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Research Article

Can We Identify Abnormalities in Normal Appearing White Matter of Patients with Clinically Isolated Syndrome? Use of Magnetization Transfer Imaging

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Summary

Objective: To reveal hidden pathological distortions in normal appearing white matter (NAWM) and corpus callosum (NACC) of patients with clinically isolated syndrome (CIS) using advanced magnetic resonance imaging (MRI) sequences.
Methods: Twelve patients with CIS and 12 age and sex-matched healthy individuals were enrolled in the study. Duration of the disease and first and last Expanded Disability Status Scale (EDSS) scores were recorded. In both groups, SE T1 WI, PD WI, SE T2 WI, FLAIR, T1-W magnetization transfer imaging (MTI), GE T2 WI, GE T2-W MTI, diffusion weighted (DWI) and diffusion tensor imagings (DTI) were performed and used for obtaining apparent diffusion coefficient (ADC), fractional anisotropy (FA), T1 magnetization transfer ratio (MTR), and GE MTR in each group. Values obtained by measurements of these parameters from periventricular NAVW (4 locations) and NACC (2 locations) were compared between patient and control groups. Duration of the disease, and first and last EDSS scores were compared with T1 MTR values. Statistical significance was set as $p < 0.05$.
Results: Mean T1 MTR values were significantly different at all locations, while GE MTR, ADC and FA values were not. Disease duration was found to have a moderate negative significant correlation with T1 MTR values at the splenium of the corpus callosum (r: -0.653, p: 0.021).
Conclusions: We believe that T1-W MTI and T1 MTR will be of benefit in demonstrating subtle pathological distortions of the NAWM and NACC of patients with CIS.

Key words: Multiple sclerosis; clinically isolated syndrome; white matter; magnetic resonance imaging; magnetization transfer imaging; diffusion weighted imaging; diffusion tensor imaging

Klinik İzole Sendromlu Hastalarda Normal Görünümlü Beyaz Madde Anormallikleri Tanımlayabilir miyiz? Magnetizasyon Transfer Görüntülemenin Kullanımı

Özet

Amaç: Klinik izole sendromlu (KIS) hastalarda normal görünen beyaz cevher (NGBC) ve korpus kallosumda (NGKK) saklı kalmış patolojik bozulmaları ileri manyetik rezonans görüntüleme (MRG) sekansları ile ortaya çıkarmak.
Yöntem: Klinik izole sendrom tanılı12 hasta ile aynı yaş ve cinsiyette sağlıklı olgular çalışmaya alındı. Hastalık süresi ile ilk ve son Genişletilmiş Özürlülük Durum Ölçeği (GÖDÖ) skorları kaydedildi. Her iki grupta SE T1 ağırlıklı, PD ağırlıklı, SE T2 ağırlıklı, FLAIR, T1 ağırlıklı magnetizasyon transfer görüntüleme (MTG), GE T2 ağırlıklı, GE T2 ağırlıklı MTG, difüzyon ağırlıklı (DAG) and difüzyon tensor görüntüleme (DTG)

gerçekleştirildi ve apparent diffusion coefficient (ADC), fraksiyonel anizotropi (FA), T1 magnetizasyon transfer oranı (MTO), ve GE MTO'larının elde edilmesi için kulanıldı. Periventriküler NGBC (4 lokalizasyon) ve NGKK'dan (2 lokalizasyon) yapılan ölçümler ile elde edilen değerler hasta ve kontrol grupları arasında karşılaştırıldı. Hastalık süresi, ilk ve son GÖDÖ değerleri T1 MTO ile karşılaştırıldı. İstatistiksel anlamlılık $p < 0.05$ olarak belirlendi.

Bulgular: Hasta ve kontrol grubunun ortalama T1 MTO ölçümleri tüm lokalizasyonlarda anlamlı farklılık gösterirken, GE MTO, ADC ve FA değerleri göstermedi. Korpus kallosum spleniumunda hastalık süresi ile T1 MTO ölçümleri arasında negatif yönde orta güçte anlamlı korelasyon bulundu (r:- 0.653, p: 0.021)

Sonuç: KİS hastalarında NGBC ve NGKK'da gizli patolojik değişimleri göstermede T1 ağırlıklı MTG ve T1 MTO'nun yararlı olacağını düşünmekteyiz.

