Original Article

THE COGNITIVE DYSFUNCTIONS OF MULTIPLE SCLEROSIS: DO WE FACE FROM THE EARLY TERMS?

Nilufer Cetisli Korkmaz[1], Levent Sinan Bir[2], Emre Baskan[3], Tuba Can[4], Talip Cabuk[5]

ABSTRACT

Objectives: The diversity of physical and cognitive impairments seen in Multiple Sclerosis (MS), make it difficult to make the definition and classification of physical and cognitive disabilities and to identify the factors that influence neurorehabilitation programs and outcomes. In the view of the complexities of both Multiple Sclerosis (MS) and the rehabilitation process, this preliminary study's aim was to determine the cognitive dysfunctions by conducting on early term relapsing-remitting MS (RRMS) patients.

Methodology: Cognitive performances of 27 early term RRMS patients and 27 individually s ex-age matched volunteer healthy controls (HC) were compared. Each patient underwent a complete clinical assessment, including depression, disability and comprehensive cognitive function [attention: Stroop tests, memory and perception: Wechsler Memory Scale-Revised (WMS-R) subtests].

Results: There were statistically significant differences between groups for all subtests of Stroop ($p<0.05$), WMS-Digit Span ($p<0.05$), WMS-Logical Memory ($p<0.001$) and WMS-Visual Reproduction ($p<0.001$). The significance remained while the depression's effect was controlled. There was a statistically significant difference between visual reproduction of immediate (WMS-VRI) and delayed (WMS-VRD) memory in RRMS patient group ($p<0.05$). In the light of results it was recorded that, deficient cognitive performance is predominantly apparent in early term RRMS patients.

Conclusion: Cognitive assessment and rehabilitation must be in the context of multidisciplinary rehabilitation of RRMS patients from the early terms.

KEY WORDS: Relapsing-Remitting Multiple Sclerosis (RRMS), Cognitive Dysfunctions, Stroop Color-Word Interference Test, Wechsler Memory Scale-Revised (WMS-R), Attention, Memory, Depression, EDSS, Multidisciplinary, Rehabilitation.

Pak J Med Sci July - September 2010 Vol. 26 No. 3 623-628

How to cite this article:

Korkmaz NC, Bir LS, Baskan E, Can T, Cabuk T. The cognitive dysfunctions of multiple sclerosis: Do we face from the early terms? Pak J Med Sci 2010;26(3):623-628

Correspondence:

Nilufer Cetisli Korkmaz, PT. Ph.D.
School of Physical Therapy and Rehabilitation,
Pamukkale University,
Rektorluk Binasi B Kati
20070 Kinikli-Denizli, TURKEY.
Email: niluferc75@yahoo.com

* Received for Publication: December 8, 2009
* Revision Received: December 10, 2009
* Revision Accepted: April 11, 2010

INTRODUCTION

In most neurological diseases, like Multiple Sclerosis (MS), damage is rarely localized to one small area. Attention, memory and executive functions are accepted as three cognitive domains, which were mostly impaired in MS patients.[1-5] For a long time cognitive impairment in patients with MS has been underestimated by health professionals and considered less

important than physical disability. This is no longer true because of its' crucial role.[1] Cognitive dysfunction, mainly frontal, prevalence may vary between 30-70%.[1,4-6] Furthermore, impairments in each of these cognitive processes can have devastating effects on people's daily life functioning.[4,7,8]

If cognitive impairments are recognized early, it may facilitate the planning of other rehabilitation services, as well as reducing the patients' dependence level.[2] Because of these and in view of the complexities of both MS and the rehabilitation process, this preliminary study was conducted on a small group of patients with early term Relapsing-Remitting MS (RRMS) to determine the profile of cognitive dysfunctions by comparing with volunteer healthy controls (HC).

METHODOLOGY

We compared the performances of 27 patients RRMS (19 were diagnosed as clinically definite RRMS, 8 were McDonald MS), with 27 individually sex-age matched healthy volunteers for a comprehensive cognitive dysfunction assessment. Ninteen patients were diagnosed as clinically definite RRMS with 2 ≤ attack, eight patients who had only one attack but were diagnosied at as RRMS with McDonald's criteria. A phsiotherapist explained the aims and condiction to all subjects. Written informed consent was obtained from patients. Outpatients with RRMS were selected according to: stable phase of the disease & no steroid treatment for one month before inclusion. Exclusion criteria were: neuropsychiatric disorders other than MS, major depression (Beck Depression Inventory cut-point of 21),[9] prior testing with the same cognitive dysfunction tests, severe physical (motor, visual, speech articulation) impairments presence. Control data were obtained by testing a population of 27 HC matched with RRMS patients for age-sex. Subjects with any neuropsychiatric disorder, a history of head trauma or alcohol/drug abuse were not included.

