

Longitudinal Study of Cognitive Impairment in Multiple Sclerosis: A 5-year Follow-up

Multipl Sklerozda Kognitif Etkilenme; 5 Yıllık Takip Çalışması

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ABSTRACT

Objectives: Cognitive impairment can be demonstrated in 40 to 65% of MS patients, starting from early stages. The aim of this study was to investigate alteration in cognitive impairment during long-term follow-up and the association with the disease characteristics.

Method: Twenty-five MS patients (15 men, 10 women) were reexamined after an average of 5.3 years (range: 4.9-5.8). The disease duration, type, Expanded Disability Status Scale (EDSS) scores at the initial and last evaluations were recorded. They underwent a comprehensive neuropsychological evaluation. Major depression was excluded.

Results: The mean age of the patients was 39.2±9.3 years and the mean duration of the disease was 11.4±5.14 years. The mean EDSS score at the beginning and last follow-up were 2.92±1.52 and 3.56±1.92, respectively. At the end of the follow-up period, the patients performed poorly on the Corsi Block-Tapping Test ($p<0.001$) and there was a significant difference in maximum word line in the verbal memory processes test (VMPT) ($p<0.001$). Short-term memory scores, assessed with the Wechsler Memory Scale (WMS), decreased slightly, but the total recall score was significantly worse ($p<0.001$). There was also significant decrease in executive functions according to the stroop test ($p<0.001$), and the Wisconsin Card Sorting Test (WCST) results in patients with a longer disease course were worse. Besides, there was a trend for worsening in the clock-drawing test. The language skills were well preserved. Patients with a disease duration of ≥ 10 years scored worse on the stroop test, clock-drawing test, Benton Line Orientation Test (BLOT), WCST, and VMPT.

Discussion: The cognitive deficits tended to worsen during long-term follow-up. There was no correlation between severity of disability and cognitive impairment. However, there seems to be an association between results of some tests and disease duration. (*Archives of Neuropsychiatry* 2012;49: 29-32)

Key words: Multiple sclerosis, cognitive impairment, cognitive dysfunction, neuropsychological evaluation

ÖZET

Amaç: Kognitif bozukluk, erken dönemden itibaren MS hastalarının %65'inde görülebilmektedir. Bu çalışmanın amacı, uzun dönem takipte kognitif bozukluktaki değişimi araştırmak ve hastalık özellikleriyle ilişkisini saptamaktır.

Yöntemler: Yirmibeş MS hastası ortalama 5,3 yıllık (4,9-5,8) takip süresi ardından tekrar değerlendirildi. Hastalık süresi, tipi, ilk ve son değerlendirmedeki EDSS kaydedildi. Tüm hastalar detaylı bir nöropsikolojik değerlendirmeden geçti. Major depresyonu olanlar dışlandı.

Bulgular: Ortalama yaşı 39,2±9,3 olan hastaların 15'i erkek, 10'u kadındı. Ortalama hastalık süresi 11,4±5,14 yıl, başlangıç ve en son kontroldeki EDSS skorları sırasıyla 2,92±1,52 ve 3,56±1,92 bulundu. Takip sonrası tekrarlanan testlerden Corsi Block-Tapping Testte hastalar düşük performans gösterdi ($p<0,001$) ve sözel bellek süreçleri testinde (VMPT), en fazla kelime öğrendikleri satırda anlamlı farklılık görüldü ($p<0,001$). WMS-görsel, kısa süreli bellek puanlarında hafif bir düşme görüldü, toplam hatırlama puanlarında ise anlamlı bir azalma saptandı ($p<0,001$). Hastalık süresi uzun olan hastalarda, yürütücü işlevlerde "stroop test" ($p<0,001$) ve "Wisconsin Card Sorting Test (WCST)"lerine göre anlamlı bir bozulma da saptandı. Ayrıca saat çizme testinde de bir bozulma gözlemlendi. Dil işlevlerinin korunduğu görüldü. Hastalık süresi ≥ 10 yıl olan hastalarda stroop, saat çizimi, Benton Line Orientation Test (BLOT), WCST, ve VMPT testlerinde daha düşük skorlar elde edilmiştir.