Anahtar Kelimeler: Multipl skleroz; klinik izole sendrom; beyaz madde; magnetik rezonans görüntüleme; magnetizasyon transfer görüntüleme; difüzyon ağırlıklı görüntüleme; difüzyon tensor görüntüleme

INTRODUCTION

Multiple sclerosis (MS) is the most common inflammatory demyelinating disease of the central nervous system[1,3]. Clinical onset in most patients with typical MS is in the form of an acute or subacute demyelinating attack described as optic neuritis, isolated brainstem, isolated partial spinal cord syndrome or isolated hemispheric syndromes due to damage in a single part of the central nervous system[24]. This type of disease presentation, which is suggestive of MS, is known as clinically isolated syndrome (CIS)[11].

Conventional magnetic resonance imaging (MRI) is the preferred imaging method for the diagnosis of MS[14]. However, conventional MRI cannot display the microstructural changes in normal-appearing white matter (NAWM), which may be relevant to the severity of the disease and could change the therapy regimen. These changes can be shown with advanced MRI sequences[2,3,6,9,10,12,13,16,29,31]. Like MS, showing microstructural pathological changes in NAWM in patients with CIS is important in helping to slow down disease progression to MS by early treatment. But there is no consensus about the microstructural changes that may present in the NAWM of patients with CIS by MRI[3,5,9,11,13,19,20,26,28,30,31]. In this study we aimed to demonstrate the presence of possible microscopic structural changes by examining the NAWM and normal appearing corpus callosum (NACC) of patients with CIS with T1-weighted (W) - magnetization transfer imaging (MTI), T2-W gradient echo (GE) MTI, diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) in comparison with an age and sex-matched healthy control group.

MATERIAL AND METHODS

Patients

Permission for the research was received from the Institutional Ethics Committee. Information about the purpose of the study and how the study would be performed was given to all patients and the control group, and an informed consent form was signed.

Twelve patients (6 male, 6 female patients) with one demyelinating attack, followed-up with a diagnosis of CIS by the Department of Neurology of our institution, and age and sex matched healthy individuals in a control group were included in the study. The control group was evaluated to exclude CIS or MS

disease by the Department of Neurology of our institution.

The diagnosis of patients (optic neuritis or transverse myelitis) and disease duration (month) were determined. The Expanded Disability Status Scale (EDSS) test was performed for patients with CIS at the time of the first diagnosis and prior to MRI by the Department of Neurology of our institution in order to measure and evaluate inability in 8 functional systems[21]. A score was given to the patients between 0 and 10 in proportion to the severity of disease in which a score of 0 indicates a normal neurological examination, while 10 points indicate death due to MS.

Magnetization Resonance Imaging

MRI was performed with a 1.5 Tesla magnetic resonance imager (Magnetom Symphony 1.5-T, Siemens Medical Solutions, Erlangen, Germany). Proton density (PD) and spin-echo (SE) T2-weighted imaging (WI) were performed for the patient and control groups to identify the existence of lesions in white matter and corpus callosum. In the patient and control groups, SE T1 WI, PD WI and SE T2 WI, fluid attenuated inversion recovery (FLAIR), T1-W MTI, GE T2-WI, GE T2-W MTI, DWI and DTI sequences were performed. For magnetization transfer ratio (MTR) measurements, T1-W MTI and GE T2-W MTI sequences, for the measurement of apparent diffusion coefficient (ADC) DWI, and for the measurement of fractional anisotropy (FA) DTI analysis were used.

MRI sequences

** SE T1 WI: Axial, slice thickness: 5 mm, TR: 517 milisecond (msn), TE: 11 msn, average: 2, matrix: 208x256, FOV: 240 mm, 20 images.

** Dual echo PD WI and SE T2 WI: Axial, slice thickness: 5 mm, TR: 3090 msn, TE: 14/86 msn, average: 2, matrix: 448x512, FOV: 230 mm, 40 images.

** FLAIR sequence: Axial, slice thickness: 5 mm, TR: 9560 msn, TE: 114 msn, TI: 2300 msn, average: 1, matrix: 256x256, FOV: 230 mm, 20 images.

** T1 W MTI: Axial, slice thickness: 5 mm, TR: 517 msn, TE 11 msn, average: 2, matrix: 208x256, FOV: 240 mm, 20 images.

** GE T2-WI: Axial, slice thickness: 5 mm, TR: 794 msn, TE: 26 msn, FA: 20, average: 1, matrix: 166x256, FOV: 230 mm, 20 images.

** GE T2-W MTI: Axial, slice thickness: 5 mm, TR: 794 msn, TE 26 msn, FA: 20, average: 1, matrix: 166x256, FOV: 230 mm, 20 images.