Each patient underwent a complete clinical examination, including depression [Beck Depression Inventory (BDI)], disability [Expanded Disability Severity Scale (EDSS) and Hauser Ambulation Index (AI)] and comprehensive cognitive function examination [attention: Stroop tests, memory and perception: Wechsler Memory Scale-Revised subtests].

Stroop Color-Word Interference Test (SCWT): The cognitive mechanism involved in this task is called directed attention, participants have to manage their attention, inhibit or stop one response in order to say something else.[10-13] In addition to the naming time scores, an interference score was derived by subtracting the word naming score from the actual score.[12,13]

Wechsler Memory Scale-Revised (WMS-R): WMS-R was designed to assess attention, learning, memory and working memory for individuals in the age range of 16-89 years. The In WMS-R, the Working Memory score indicates how well the patient did on tasks that required them to remember and mentally organize information.[14,15] We choose to select and administer a partial WMS-R battery for learning and memory.

Digit Span, requires repetition of number strings forwards and backwards. It measures concentration, attention and immediate memory.[10,11,14] Paragraph recall of verbal material was assessed in accordance with standardized procedures in *Verbal memory subtests* (*Logical memory*). Two stories are presented orally.[10,15] Four geometric designs studied for five seconds. each; subject attempts to copy each design for *Nonverbal learning and memory* (*Visual Reproduction*).[15]

Statistical Analysis: Descriptive statistics were used. The changes of performance of RRMS patients and HC group as a whole were assessed by the Mann-Whitney-U test or the Kruskal-Wallis test. The Wilcoxon-signed ranks test was used to look for significant changes. A multivariate analysis of covariance (MANCOVA) was performed with scores on the cognitive function tests to establish the overall significance of the differences between the groups. Depression (BDI) was used as the covariate. Finally, Pearson's r was used to evaluate correlations between pairs of EDSS and cognitive performances. Significance level was selected as 0.05.

Table-I: Characteristics of the Study Sample.

		MS		*Control*	
		n	%	*n*	%
Participants		27	50	27	50
Gender	Female	21	77.8	21	77.8
	Male	6	22.2	6	22.2
RRMS Subgroups	Patients with ≤ 2 attack	19	70.4		
	Patients with 1 attack	8	29.6		
Extremity Involvement	No	6	22.2		
	Monoparesis-plegia	5	18.5		
	Hemiparesis-plegia	9	33.3		
	Paraparesis-plegia	4	14.8		
	Quadriparesis-plegia	3	11.1		

RESULTS

The RRMS patients' sample and HC did not differ in age and gender factors. Demographic and disease-related characteristics for the total sample are summarized in Table I-II. Ninteen out of twenty seven patients were with ≤ 2 attacks while eight of these had one attack but dismination in time space was demonstrated by MRI (Table-I). It was seen that our RRMS patient sample have mild degree of physical impairment (Table-II).

Results on subtests measuring cognitive function for the total sample showed that memories, attention, speed of information processing and executive functioning have been shown to be affected while the RRMS patients were in the early term. RRMS patients finished later than the individuals in their age group on tasks requiring them to remember and mentally organize auditory information. When we reviewed the interference score between them, it was seen that the highest scores were between word reading and color naming (Stoop-W/C) (p=0.001) with a significant difference between the groups (p<0.05).

In general meaning, RRMS patients scored lower than the HC on tasks requiring to remember auditory and visual information immediately after it was presented (Logical Memory and Visual Reproduction; p<0.001) (Table-III). In the light of these results it was observed that, deficient cognitive performance is predominantly apparent from these tests. The multivariate test of the MANCOVA was significant (Lambda=0.573, F=3.136, p<0.005). When adjustment was made, the two groups differed significantly in performance on the all other cognitive function subtests (except Stroop-W/C scores), with the MS group showing significantly worse scores than the healthy control group (p<0.05).

Stroop-W is the easiest subpart. Because of this we compared other subpart with this. All other parts were significantly different from Stroop-W, in both groups. In RRMS group, the biggest differences were recorded between Stroop-W and Stroop-CW (Table-IV). With these results memory, attention, speed of information processing and executive functioning has been shown to be affected in RRMS patients, while

Table-II: Demographic Characteristics of the Study Samples.

