD); unit: ms.