** DWI: EPI, Axial, slice thickness: 5 mm, TR: 3700 msn, TE 97 msn, b:0 sn/mm^2 and b: 1000 sn/mm^2, EPI factor: 128, bandwidth: 1260 Hz/px, average: 3, matrix: 128x128, FOV: 230 mm, 40 images.

** DTI: EPI, Axial, slice thickness: 5 mm, TR: 5000 msn, TE: 118 msn, EPI factor: 128, bandwidth: 1388 Hz/px, averages: 3, matrix: 144x144, FOV: 230 mm, 260 images.

Measurements:

Measurements of NAWM and NACC of the patient and control groups were performed at the locations listed below (Figure).

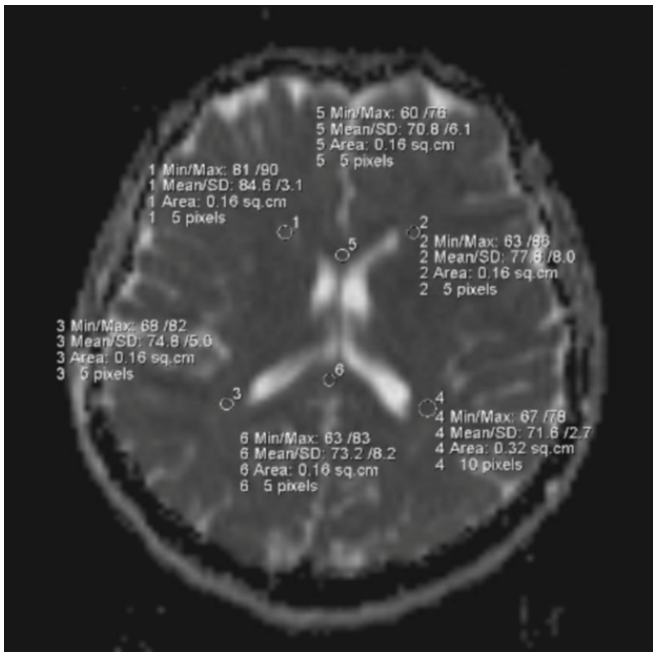

Figure : *Locations of measurements. Genus and splenium of the corpus callosum and frontal and occipital horns of the lateral ventricles as seen in the axial ADC image.*

1 - Right frontal lobe normal-appearing periventricular white matter

2 - Left frontal lobe normal-appearing periventricular white matter

3 - Right parietal lobe normal-appearing periventricular white matter

4 - Left parietal lobe normal-appearing periventricular white matter

5 – Genus of the normal-appearing corpus callosum

6 – Splenium of the normal-appearing corpus callosum

Region of Interest (ROI) measurements:

Region of interest (ROI) measurements were performed on a workstation (Leonardo Workstation, Siemens Medical Solutions, Erlangen, Germany). On the workstation, the measurements were performed on ADC and FA maps, SE T1-WI, T1-W MTI, GE T2-WI and GE T2-W MTI with a mean of 0.2 cm^2 ROI without clinical knowledge and neurological examination of the patient and the control groups at the described locations listed above. SE T2-WI was used as an anatomical reference in order to not to make measurements from the lesions and a 1 mm safety margin was left to prevent partial volume effects. If there was a lesion, the ROI measurements were performed from the NAWM surrounding the lesion.

For the calculations of MTR's (T1-MTR and GE-MTR) in the described locations, SE T1 WI, T1-W MTI, GE T2-WI and GE T2-W MTI weighted images were used. ROI measurements were performed and the mean signal intensity (Ms) obtained from T1-W MTI or GE T2-W MTI was subtracted from the mean signal intensity (Mo) obtained from SE T1 WI or GE T2-WI and divided by the Mo value. The value obtained was multiplied by 100 and MTR values were calculated[13].

Statistical Analysis

Twenty-four cases included in the study were divided into patient and control groups. In both groups, the ADC, FA, T1

and MTR values, obtained by the measurements from the described locations, were compared to determine micropathological structural changes in NAWM and the NACC. Mann-Whitney U test was used for comparison of means between groups in the statistical analyses. Disease duration and the first and last EDSS scores of patients with CIS were compared with T1 MTR values by Spearman's rank differences correlation test to show the degree of relationship between variables. Correlation coefficient (r):

0.00 to 0:25 very weak correlation

0.26 to 0:49 weak correlation

0.50 - 0.69 moderate correlation

0.70 - 0.89 high correlation

0.90 - 1.0 was evaluated as a very high correlation. Statistical significance was considered as $p < 0.05$ and bidirectional.