	RRMS		*Control*		*z*	*p*
	X	*SD*	*X*	*SD*		
Age (years)	33.11	11.39	31.22	10.93	-0.563	>0.05
BDI	16.19	9.89	5.85	6.32	-4.315	<0.001
Duration of Disease (years)	5.30	4.45				
Number of Relapses	2.93	1.75				
Time After Relapse (months)	1.93	1.39				
EDSS	1.30	1.24				
AI	0.15	0.36				

BDI= Beck Depression Inventory, EDSS= Expanded Disability Severity Scale, AI= Hauser Ambulation Index

Table-III: Cognitive Tests' Scores of the Study Samples.

	RRMS		*Control*		*z*	*P*	*Corrected with Depression*	
	X	*SD*	*X*	*SD*			*F*	*p*
Stroop-Word	25.70	8.72	20.82	3.92	-3.079	<0.005	3.80	<0.05
Stroop-Color	37.33	12.85	28.85	5.63	-3.605	<0.001	5.14	<0.01
Stroop-Color Word	74.11	32.54	51.37	7.74	-3.914	<0.001	8.20	=0.001
Stroop-Word/Color	11.63	6.03	8.04	5.70	-2.504	<0.05	2.54	>0.05
Stroop-Word/Color Word	48.41	28.02	30.56	7.07	-3.394	=0.001	7.12	<0.005
WMS-Digit Span-Forward	5.63	1.25	6.44	1.05	-2.393	<0.05	3.53	<0.05
WMS-Digit Span-Backward	3.70	1.10	4.82	1.00	-3.401	<0.001	7.67	=0.001
WMS-Logical Memory-Im.	14.41	4.93	20.70	3.21	-4.572	<0.001	15.17	<0.001
WMS- Logical Memory-Del.	13.33	4.71	19.85	3.17	-4.764	<0.001	17.67	<0.001
WMS-Visual Reproduction-Im.	7.82	3.59	12.04	2.96	-4.332	<0.001	11.11	<0.001
WMS-Visual Reproduction-Del.	7.00	4.49	12.00	3.01	-4.122	<0.001	11.39	<0.001

Im. = Immediate, Del. = Delayed

they were in the early term.

It was further observed that recognition memory and implicit learning did not remain intact in RRMS group. The highest difference was recorded between Digit Span Forward (WMS-DSF) and Backward (WMS-DSB) ($p<0.001$). While there was a statistically significant difference between visual reproduction of immediate (WMS-VRI) and delayed (WMS-VRD) in RRMS patient group ($p<0.05$), there were not any difference in HC group ($p>0.05$) (Table-IV).

To determine whether there was a relationship between our subjects' cognitive performances and clinical characteristics (EDSS), we performed a correlation analysis and found no significant association ($p>0.05$).

DISCUSSION

In broad terms, cognitive processes comprise sensation, perception, memory, attention and executive functions. These operations, although functionally interrelated, are controlled by different parts of the brain. Because of this, it was suggested that cognitive impairment presents a major barrier to rehabilitation.[3,7]

Studies still address the frequency and pattern of cognitive impairments with special regard to early term MS.[1] But results from studies performed in one country or region are not easily extrapolated to another country or region.[16] To our knowledge, this preliminary study is the first to present detailed data on cognitive function in a sample of early term RRMS patients in

Table-IV: Differences between Cognitive Tests in the Groups.

	RRMS			*Control*		
	X ± SD	*z*	*p*	*X ± SD*	*z*	*p*
Stroop-Word	25.70±8.72	-4.466	<0.001	20.82±3.92	-4.552	<0.001
Stroop-Color	37.33±12.85			28.85±5.63		
Stroop-Word	25.70±8.72	-4.458	<0.001	20.82±3.92	-4.544	<0.001
Stroop-Color Word	74.11±32.54			51.37±7.74		
WMS-DSF	5.63 ± 1.25	-4.529	<0.001	6.44 ±1.05	-4.371	<0.001
WMS-DSB	3.70 ± 1.10			4.82 ±1.00		
WMS-LMI	14.41±4.93	-2.241	<0.05	20.70±3.21	-2.680	<0.01
WMS-LMD	13.33±4.71			19.85±3.17		
WMS-VRI	7.82±3.59	-2.105	<0.05	12.04±2.96	-0.394	>0.05
WMS-VRD	7.00±4.49			12.00±3.01		

DSF= Digit Span-Forward, DSB= Digit Span-Backward, LMI=Logical Memory-Immediate, LMD=Logical Memory-Delayed, VRI=Visual Reproduction-Immediate, VRD=Visual Reproduction-Delayed

Turkey. We also consider surveys of this kind to be important for the health professionals and the future studies on RRMS patients' cognitive impairments and for organization of rehabilitation services. Our findings showed that MS patients displayed cognitive dysfunctions. Our results are in agreement with the results of performed population-based studies in the literature.[10,16,17]

There is no general agreement in defining reliable cut-off points for cognitive impairment in the literature. Because of this mostly, the best way to adequately interpret the differences is to compare the patient sample with a carefully matched HC group.[1] In coherent with the literature, we compared the RRMS patient sample with age-gender matched HC group. To interpret the Stroop tests' and WMS-R subtests' results for interference, each subtests' scores were compared with each other.

