



## Research Article

### Changes in The Normal Appearing White-Gray Matter and Cognitive Impairment in Clinically Isolated Syndrome

Müge KOÇAK<sup>1\*</sup>, Kadriye AĞAN<sup>1\*</sup>, Aynur MOLLAHASANOĞLU<sup>1</sup>, Gazanfer EKINCI<sup>2</sup>, Neşe Tuncer-ELMACI<sup>1</sup>, Dilek GÜNAL<sup>1</sup>

<sup>1</sup>Marmara University School of Medicine, Neurology, Istanbul, Turkey <sup>2</sup>Marmara University School of Medicine, Radiology, Istanbul, Turkey \*The first 2 authors (M.K. and K.A.) contributed equally to this study. The first 2 authors (M.K. and K.A.) contributed equally to this study; therefore, they share first authorship

## Summary

**Background and purpose:** To assess the normal appearing white and grey matter changes in clinically isolated syndrome (CIS) patients and their correlations if present to neurocognitive tasks. Those changes can be revealed by magnetization transfer imaging (MTI) and Diffusion-tensor magnetic imaging (DTI) technique.

**Methods:** Diffusion-tensor magnetic and magnetization transfer imaging measurements at normal appearing left-right dorsolateral prefrontal cortex, right-left anterior cingulate gyrus, corpus callosum genu-splenium were made. In order to assess whether or not the cognition was affected following neurocognitive tests [Wisconsin Card Sorting Test (WCST), California Verbal Learning Test (CVLT), Stroop Test(ST), Digit Range (DR) and the Paced Auditory Serial Addition Test (PASAT)] were performed.

**Results:** Patients were found to have a lower fractional anisotropy (FA) compared the controls in the left dorsolateral prefrontal cortex at DTI technique. Neurocognitive assessment showed that patients did not perform well in WCST, CVLT, ST, DR. Results were associated with abnormal FA in the left dorsolateral prefrontal cortex.

**Conclusions:** Results showed the presence of deficits of executive function such as attention, working memory, strategy formulation, and monitoring ongoing mental activity and speeded information processing in CIS patients. These findings suggest that early cortical changes can be seen even in CIS patients and responsible for early neurocognitive impairments.

**Key words:** Clinically isolated syndrome, cognition, normal appearing white-grey matter

### Klinik izole Sendromlarda Normal Görünümlü Beyaz-gri Cevherdeki Değişiklikler ve Kognitif Etkilenim

## Özet

**Amaç:** Klinik izole sendromlu hastalarda normal görünen beyaz ve gri cevheri kontrol etmek ve eğer var ise bunun nörokognitif işlevler ile olan ilgisini araştırmak. Bu değişiklikler magnetizasyon transfer ve difüzyon tensor görüntüleme teknikleri ile araştırılacaktır.

**Metod:** Difüzyon tensor magnetik rezonans ve magnetizasyon transfer görüntüleme teknikleri ile normal görünen sağ ve sol dorsolateral prefrontal korteks, anterior singulat girus ve korpus kallozum genusunda ölçümler yapıldı. Kognitif işlevlerin etkilenip etkilenmediğini anlamak amacı ile de Wisconsin Kart Eşleşme Testi (WCST), California Sözel Öğrenme testi

(CVLT), Stroop testi (ST), Sayı Dizisi Testi (DR) ve Paced Auditory Serial Addition Test (PASAT) uygulandı.

**Bulgular:** Difüzyon tensor incelemelerinde kontrol grubuna göre hasta grubunda sol dorsolateral prefrontal kortekste düşük fraksiyonel anizotropi bulundu. Bu hasta grubunun nörokognitif testlerde de (Wisconsin Kart Eşleşme Testi, California Sözel Öğrenme testi, Stroop testi ve Sayı dizisi) başarısız oldukları saptandı. Bu sonuçların sol dorsolateral prefrontal korteksteki anormal fraksiyonel anizotropiye bağlı olduğu düşünüldü.

**Sonuç:** Klinik izole sendromlu hastalarda dikkat, işleyen hafıza, strateji geliştirme ve devam eden zihinsel aktiviteyi ve hızlandırılmış bilgi işleme gibi yürütücü işlevlerde eksiklik gösterilmiştir. Elde edilen bu bulgular erken kortikal değişikliklerin klinik izole sendrom hastalarında dahi görülebileceğini ve erken dönem nörokognitif etkilenimden sorumlu olabileceğini göstermektedir.