Sonuç: Kognitif etkilenme zaman içerisinde artış gösterme eğilimindedir. Bu çalışmada özüllülük derecesi ile kognitif bozulma arasında bir anlamlı bir ilişki saptanamamıştır. Fakat hastalık süresi ile bazı testlerin ilişkili olabileceği gözlenmiştir. (*Nöropsikiyatri Arşivi* 2012;49: 29-32)

Anahtar kelimeler: Multipl skleroz, kognitif bozukluk, kognitif disfonksiyon, nöropsikolojik değerlendirme

Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system, along with neurodegenerative

features like oligodendrocyte and axonal damage. As cognitive and behavioral dysfunction is encountered commonly in MS (1), neurocognitive assessment is becoming an important tool in evaluation of MS patients (2).

Neurocognitive deficit can be found in 40 to 65% of patients, even in clinically isolated syndromes in whom no cognitive deficits are detected with routine neurological examination (2,3). However, the frequency of cognitive impairment reported in MS patients is variable due to differences in methodology and patient selection. Although cognitive involvement even in early stage of the disease is well known in MS, the longitudinal alteration of this dysfunction is not widely studied (4).

Mild cognitive deterioration over time has been observed in several studies (5,6). Kujala et al. reported that 60% of the patients with less than 2 years disease duration had isolated or moderate cognitive defects (7). Authors also showed that, these patients get worse over the following 3 years. On the other hand, if they had intact cognitive functions, they retained their stability for the next 3 years (3,7).

The aim of this study was to investigate the alteration of cognitive impairment over long-term follow-up, and association with the disease characteristics.

Methods

A comprehensive neuropsychological battery was administered to 45 consecutive relapsing-remitting MS patients with Expanded Disability Status Scale (EDSS) scores (EDSS) ≤ 6.5 between February 1998 and March 1999 (8). All of the 45 patients assessed at Bakirkoy Hospital for Psychiatric and Neurological Diseases were contacted for reevaluation approximately 5 years after the initial assessment. Twenty-five MS patients, who could be reached, were reexamined after an average of 5.3 years (range: 4.9-5.8). Twenty of them were still relapsing-remitting, and five have become secondary progressive.

The patients were assessed by a neurologist. Medical history for the intervening period was obtained and a detailed neurological examination was done. None of the patients were in acute relapse at time of reevaluation. Neurological status of the patients was assessed by EDSS. Characteristics of the patients, disease duration, age at disease onset, EDSS score at initial and last evaluation were recorded. They also underwent a psychiatric evaluation and depression was assessed by the Hamilton Depression Rating Scale. Patients with major depression were excluded. All patients underwent a mini-mental status test (MMST) and a comprehensive neuropsychological evaluation. Attention span was assessed using Digit Span Test for verbal and the Corsi Block Tapping Test for visual attention. The Verbal Memory Processes Test (VMPT), visual reproduction subtests of the Weschler Memory Scale (WMS-v), and MMST

were used to investigate memory and learning capacity. Visuospatial skills and construction ability was assessed by the Benton Line Orientation Test (BLOT). Executive functions were evaluated by the stroop test, digit span test, clock-drawing test and the Wisconsin Card Sorting Test (WCST) additionally to the first evaluation. Language skills were investigated by the Cookie Theft picture description task and Boston Naming Test (BNT).

The data were analyzed using SPSS for Windows version 13.0; Student's t-test and one-way ANOVA were used for analysis.

Results

Twenty-five patients [15 men (60%), 10 women (40%)] were evaluated after an average of 5.3 years (range: 4.9-5.8). The mean age of the patients was 39.2 ± 9.3 (range: 25-61) years. 56% of patients were aged between 20-40 years, 44% between 40-60 years, and 4% above 60 years. Forty percent had 5 years, 20% 6-10 years and 40% 11-15 years of education. The mean disease duration was 11.4 ± 5.14 years (range: 5-21); 11 (44%) patients had duration of ≤ 10 years, 8 (32%) had between 11-14 years, and 6 (24%) had 15 years or more. Twenty-one patients (84%) were scored between 0 and 8 on the Hamilton Depression Scale and 4 (14%) ≥ 9 (maximum 11 points). The mean EDSS scores at the beginning and last follow-up were 2.92 ± 1.52 and 3.56 ± 1.92 , respectively. The change in EDSS score was statistically significant ($p=0.035$). Sixteen patients (64%) had less than 1-point change in EDSS, and 9 (36%) had ≥ 1 point change. Demographic characteristics of the patients are summarized in Table 1. Only 5 (20%) patients scored worse on MMST, and overall change in MMST was not statistically significant.