Depression level of participants were categorized according to four level; no depressive(0–9), minimal(10–15), mild(16–19), moderate(20–29), severe signs of depression (30 and higher).[18] In general meaning our RRMS patients have minimal to mild signs and they have been significantly higher depression scores than HC ($p<0.001$). An alternative cut-point of 21 for major depression was used, which classified none of the current sample as having major depression.[9] The influences of depression (BDI) were controlled statistically with MANCOVA. Of particular importance, all these results showed that depression is commonly seen from the early terms in RRMS patients, but not affecting the cognitive functions so much, especially in early terms. More definite results depend on larger future studies.

In 2006 Shevil E. and Finlayson M. described the wide range of cognitive changes and concluded that, it becomes apparent that experiencing cognitive changes is more complex and interrelated than perhaps previously thought.[5] When we compared with HC group, we also found statistically significant differences in attention, concentration and information processing (Stroop subtests; $p<0.005$), learning and long and short term memory (WMS-R memory subtests; $p<0.001$), executive functions and conceptual thinking (WMS-Digit Span subtests; $p<0.05$). Therefore, we thought that when professionals who work with MS clients encounter cognitive changes they must try to address these multiple layers of dysfunction.

As seen in the results, as the difficulty of Stroop subtest was increased, the time needed to complete the test was increased, because the difference score was increased. The length of the trials presumably allows for demonstration of cognitive slowing over the extended trials.

Olivares T and colleagues investigated the neuropsychological profile in the first few years post-onset of 33 RRMS patients and 33 individually pair-matched controls. However, they recorded no significant differences between groups that were observed in the Stroop Test interference scores.[11] We founded significant difference between the groups in the interference scores, Stroop-W/C ($p<0.05$) and Stroop-W/CW ($=0.001$). This showed us that our RRMS patients have problems in inhibiting an automatized reading response and producing a competing color-naming response and had to think considerably more, while they were in early terms.

The relative difference between working, immediate or delayed memory, might relate to poor attentional skills or working memory abilities.[10] It was observed that in RRMS patients' DSF and DSB scores were significantly lower than the HC'. Lower scores are generally obtained by persons with an attention deficit or anxiety.[10,14] This decline was interpreted to indicate that individuals were succumbing to cognitive fatigue. In the light of the findings, we thought that not only cognitive impairments can be seen in RRMS patients; cognitive fatigue was also a problem that must be taken into consideration from the early terms. Different aspects of attention had been assessed in MS patients. In the literature it was reported that, most of the patients did not show generalized performance decrease, but a rather selective impairment of one or more of these attention and memory domains.[2,4] But, we obtained important impairments in all subtests' of WMS-R ($p<0.001$).

In previous reports many researcher seek association between MS disease clinical characteristics and subjective complaints of patients.[10,17] As in these studies, we had found that there were no correlation between EDSS and any of the cognitive tests that we applied ($p>0.05$). This is almost expected. Because EDSS score mostly emphasizes the physical disability and cognitive disabilities can be seen before the appearance of physical disabilities.

Our results are partly in contrast to former studies which were unable to find a cognitive dysfunction in MS patients.[8,11] While our cognitive assessment was restricted to cognitive function testing and our preliminary study was done on limited number of patients, we had found cognitive dysfunction in early term RRMS patients. Presumable relevance of some deficits could indicate the need for future research on the relationships between cognitive test performance, functioning and fatigue.

CONCLUSION

Cognitive dysfunctions are often termed invisible injuries, while they are very frequent. Further evaluations therefore seem justified to work with them. Cognitive assessment and rehabilitation may be more appropriate in the context of multidisciplinary early rehabilitation. This present study opens the door for the development of objective measures of cognitive functions that could prove to be more suitable for addressing the cognitive dysfunctions in RRMS population's neurorehabilitation.