RESULTS

Of the 24 subjects (12 patients and 12 controls) included in this study, 12 were female (50%) and 12 were male (50%). The mean age of the patients and the control group was 36.33 ± 9.53 years (range of 24 to 53 years, interquartile range 15 years). Mean disease duration was 21.33 ± 15.46 months (range of 3 to 60 months, interquartile range 19 months). The clinical diagnosis was transverse myelitis in 7 patients and optic neuritis in 5 patients. The mean first and last EDSS score of the patients were 1.67 ± 1.07 (range 0-3) and 0.83 ± 1.03 (range 0-3).

In PD WI and SE T2 WI, there was no white matter abnormality in 5 patients and no additional lesion in 7 patients in the CIS group. There was no detected abnormal signal intensity in the white matter and the corpus callosum by PD WI and SE T2 WI in the control group.

The mean ADC, FA and GE MTR values of the patient and control groups were compared and there was no significant difference in any locations (Table 1). In the patient group, T1 MTR values were lower than the control group and showed significant differences in all locations (Table 1). Disease duration and the first and last EDSS scores were compared with T1-MTR values at all locations, and only a moderate negative correlation between disease duration and corpus callosum splenium was found to be statistically significant ($r = - 0.653$, $p = 0.021$) (Table 2).

Table 1. Comparions of mean ADC, FA GE MTR and T1 MTR values between CIS and control group.

		RFPVWM		LFPVWM		RPPVWM		LPPVWM		CC Genu		CC splenium	
		mean±SD	p	mean±SD	p	mean±SD	p	mean±SD	p	mean±SD	p	mean±SD	p
ADC	CIS	0.753±0.069	*0.70*	0.718±0.053	0.41	0.811±0.054	*0.60*	0.797±0.05	0.4	0.695±0.103	*0.64*	0.71±0.064	*0.88*
	Control	0.764±0.078		0.705±0.055		0.800±0.060		0.774±0.065	3	0.704±0.084		0.712±0.069	
FA	CIS	0.445±0.067	*0.20*	0.481±0.106	0.79	0.5±0.087	*0.16*	0.523±0.071	0.2	0.79±0.038	*0.13*	0.84±0.093	*0.95*
	Control	0.499±0.106		0.492±0.07		0.544±0.071		0.546±0.097	8	0.765±0.045		0.849±0.059	
GE	CIS	41.46±4.05	*0.10*	38.35±4.62	0.43	40.55±3.89	*0.11*	38.89±4.00	0.1	40.36±4.42	*0.50*	42.98±3.51	*0.26*
MTR	Control	40.21±1.7		40.1±2.18		42.63±2.21		40.84±2.62	9	41.19±4.6		77.2±113.39	
T1	CIS	25.008±5.54	*0.01*	25.45±4.84	0.01	25.03±5.94	*0.009*	24.7±5.6	0.0	26.62±5.43	*0.02*	26.17±5.93	*0.004*
MTR	Control	28.45±1.99		28.34±1.49		28.55±1.48		28.34±1.27	1	30.07±1.68		30.2±1.82	

Table 2. Correlations between T1 MTR values and disease duration, first and last EDSS scores.

		Disease duration (month)	First EDSS score	Last EDSS score
RFPVWM	r	-0.265	0.233	0.230
	p	0.404	0.466	0.471
LFPVWM	r	-0.16	0.006	-0.021
	p	0.62	0.985	0.949
RPPVWM	r	-0.554	0.272	0.155
	p	0.061	0.392	0.631
LPPVWM	r	-0.333	0.398	0.52
	p	0.29	0.2	0.083
CC Genu	r	-0.473	0.263	0.23
	p	0.121	0.41	0.471
CC splenium	r	-0.653	0.004	-0.155
	p	0.021	0.99	0.631

DISCUSSION

Clinically isolated syndrome, suggestive of MS, can emerge as an acute or subacute demyelinating attack due to damage of a single part of the central nervous system[11,24]. Conventional MRI has a significant role in the diagnosis and follow-up of the disease, but a limited role in displaying abnormalities in NAWM and NACC, which are important for initiating early treatment in terms of conversion to MS[8,23]. In our study, ADC, FA, GE MTR and T1 MTR values of patients with CIS obtained from NAWM and NACC were compared with the control group and T1 MTR values showed significant differences. To our knowledge, this study was unique in comparing all these parameters with a same age and sex matched control group.