**Anahtar Kelimeler:** Klinik izole sendrom, kognisyon, normal görünümlü beyaz-gri cevher

## INTRODUCTION

The onset of multiple sclerosis (MS), which is a chronic inflammatory demyelinating disease of the central nervous system (CNS), presents as a subacute clinically isolated syndrome (CIS) of the optic nerves, brainstem, or spinal cord in 85% of young adults with MS<sup>(15)</sup>.

Multiple sclerosis (MS) has been classically regarded as a white matter disease. However, recent histopathological studies have convincingly shown that grey matter regions are also heavily affected. Grey matter damage starts early in the disease and substantially affects cognitive function. Detection of cortical grey matter lesions by use of standard MRI techniques has proved challenging, and more advanced techniques are needed<sup>(12)</sup>.

Technologic advances of MR in recent years have dramatically improved our understanding of MS disease. With the advent of newer quantitative MR techniques—including volumetric MR imaging, magnetization transfer imaging (MTI), diffusion tensor imaging (DTI), and proton MR (1H-MR) spectroscopy—are used for detected microscopic differences of MS<sup>(13)</sup>.

Cognitive impairment in multiple sclerosis occurs in an estimated 40-60% of cases.

Learning and memory, attention, information processing, visuospatial abilities and executive functions are the most affected cognitive domains in multiple sclerosis. It is difficult to detect cognitive impairment during routine neurological examinations. Although the type of multiple sclerosis, and the duration of disease are correlated with cognitive impairment and cognitive impairment can be detected in the early stages of the disease when there is no physical disability. Lesion loads and cortical atrophy are also associated with cognitive impairment in multiple sclerosis patients<sup>(20)</sup>.

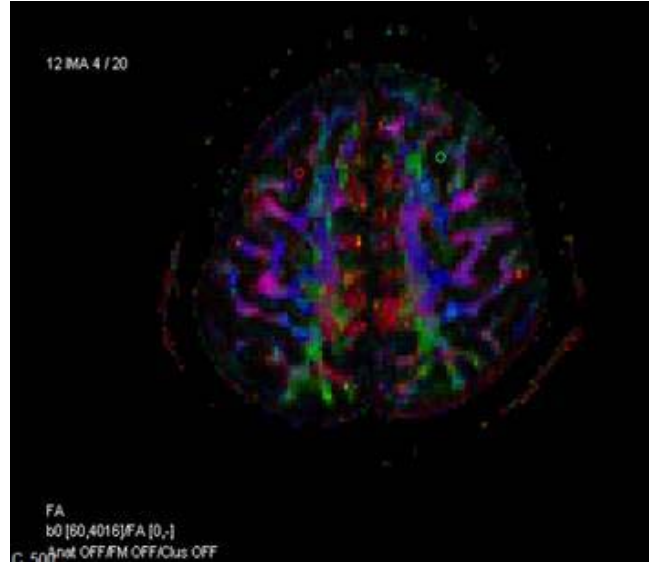
The present study aimed to assess changes in the normal appearing white matter (NAWM) and normal appearing gray matter (NAGM) by using magnetization transfer imaging (MTI), diffusion-tensor magnetic imaging (DTI), and fractional anisotropy (FA) mapping in patients with CIS, and to evaluate correlations of these changes, if present, with neurocognitive tasks.

## MATERIAL AND METHODS

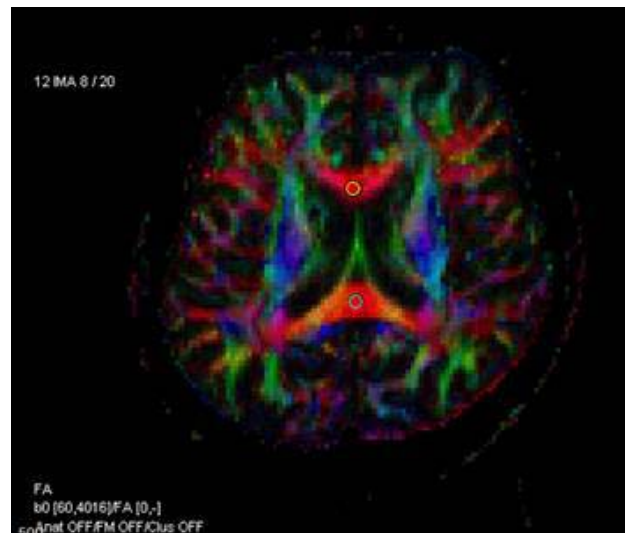
The present study was performed in 16 patients with CIS and in 16 demographically matched controls. Diffusion-tensor magnetic imaging, FA and MTI measurements were performed in the normal appearing left and right