REFERENCES

1. Hoffmann S, Tittgemeyer M, von Cramon DY. Cognitive impairment in multiple sclerosis. Curr Opin Neurol 2007;20:275–280.
2. Langdon DW, Thompson AJ. Multiple sclerosis: A preliminary study of selected variables affecting rehabilitation outcome. Mult Scler 1999;5:94-100.
3. Nocentini U, Pasqualetti P, Bonavita S, Buccafusca M, De Caro MF, Farina D, *et al*. Cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. Mult Scler 2006;12:77-87.
4. Plohmann AM, Kappos L, Ammann W, Thordai A, Wittwer A, Huber S, *et al*. Computer assisted retraining of attentional impairments in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 1998;64:455-462.
5. Shevil E, Finlayson M. Perceptions of persons with multiple sclerosis on cognitive changes and their impact on daily life. Disability and Rehabilitation 2006;28(12):779–788.
6. Wade DT. Section 4. Measures for use in neurological disability: 15. Measures of "focal" disability, 'Measurement in Neurological Rehabilitation', Wade DT (Ed), New York: Oxford University Press. 1992, pp 166-174.
7. Lincoln NB, Dent A, Harding J, Weyman N, Nicholl C, Blumhardt LD, et al. Evaluation of cognitive assessment and cognitive intervention for people with multiple sclerosis. J Neurol Neurosurg Psychiatry 2002;72:93–98.
8. Hildebrandt H, Lanz M, Hahn HK, Hoffmann E, Schwarz B, Schwendemann G, et al. Cognitive training in MS: Effects and relation to brain atrophy. Restorative Neurology and Neuroscience 2007;25:33–43.
9. Morley S, William AC de C, Black S. A confirmatory factor analysis of the Beck Depression Inventory in chronic pain. Pain 2002;99:289–298.
10. Bryant D, Chiaravalloti ND, DeLuca J. Objective measurement of cognitive fatigue in Multiple Sclerosis. Rehabilitation Psychology 2004;49(2):114–122.
11. Olivares T, Nieto A, Sanchez MP, Wollmann T, Hernandez MA, Barroso J. Pattern of neuropsychological impairment in the early phase of relapsing-remitting multiple sclerosis. Mult Scler 2005;11:191-197.
12. Baron IS. III. Domains and tests: 6. Executive Function, 'Neuropsychological evaluation of the child', Baron IS (Ed), New York: Oxford University Press. 2004, pp 133-214.
13. Parmenter BA, Denney DR, Lynch SG. The cognitive performance of patients with multiple sclerosis during periods of high and low fatigue. Mult Scler 2003; 9:111-118.
14. Baron IS. III. Domains and tests: 7. Attention, 'Neuropsychological evaluation of the child', Baron IS (Ed), New York: Oxford University Press. 2004, pp 215-261.
15. Baron IS. III. Domains and tests: 11. Learning and memory, 'Neuropsychological evaluation of the child', Baron IS (Ed), New York: Oxford University Press. 2004, pp 351-405.
16. Einarsson U, Gottberg K, von Koch L, Fredrikson S, Ytterberg C, Jin YP, *et al*. Cognitive and motor function in people with multiple sclerosis in Stockholm County. Mult Scler 2006;12:340-353.
17. MacAllister WS, Belman AL, Milazzo M, Weisbrot DM, Christodoulou, C, Scherl WF, *et al*. Cognitive functioning in children and adolescents with multiple sclerosis. Neurology 2005;64:1422–1425.
18. Jonsson A, Andresen J, Storr L, Tscherning T, Sorensen PS, Ravnborg M. Cognitive impairment in newly diagnosed multiple sclerosis patients: A 4-year follow-up study. J Neurological Sciences 2006;245:77–85.

Authors Contribution:

N CETISLI KORKMAZ; conceived, designed the study, did data collection and statistical analysis, manuscript writing.
LS BIR; hypothized and organized the study did data collection, review of manuscript.
E BASKAN; did data collection, helped in manuscript writing.
T CAN; helped in manuscript writing.
T CABUK; gave opinion about the cognitive test.

Authors:
1. Nilufer Cetisli Korkmaz, PT. PhD,
   School of Physical Therapy and Rehabilitation.
2. Levent Sinan Bir, MD. PhD,
   Professor, Dept. of Neurology, Faculty of Medicine.
3. Emre Baskan, PT. PhD
   School of Physical Therapy and Rehabilitation.
4. Tuba Can, PT. MSc,
   School of Physical Therapy and Rehabilitation.
5. Talip Cabuk, Psychologist, Mediko.

1-5. Pamukkale University, Denizli, Turkey.