The test results at initial evaluation and during follow-up were analyzed with paired samples t-test and the results are shown in Table 2. Ninety-two percent of the patients were successful on the Cookie Theft picture description task and only 8% were considered insufficient.

We investigated whether there was a correlation between disability and cognitive impairment. The patients were divided into two groups according to the change in disability: Group 1- Less than 1-point change in EDSS and group 2- ≥ 1 -point change. We could not find any significant differences between the groups in EDSS scores and in any of the neuropsychological tests at follow-up.

The association between disease duration and neuropsychological test results at follow-up was assessed using one-way ANOVA. The patients were also grouped according to their disease duration: Group 1- Disease duration ≤ 10 years and group 2- Disease duration > 10 years. Regarding disease duration, some significant differences in some of the tests were present which are shown in Table 3.

On the WCST, the mean completed category was 3.44 ± 2.29 out of 6 categories. The mean scores for men and women were 3.87 ± 2.39 and 2.80 ± 2.10 , respectively, and there was no statistical difference ($p=0.422$).

One-way ANOVA was used to determine the association of the WCST with disease duration and education. Education had

Table 1. Demographic features of the patients

Total number of patients (female: male)	25 (10:14)
Mean age (year)	39.2 ± 9.3 (range: 25-61)
Mean duration of the disease (year)	11.4 ± 5.14 (range: 5-21)
Mean EDSS at the beginning	2.92 ± 1.52
Mean EDSS at follow-up	3.56 ± 1.92
Mean follow-up time (year)	5.3 (range: 4.9-5.8)

Table 2. Comparison of Neuropsychological Test Results

		Initial (mean±SD)	Last (mean±SD)	p-value*
MMST		30.72±4.40	30.88±5.20	0.790
Attention	Digit Span	9.48±2.68	9.44±2.20	0.910
	Corsi Block	10.56±2.16	7.88±2.17	0.000
Stroop Test	1st card time (s)	18.12±6.65	15.16±6.63	0.040
	5th card time (s)	39.08±13.43	29.92±8.26	0.000
	Difference (s)	20.96±11.60	14.96±9.59	0.002
	Error	0.84±1.21	1.76±2.11	0.067
VMPT	Correction	0.80±0.96	0.96±1.27	0.597
	STM	6.04±1.69	6.28±2.11	0.591
	MWL	1.64±2.97	6.68±1.86	0.000
	TLS	105.16±18.43	109.36±18.32	0.069
	SRS	12.16±2.45	11.80±2.57	0.466
	RS	2.72±2.17	3.12±2.40	0.395
	THP	14.88±0.44	14.92±0.28	0.714
	MLS	13.28±1.72	13.32±1.73	0.870
WMT	STM	10.12±2.80	9.00±4.01	0.083
	SRS	8.36±3.85	7.60±4.47	0.208
	TRS	12.12 (±2.89)	5.08±3.63	0.000
BLOT		19.52 (±7.59)	20.16±5.55	0.485
Clock-drawing test		1.84 (±0.47)	1.64±0.64	0.057
Boston Naming Test		19.40 (±1.00)	19.32±0.80	0.714
Reception		12 (±0.00)	11.92±0.28	0.157

* p<0.05 were considered statistically significant. MMST: Mini-mental status test, VMPT: Verbal Memory Processes Test, WMS-v: Weschler Memory Scale-visual, STM: Sshort-term memory, MWL: Maximum word line, TLS: Total learning score, SRS: Spontaneous recall score, RS: Recognition score, TRS: Total recall score, MLS: Maximum learning score, BLOT: Benton line orientation test

Table 3. Results of neuropsychological tests comparison regarding disease duration

	p-value	f-value
VMPT		
TLS	0.023	5.959
SRS	0.002	11.866
RS	0.002	11.874
MWL	0.011	7.649
STM	NS	NS
Stroop Test 5th card time	0.048	4.366
Difference	0.053	4.145
Clock-drawing test	0.06	3.924
BLOT	0.02	6.273
WCST	0.017	6.595