dorsolateral prefrontal (DLPF) cortex, right and left anterior cingulate gyrus, right and left dentate nucleus, corpus callosum genu/splenium (Figures 1, 2, 3 and 4). The following neurocognitive tests were used to assess the cognition: the Wisconsin Card

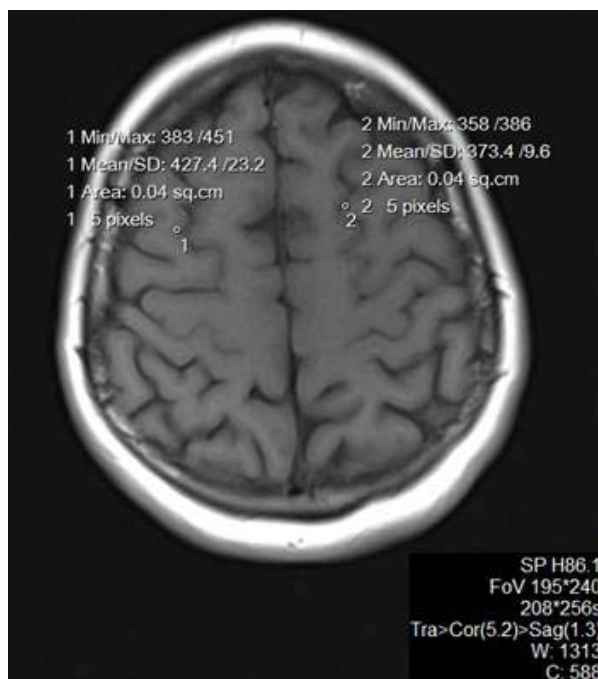
Sorting Test (WCST), the California Verbal Learning Test (CVLT), the Stroop Test (ST), the Digit Span Test (DST), and the Paced Auditory Serial Addition Test (PASAT).



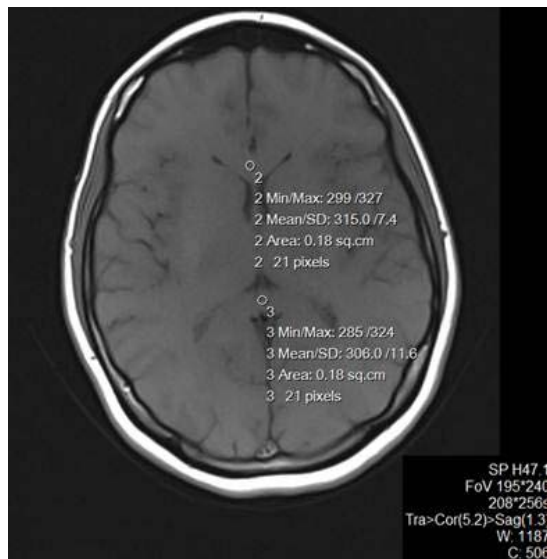
**Figure 1:** FA map into NAGM (left and right DLPF cortex)



**Figure 2:** FA map into NAWM (Corpus callosum genu and splenium)



**Figure 3:** MTR map into NAGM (left and right DLPF cortex)



**Figure 4:** MTR map into NAWM (Corpus callosum genu and splenium)

## RESULTS

Demographic and clinical data of the patients are presented in Table 1-2. There were no significant differences between the CIS and control groups with respect to age or gender. DTI measurements performed in the left DLPF cortex revealed that the patients had higher FA values than the controls ( $p=0.019$ ) (Table 3-4). Neurocognitive assessment demonstrated

that the patients did not perform well in the WCST ( $p=0.029$ ), CVLT ( $p=0.001$ ), ST ( $p=0.002$ ), and DST ( $p=0.002$ ) (Table 5). These results were associated with abnormal FA in the left DLPF cortex. No significant differences were observed between the patient and control groups in terms of their PASAT scores ( $p=0.08$ ).

**Table 1.** Demographic and clinical data of the optic neuritis patients and controls M, male; F, female; EDSS, expanded disability status scale; OCB, oligoclonal band.

