Original Article / Özgün Araştırma

Differentiating Mild Forms of Cognitive Impairment and Dementia: Where Other Tests Fail, Verbal Memory Assessment May Prove Critical

Bilişsel Bozulmanın Hafif Formları ve Demans Ayrımı: Sözel Bellek Değerlendirmesi Diğer Testler Başarısız Olduğunda Geçerli Olabilir

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Keywords
Cognitive impairment, dementia, neurocognitive tests, Öktem verbal memory processes test

Anahtar Kelimeler
Bilişsel bozulma, demans, nörobilişsel testler, Öktem sözel bellek süreçleri testi

Received/Geliş Tarihi : 24.01.2021
Accepted/Kabul Tarihi : 26.03.2021

doi:10.4274/meandros.galenos.2021.53824

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Abstract

Objective: Mild cognitive impairment (MCI) and mild dementia are common. In both cases, objective symptoms of cognitive impairment are present; as such, diagnosis is based on patient history and cognitive examination. This study aimed to investigate the role of neurocognitive tests in the discrimination of these disorders, by comparing mild dementia with MCI.

Materials and Methods: A battery of neurocognitive tests were applied to patients admitted to the neurology and psychiatry clinics with diagnoses of MCI (n=30) or Alzheimer-type dementia (mild, n=23; moderate, n=19).

Results: The three groups demonstrated significant differences in the neurocognitive tests, but the mild dementia and MCI groups almost always had similar results. Only the Öktem verbal memory processes test showed significantly different results in the comparison of MCI and mild dementia, with better scores in the MCI group than in the mild dementia group in terms of total learning and delayed free recall subtests (p=0.023 and p=0.001).

Conclusion: The short-term memory recall (total learning) and long-term memory recall (delayed free recall) subtests of the verbal memory processes test can guide in the discrimination of MCI from mild dementia.

Öz

Amaç: Hafif bilişsel bozulma (MCI) ve hafif demans yaygın olarak görülmektedir. Her iki durumda da, bilişsel bozulmanın nesnel semptomları bulunur ve tanı hastanın öyküsü ve bilişsel muayene ile konur. Bu çalışmada, biz nörobilişsel testlerin bu iki durumu ayırt etmedeki rolünü araştırmayı amaçladık. Bu iki durumu saptamak zor olduğu için MCI ve hafif demans üzerine odaklandık.

Gereç ve Yöntemler: Nörobilişsel testlerden oluşan bir batarya MCI (n=30) ve Alzheimer tipi demans (hafif, n=23; orta, n=19) hastalarına uygulanmıştır.

Bulgular: Üç grup nörobilişsel testler açısından anlamlı farklılıklar göstermiştir. Ancak, hafif demans ve MCI'da genellikle benzer sonuçlar olduğu görülmüştür. Sadece Öktem sözel bellek süreçleri testi hafif demans ve MCI arasında anlamlı

farklılık göstermiştir ve MCI'da hafif demansa total öğrenme ve gecikmiş kendiliğinden hatırlama skorları açısından daha iyi sonuçlar görülmüştür (p=0,023 and p=0,001).
Sonuç: Sözel bellek süreçlerinin total öğrenme ve gecikmiş kendiliğinden hatırlama alt testleri hafif demans ve MCI tanılarının ayırımında bize yol gösterici olabilir.

Introduction

Mild cognitive impairment (MCI) is a term used to describe a clinically-relevant cognitive deterioration that lies between natural ageing-related cognitive changes and mild dementia (1). While such individuals demonstrate objective evidence of cognitive impairment, their functionalities are either normal or close to normal, generally indistinguishable from their past lives (1,2). Although MCI is often associated with Alzheimer's dementia, it can develop due to many causes (1). Some patients with MCI develop dementia, while some remain stable or return to normal cognitive function. The frequency of regaining normal cognitive function among patients with MCI has been reported to be 4-15% in clinical studies (3,4) and around 29-55% in community-based studies (5,6). Efforts to recognize and treat mild dementia has made it critical to identify which types of MCI may result in cognitive worsening. The results of studies focused on this topic have demonstrated that the presence of non-amnestic type MCI, having high Mini-Mental State Exam (MMSE) scores, being young, and absence of the APOE 4 allele are factors associated with reduced risk of progression to dementia (7).

Early or mild dementia is a condition in which cognitive impairment and reduced cognitive functionality are shown in many areas (e.g. attention, learning, memory and language). Early cases manifest as difficulties in performing complex tasks and progress into problems in simple daily activities. In contrast to MCI, individuals with dementia almost always demonstrate worsening cognitive capabilities, progressing into moderate to severe dementia with time.

In relation with the increasing age of the population, MCI and mild/moderate dementia have become common disorders today. Early diagnosis and treatment are crucial to reduce cognitive worsening and the subsequent loss of ability, especially in MCI. Our aim in this study was to assess whether neurocognitive tests could be effective in distinguishing MCI from Alzheimer's disease-related mild or moderate dementia.