Quantitative information related to myelin destruction in demyelinating diseases may be obtained with DWI and the ADC maps, which reflect the movement of water molecules in tissues. In patients with MS, ADC values of hyperintense lesions and NAWM detected on T2-WI were observed to be significantly higher than the healthy control group[6,11,12,16]. Also, decreased FA values in DTI were shown in NAWM, in accordance with MTI, indicating myelin damage in axonal structures[10,18]. Although it is a demyelinating disease, we did not find a significant difference in ADC and FA values of NAWM and NACC between patients with CIS and the control group in our study. In a study conducted by Ge et al., there was no significant difference in ADC and FA values in the frontal and occipital NAWM in 15 patients with early MS and 12 control patients[13]. Similarly, Caramia et al. did not find a statistically significant difference in ADC values of 19 patients with a single demyelinating attack[5]. Also, Vishwas et al. compared mean ADC and FA values of 20 children with MS, 27 children with forms of CIS and a sex and age matched control group in their study and found no significant difference between CIS and control group

in 3 major normal appearing white matter pathways, while they found significant abnormalities at the same locations in children with MS[31]. Gallo et al. compared 45 early diagnosed CIS patients with a control group including 22 healthy subjects with MTI histograms and showed that the average diffusivity increased and FA values decreased, with statistically significant differences ($p = 0.01$ and $p < 0.001$, respectively)[11]. However, the patient group showed clinical evidence for a diagnosis of MS by dissemination in time in 29 patients and dissemination in space in 45 patients, which might have affected their results[11]. Raz et al. compared 34 CIS diagnosed patients with 16 healthy volunteers as a control group and concluded that there was diffuse brain damage secondary to white matter changes in CIS patients, which could be displayed by FA reduction[27]. But, similarly to Gallo et al., 33 of these patients developed into MS in a one year follow-up, which could explain the significant FA reduction in CIS diagnosed patients in their study[28].

The MTI technique, which can be added to conventional MRI sequences, is used to characterize MS lesions and can be used to reveal hidden disease in NAWM[7,22]. MTR values obtained by MTI are directly proportional to the concentration of macromolecules such as myelin, so reduced MTR can show the presence of pathological and / or microstructural tissue injury[17]. Recent MTI studies on patients with MS indicated statistically significant differences in MTR values at NAWM and NACC[2,3,9,13,29]. But studies on patients with CIS have given controversial results[3,9,19,20,26,30]. In our study, which was unique in comparing the GE MTR and T1 MTR values between patients with CIS and an age and sex matched control group, T1 MTR values from NAWM AND NACC in CIS patients were found to be lower than the control group with a statistically significant difference at all locations listed above. GE MTR values of the patients were lower than the control group except for one location, but they were not significant differences. Decreased T1 MTR values of patients in NAWM and NACC suggest that microstructural pathological changes may start in patients with CIS. In addition, our results may indicate that T1-W MTI is more sensitive for showing pathological changes than GE-W MTI. Sequence selection, absence of standards in the measurement locations and methods are important factors for the different results in MTI studies in patients with CIS. We believe that prospective studies of MTI sequences, locations and methods of measurements are essential to reflect the loss or damage of myelin in patients with CIS.

Ranjeva et al. and Pike et al. did not find a correlation between the first and last EDSS scores and T1 MTR values of patients diagnosed with MS, while Traboulsee et al. found a moderate negative correlation between EDSS and normal appearing brain tissue MTR values of patients with MS[25,26,30]. In our study, there were no correlations between first and last EDSS with T1 MTR values. Catalaa et al. did not detect a correlation between disease duration and MTR values in their study of 23 patients with MS[4]. In our study, there were negative correlations between disease duration and T1 MTR values, but only in the splenium of the NACC a moderate negative correlation was found to be statistically significant. This may be due to relatively low disease duration in our study, which may explain our results. Disease duration may alter the MTR values related to the demyelinating process in patients with CIS. Also the fibers at the splenium of the corpus callosum are thinner than the fibers at the genu of the corpus callosum and thus may be more sensitive to inflammatory processes in CIS.

There were some limitations of our study. Firstly, patient diagnosis and disease durations were not homogenous in the CIS group. Secondly, our study group was relatively small. Finally, we did not

evaluate the interobserver and intraobserver reliability of our findings.

In conclusion, hidden microstructural pathological changes in NAWM and NACC can be demonstrated by advanced MRI in patients with CIS. T1-W MTI evaluation of NAWM and NACC of patients with CIS can be useful for a decision for early treatment of the disease.

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We declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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