Patients	Age, Sex	Disease duration (months)	First EDSS	Last EDSS	OCB
Patient 1	32, M	2	2.0	0	Positive
Patient 2	32, M	20	2.0	0	Positive
Patient 3	35, F	53	1.0	0	-
Patient 4	52, M	60	2.0	2.0	-
Patient 5	25, F	22	2.0	0	-
Patient 6	41, F	28	3.0	3.0	Negative
Patient 7	18, F	8	2.0	0	Positive
Patient 8	32, M	14	2.0	0	-
Patient 9	26, F	4	4.0	0	Negative
Patient 10	25, F	4	1.0	0	Negative

**Table 2.** Demographic and clinical data of the transverse myelitis patients and controls M, male; F, female; EDSS, expanded disability status scale; OCB, oligoclonal band.

Patients	Age, Sex	Disease duration (months)	First EDSS	Last EDSS	OCB
Patient 1	32, M	3	6.0	2,5	Negative
Patient 2	30, F	8	2.0	0	Positive
Patient 3	35, M	16	3.0	2	Negative
Patient 4	23, M	10	2.0	0	Positive
Patient 5	32, M	6	2.0	0	Positive
Patient 6	37,F	34	1.0	0	Negative

**Table 3.** Magnetization transfer ratio (MTR)

	Patient group (Mean±SD) n:16	Control group (Mean±SD) n:16	p
Right anterior cingulate gyrus	19.48±4.47	21.04±3.70	0.307
Left anterior cingulate gyrus	19.42±3.65	20.24±3.95	0.557
Corpus callosum genu	28.73±1.05	28.82±2.00	0.884
Corpus callosum splenium	29.01±1.73	29.06±2.19	0.949
Right cerebellar dentate nucleus	27.41±3.47	28.16±2.23	0.491
Left cerebellar dentate nucleus	27.66±2.57	28.33±1.90	0.491
Right dorsolateral prefrontal cortex	22.33±4.59	19.49±5.69	0.145
Left dorsolateral prefrontal cortex	18.84±2.20	18.84±2.20	0.145

**Table 4.** Fractional anisotropy (FA)

	Patient group (Mean±SD) n:16	Control group (Mean±SD) n:16	p
Right anterior cingulate gyrus	0.27±0.21	0.21±0.05	0.309
Left anterior cingulate gyrus	0.29±0.25	0.20±0.04	0.212
Corpus callosum genu	0.72±0.22	0.79±0.05	0.292
Corpus callosum splenium	0.77±0.25	0.85±0.04	0.236
Right cerebellar dentate nucleus	0.56±0.12	0.56±0.08	0.853
Left cerebellar dentate nucleus	0.59±0.09	0.58±0.07	0.760
Right dorsolateral prefrontal cortex	0.25±0.79	0.26±0.88	0.863
Left dorsolateral prefrontal cortex	0.28±0.29	0.24±0.61	<b>0.019</b>

**Table 5 a-b.** Neurocognitive tests scores PASAT, the Paced Auditory Serial Addition Test; CVLT, the California Verbal Learning Test; WCST, the Wisconsin Card Sorting Test.

	Patient group (Mean±SD) n:16	Control group (Mean±SD) n:16	P
<b>Digit span</b>			
Forward	5.44±0.81	6.44±0.81	<b>0.002</b>
Backward	4.38±0.80	5.25±0.93	<b>0.008</b>
<b>PASAT</b>	52.813±5.443	55.500±2.477	0.0874
<b>Stroop test</b>			
Time differences	36.43±14.55	37.06±7.67	0.881
Spontaneous corrections	3.12±2.85	0.50±0.81	<b>0.002</b>
<b>Animal fluency</b>			
Number of the animal names in one minute	19.93±4.14	25.37±4.04	<b>&lt;0.001</b>