Materials and Methods

Study Group

In our study, we evaluated an extensive set of neurocognitive tests in 72 patients who applied to Adnan Menderes University Hospital's neurology or psychiatry clinics and had been diagnosed with MCI (n=30) or mild (n=23) or moderate (n=19) Alzheimer-type dementia between June 2017 and May 2018. Patients with early-onset dementia or cognitive loss, individuals with a history of head trauma or non-Alzheimer's dementia, those with severe systemic diseases (including cancer, advanced organ failure that could affect cognition and metabolic diseases), and subjects that were receiving medical treatment for any neurological or psychiatric disease were excluded.

Ethics

The study plan was approved by the Ethics Committee of the Aydın Adnan Menderes University Faculty of Medicine on 07.06.2018, with the protocol number 2018/1417. Since the test results and diagnostic evaluations of patients were retrospectively evaluated and no interviews were conducted with the patients or their relatives during the study, written informed consent was not obtained from the patients.

Measurements

The severity of dementia was determined by using the Clinical Dementia Rating (CDR) scale (8). Stage 0 is normal, stage 0.5 is questionable dementia, stage 1 is mild dementia, stage 2 is moderate dementia, stage 3 is severe dementia. All neurocognitive assessments were conducted by a psychologist who was trained for the tests. Participants were applied the Wechsler Memory Scale-Revised (WMS-R) digit span (forward and backward digit span) subtest (9), -III mental control subtest (10), verbal fluency test (11), WMS-IV Logical memory-immediate recall subtest (12), Wechsler Adult Intelligence Scale-Revised Form (WAIS-R) Binary Similarities Subtest (13), Öktem Verbal Memory Processes Test (14), Judgement of

Line Orientation Test, Benton Facial Recognition Test (15), Boston Naming Test (16), clock-drawing test (17) and MMSE (18). Patient groups were compared with regard to results obtained from each test.

In the WMS-R digit span test, the patient is asked to repeat numbers in the same order they were spoken, while in the backward digit span, the patient is asked to repeat numbers in the reverse order. The WMS-III mental control subtest involves counting in series. Depending on the patient's education level, tests include counting backward from 20, counting by threes from 1 to 40, counting the days of the week or months in reverse order. The Verbal Fluency Test evaluates patients' semantic fluency via articulation of animal and fruit-name pairs, and their lexical fluency which is checked by the articulation of the letters, K, A and S. In the WMS-IV logical memory-immediate recall subtest, patients' capability in following a storyline and recall is evaluated. Finally, in the WAIS-R Binary Similarities subtest, the patient is told the name of two objects that do not resemble each other and the their task is to identify and explain the common aspects of these two objects.

Öktem Verbal Memory Processes Test: Consists of two steps. In the first, 15 words are read 10 times to the patient. After each set, the patient is asked to repeat what they can remember (total learning). In the second step, patients are asked to repeat the 15 words after 45 minutes (delayed free recall). In the Judgement of Line Orientation test, the patient is asked to identify which two lines among 11 lines from the bottom page match the angles of the two lines in the top of the page. The Benton Facial Recognition Test consists of face-matching (one target face, six options to choose from) tasks applied consecutively in two phases. In the initial phase, the target image has an exact match among the given options; whereas, in the second phase the faces in the options section are altered in terms of orientation or lighting characteristics and the patient is asked to select the single target to three of these images. The aim of the Boston Naming Test is to evaluate patients' skill in naming pictured objects. As the name clearly states, the clock-drawing test is applied by asking the patient to draw an analogue clock according to pre-determined conditions.

The MMSE consists of 8 "categories" or sub-dimensions that assess time/place orientation, recall/repeating ability, arithmetic, language and complex commands (the latter is often addressed by drawing a standardized shape). The target score indicating normal cognition is 24 points (out of a possible 30). Scores equal to or lower than 9 are associated with severe cognitive impairment, 10-18 points suggest moderate impairment and 19-23 suggests mild impairment.

Statistical Analysis

Statistical evaluation of data was conducted using the IBM SPSS Statistics (version 18.0) package program. The Kolmogorov-Smirnov test was used to investigate the suitability of the data for normal distribution. Because the data is not normally distributed, Kruskal-Wallis test is used for group comparisons for continuous variables and shown with mean ± standard deviation and comparisons between groups were performed via Welch ANOVA. Games Howell is used for post-hoc corrections. For statistical significance, $p<0.05$ value was accepted.

Results

The age range of the study group was 50-92 years, 41 of the patients were females and 31 were males. The distributions of sex, marital status and education levels were similar in the three groups. Mean age was significantly lower in the MCI group compared to the mild dementia ($p=0.017$) and moderate dementia ($p=0.001$) groups. The clock-drawing test also demonstrated a significant difference when the three groups were compared ($p=0.038$) (Table 1).