VMPT: Verbal Memory Processes Test, STM: Short-term memory, MWL: Maximum word line, TLS: Total learning score, SRS: Spontaneous recall score, RS: Recognition score, BLOT: Benton line orientation test, WCST: Wisconsin card sorting test, NS: Not significant

no impact on WCST results (p=0.121). Subgroup analysis within the educational groups revealed no statistical significance. Association between disease duration and WCST performance was assessed using one-way ANOVA. Disease duration had an impact on the mean completed category in WCST (p=0.017) (F=6.59). This difference was created by the patients with disease duration less than 10 years. There was a negative correlation between EDSS and WCST scores (r=0.172 and p=0.412).

Discussion

Cognitive impairment is a common, prominent feature in MS and occurs in all MS subtypes. MS patients mainly show defects in memory, sustained attention, problem solving and visuospatial perception (2). Slowing in information processing, and abstract reasoning is also demonstrated (2). On the other hand, recognition memory, implicit learning, and speech comprehension usually remain intact (9). Memory is the most frequently impaired cognitive function in MS, however attention is less commonly endangered (10). Difficulties in learning and remembering new information represent the most common cognitive deficit (1). Kesselring et al. showed that working-memory tasks are mostly affected, whereas memory-span tasks used to evaluate short-term memory remains intact. They also observed that, the long-term memory impairment involves spontaneous and free recall with normal or or slightly impaired recognition memory (3). This shows that there is a distinct memory deficit in MS, impairing especially recall with intact information encoding (3). Kesselring et al. also reported abnormalities in visuo-spatial skills, motor speed and reaction time, reading aloud and figure copying (3).

Cognitive defects may appear according to the duration, course and severity of the disease or can be detected in early stages of the disease independent of these features (7,11). Recent studies have demonstrated that cognitive impairment is

already present in patients suffering from clinically isolated syndromes (12-14). However, little is known about the course of cognitive impairment. Piras et al. investigated cognitive dysfunction and MRI lesion burden over a median follow-up of 8.5 years. Their results showed a significant worsening of long-term verbal memory and a slowing of speed elaboration and attention with poor performances of immediate memory tests and abstract reasoning tests (digit span, digit symbol, block design, similarities). Overall, most verbal and performance Wechsler Adult Intelligence Scale (WAIS) subtests (comprehension, arithmetic, vocabulary, and digit span) showed a mild worsening in an increased number of patients after the follow-up period. This may be indicative of impairments in information processing activation to recall and organize the right response, as to word meaning, and problem solving (15). Amato et al. also designed two longitudinal studies with a mean follow-up of 4 (6) and 10 years (4). The authors concluded that cognitive dysfunction was likely to emerge and progress in a sizable proportion of patients in follow-up. Degree of physical disability, progressive disease course, and increasing age predicted the extent of cognitive decline (4).

In our study, we have seen that, after a mean follow-up period of 5 years, patients performed worse in some of the tests. They scored significantly lower in the Corsi Block Tapping Test for visual attention. They also reached the maximum word line after more repeats and the total learning score (VMPT) was slightly better, although not statistically significant. On the WMS, short-term memory scores decreased slightly, but the total recall score was significantly worse in the follow-up group.

There was also significant decrease in the stroop test used to examine executive functions. Another test for executive functions, WCST, revealed that patients with a longer disease course did worse. Also, there was a trend for worsening in the clock-drawing test results. Language skills were well preserved, only two patients performed worse on the Cookie Theft picture description task.

Although, our previous study did not show any association between disease duration and cognitive dysfunction (8), in this study, patients with disease duration of 10 years or more, scored worse on the stroop test, BLOT, WCST, and the VMPT. Besides, the clock-drawing test was slightly worse.

Usually, there is no or only a weak correlation between cognitive deficits and the degree of physical disability (5,16,17). However, Amato et al. reported that, in contrast to their first study, after disease duration of about 10 years, higher EDSS scores and progressive course of the disorder were correlated with the total number of tests failed. This suggests that, as the illness advances, neurological and cognitive deficits tend to converge (4). Our previous study did not find any correlation

between severity of disability and cognitive impairment (8). In this study, although, there was a statistically significant deterioration in disability, it did not correlate with cognitive impairment.

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