	Patient group (Mean±SD) n:16	Control group (Mean±SD) n:16	P
<b>CVLT</b>			
List A total learning (trial 1- trial 5)	55.69±7.13	64.12±6.39	<b>0.001</b>
List A trial 1 recall	7.62±1.45	8.75±1.48	<b>0.038</b>
List A trial 5 recall	13.50±1.71	15.37±0.88	<b>0.001</b>
Short delay free recall	12.44±2.06	14.87±1.09	<b>&lt;0.001</b>
Short delay cued recall	13.19±2.01	15.37±0.80	<b>0.001</b>
Long delay free recall	12.31±1.85	15.06±0.85	<b>&lt;0.001</b>
Long delay cued recall	13.06±1.81	15.44±0.81	<b>&lt;0.001</b>
False positivity	0.44±0.51	0.00±0.00	<b>0.004</b>
Intrusions	3.62±3.48	0.37±1.02	<b>0.002</b>
Perseverations	4.06±3.47	0.94±1.39	<b>0.003</b>
<b>WCST</b>			
% conceptual level responses	66.36±18.08	75.73±4.94	0.061
Perseverative responses	20.62±18.05	13.06±7.52	0.138
% perseverative errors	15.97±9.82	12.06±4.52	0.162
Number of categories completed	5.25±1.24	6.00±0.00	<b>0.029</b>
Trials to complete first category	15.19±6.19	11.12±1.40	<b>0.021</b>

**DISCUSSION**

Although MS is considered a white matter disease, demyelinated lesion in gray matter has also been reported<sup>(4,5,17)</sup>. Gray matter damage is already present at early stages of the disease and substantially effects clinico cognitive functioning<sup>(7)</sup>. Axonal demyelination in the cortex and other grey matter areas are important because the cognitive impairment that occurs in MS patients cannot barely be described simply by focal demyelination that occurs in the white matter.<sup>(13)</sup>

Cognitive impairment occurs in 40-65% of multiple sclerosis (MS) patients, typically involving complex attention, information processing speed, (episodic) memory and executive functions. It is seen in the subclinical radiologically isolated syndrome, clinically isolated syndrome, and all phases of clinical MS<sup>(14,19)</sup>.

Detection of cortical gray matter damage in the NAGM using standard MRI is deficiency.

Several studies have reverted to the use of various techniques; such as magnetization transfer ratio (MTR) imaging, DTI and FA, rather than MRI for the detection of abnormalities in the NAWM and NAGM<sup>(6,8)</sup>.

We found no difference in FA and DT measurements for the following locations bilateral cerebellar dentate nucleus for NAGM and corpus callosum / corpus callosum splenium for NAWM in our study. We speculate those results are due to that our patients were in the very early phase of their disease period. Gallo and coworkers found that grey matter involvement occurs only after white matter involvement and later in the disease period.<sup>(11)</sup>

The primary finding of the present study was that the mean FA values in the cortical NAGM, especially left dorsolateral prefrontal cortex in the patients with CIS were significantly increased as compared to the mean FA values in cortical gray matter in the healthy controls; this condition is opposite to that of MS lesions in white matter (Fig. 1-2). In a recent radiological study, Poonawalla et al.<sup>(18)</sup> reported significantly increased mean FA values of cortical lesions in MS patients relative to the cortical gray matter in healthy controls.

The secondary finding of the present study was that the patients with CIS did not perform well in the WCST, CVLT, ST and DST. However, no difference was observed between the patient and control groups in terms of their performance on the PASAT<sup>(2)</sup>. An fMRI study showed that low PASAT scores were well correlated with precentral, dorsolateral prefrontal and parietal cortex activation.<sup>(10)</sup>

We comprehend that the prefrontal cortex is principally involved in higher executive functions, working memory, and inhibition function<sup>(3,9)</sup>. The CVLT, WCST, ST and DST are the most distinctive tests of prefrontal function<sup>(1,9)</sup>. The WCST and ST is the representative ones used to measure executive function and goal-directed behavior<sup>(16)</sup>. The CVLT that has an extensive use in clinical neurology is a neuropsychological test of learning and memory<sup>(1)</sup>. Performance related verbal fluency and working memory functions were found directly related with frontal lobe lesion load. CVLT test scores were found to be low in patients with posterior dorsolateral prefrontal cortex lesions.<sup>(1)</sup>

The major problem in this study is the small sample size of the patients with valid cortical lesions. The detection rate of cortical lesions was substantially improved by the use of double inversion recovery (DIR) relative to conventional MRI, most of the cortical lesions possibly remained undetected.

In conclusion, according to the results of the present study, cortical-gray matter damage and cognitive impairment are significant in CIS. We suggest that cognitive impairment should be detected and treated at very early stages of MS.

#### Correspondence to:

Kadriye Ağan

E-mail: [kadiagan@yahoo.com](mailto:kadiagan@yahoo.com)

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