The overall comparison of scores (3 groups) obtained from tests showed significance in all scores except for the MMSE. When post-hoc corrections were performed, the moderate dementia group was found to have significantly lower scores compared to the mild dementia and MCI groups (respectively) in terms of the following tests: forward digit span ($p=0.125$ and $p=0.002$), backwards digit span ($p=0.013$ and $p<0.001$), WMS III ($p=0.036$ and $p<0.001$), semantic verbal fluency ($p=0.056$ and $p<0.0001$), lexical verbal fluency ($p=0.013$ and $p=0.001$). When looking at the WAIS-R scores, a significant difference was determined in the comparison of moderate dementia and MCI ($p<0.001$), with lower scores in the moderate dementia group. Compared to the mild and moderate dementia groups, the Öktem Verbal Memory Processes Test yielded significantly higher

Table 1. Comparison of sociodemographic characteristics of groups

	Mild dementia (n=21)		Moderate dementia (n=20)		MCI (n=29)		Statistical analysis		
	n	%	n	%	n	%	F	df	p
Sex									
Female	13	61.9	12	60.0	16	55.2	0.251	2	0.882
Male	8	38.1	8	40.0	13	44.8			
Marital status									
Married	9	42.9	10	50.0	17	58.6	3.015	4	0.555
Single	0	0.0	0	0	1	3.4			
Widowed/divorced/separated	12	57.1	10	50.0	11	37.9			
Clock-drawing test									
0	6	60.0	12	80.0	5	21.7	16.305	8	0.038
I	2	20.0	2	13.3	6	26.1			
II	0	0.0	0	0.0	3	13.0			
III	2	20.0	0	0.0	5	21.7			
IV	0	0.0	1	6.7	4	17.4			
Educational status									
Illiterate	6	28.6	8	40.0	7	24.1	10.164	10	0.426
Literate	6	28.6	5	25.0	4	13.8			
Primary school	7	33.3	7	35.0	11	37.9			
Secondary school	0	0.0	0	0.0	3	10.3			
High school	2	9.5	0	0.0	3	10.3			
University	0	0.0	0	0.0	1	3.4			

MCI: Mild cognitive impairment, df: Degree of freedom, F: Wlch's F ratio

scores for patients with MCI, both in terms of total learning (p=0.018 and p<0.0001) and also delayed free recall (p=0.001 and p<0.001). In the Benton Line Orientation Test, scores of the moderate dementia group were significantly lower compared to the MCI group (p<0.0001). In the Benton Facial Recognition and the Boston Naming Tests, the scores of those with moderate dementia were significantly lower compared to the MCI group (p=0.002 and p=0.010). Group comparisons are shown in Table 2 and Table 3.

Discussion

The assessment of our data comparing patients with MCI and Alzheimer's disease-related mild/moderate dementia indicate that individuals with moderate dementia negatively differentiate from the other subjects, while those with MCI differentiate positively, in terms of neurocognitive tests. Meaning that it was often possible to differentiate moderate dementia (but not mild dementia) from MCI with the majority of tests applied; however, remarkably, the Öktem Verbal Memory Processes Test appears to be the only test that may have a role in distinguishing mild dementia from MCI. This feature of the test, which is particularly evident in the Total Learning score, may be critical in the clinical setting when differential diagnosis is necessary.

It is important to diagnose mild dementia before significant changes occur in brain regions due to neuro-degeneration. Early and accurate diagnosis of dementia is important for risk assessment and care management. Objective findings of cognitive impairment have been shown to be present in both MCI and mild dementia (1,19-21). The differential diagnosis of MCI and mild dementia is based mainly on story and cognitive examination. One of the

Table 2. Comparison of groups' neurocognitive test scores according to Kruskal-Wallis

	Mild dementia (n=23)		Moderate dementia (n=19)		MCI (n=30)				
	Mean	SD	Mean	SD	Mean	SD	X^2	df	p
Age (years)	75.81	8.87	78.05	7.89	68.21	9.74	13.857	2	0.001
Forward digit span	2.95	1.81	1.78	1.73	3.60	1.15	11.722	2	0.003
Backward digit span	1.79	1.54	0.50	0.98	2.60	1.22	19.294	2	<0.001
WMS III	2.00	2.00	0.50	1.09	2.92	1.44	18.646	2	<0.001
WMS IV	3.60	4.60	1.23	4.43	8.32	7.11	11.914	2	0.003
Verbal fluency semantic	7.36	4.95	3.24	4.38	10.13	5.48	13.530	2	0.001
Verbal fluency lexical	10.36	7.68	1.65	5.65	12.00	9.51	12.390	2	0.002
WAIS-R	2.00	2.39	0.38	0.88	3.23	2.40	15.083	2	0.001
Öktem Total Learning	33.14	26.64	10.00	21.66	62.39	34.44	20.584	2	<0.001
Öktem Delayed Free Recall	1.50	2.76	0.50	1.41	5.87	4.01	21.619	2	<0.001
Judgement of Line Orientation	7.00	8.28	0.0	0.0	7.89	9.02	9.731	2	0.032
Benton Facial Recognition	26.53	15.95	16.47	16.41	34.04	14.55	14.187	2	0.001
Boston Naming Test	17.78	9.84	12.16	8.68	20.32	9.26	8.995	2	0.008
Mini-Mental State Exam	14.50	4.10	10.42	6.02	17.17	6.56	6.512	2	0.039

MCI: Mild cognitive impairment, WMS: Wechsler Memory Scale, WAIS-R: Wechsler Adult Intelligence Scale-Revised Form, SD: Standard deviation, df: Degree of freedom

major problems is the absence of a standard test to distinguish between Alzheimer's dementia, MCI and changes that naturally occur with aging. Despite ongoing efforts, the effectiveness of neurocognitive tests used in the assessment and distinction of normal aging, MCI and Alzheimer-type dementia are subject to debate (22-24). The MMSE is the most commonly used screening test in the clinic to detect patients with cognitive impairment (25). However, MMSE has limitations in detecting MCI and is unable to detect slight changes in cognitive impairment (26). In our study, when evaluated among 3 groups, it was found that MMSE did not demonstrate a significant difference between. However, due to the low p-value (0.068) we performed a secondary analysis (omitted from the results due to the initial insignificance) to determine whether it was effective for the identification of mild dementia or MCI. This analysis showed that MMSE was similar to the majority of tests. That is, MMSE scores were significantly different between moderate dementia and MCI, but were similar in the mild dementia versus MCI and the moderate dementia versus mild dementia comparisons. These results support the idea that the Öktem Verbal Memory Processes Test may provide an important advantage for differential diagnosis. It must be noted that a significant difference was present between the mild dementia and MCI groups in terms of age; however, the same was true for the moderate dementia versus MCI comparison, while the mild and moderate dementia groups were similar -suggesting that the effect of age may not be significant in this context.

In a study by Jia et al. (27), the mean age of the patients with mild dementia was higher than those with MCI (even though statistically insignificant), and it was found that the MCI and mild dementia groups were both at risk of worsening with time. As mentioned previously, while almost all patients with mild dementia cognitively worsen over the years, some of those with MCI may return to cognitive normality after some time. It has been shown that the age of patients with MCI is an important risk factor for the progression of cognitive worsening (7,27-30).

Table 3. Group comparisons of variables with Welch ANOVA

		df	SD	MS	F	p
Age (years)	Between groups	2	1335.753	667.877	8.258	0.001
	Within groups	67	5418.947	80.880		
	Total	69	6754.700	-		
Forward digit span	Between groups	2	34.909	17.455	7.249	0.002
	Within groups	59	142.058	2.408		
	Total	61	176.968	-		
Backward digit span	Between groups	2	46.213	23.107	14.252	<0.0001
	Within groups	59	95.658	1.621		
	Total	61	141.871	-		
WMS III	Between groups	2	60.236	30.118	12.908	<0.0001
	Within groups	55	128.333	2.333		
	Total	57	188.569	-		
WMS IV	Between groups	2	413.187	206.594	6.018	0.005
	Within groups	39	1338.813	34.329		
	Total	41	1752.000	-		
Verbal fluency semantic	Between groups	2	464.989	232.494	9.200	<0.0001
	Within groups	51	1288.812	25.272		
	Total	53	1753.870	-		
Verbal fluency lexical	Between groups	2	899.922	449.961	7.077	0.002
	Within groups	50	3179.097	63.582		
	Total	52	4079.019	-		
WAIS-R	Between groups	2	75.365	37.683	9.231	<0.0001
	Within groups	44	179.614	4.082		
	Total	46	254.979			
Öktem Total Learning	Between groups	2	26519.600	13259.800	15.646	<0.0001
	Within groups	50	42373.193	847.464		
	Total	52	68892.792	-		
Öktem Delayed Free Recall	Between groups	2	320.420	160.210	16.547	0.0001
	Within groups	50	484.109	9.682		
	Total	52	804.528	-		
Judgement of Line Orientation	Between groups	2	540.127	270.063	5.262	0.009
	Within groups	39	2001.778	51.328		
	Total	41	2541.905	-		
Benton Facial Recognition	Between groups	2	3273.720	1636.860	6.766	0.002
	Within groups	57	13789.930	241.929		
	Total	59	17063.650	-		
Boston Naming Test	Between groups	2	761.794	380.897	4.438	0.016
	Within groups	62	5321.745	85.835		
	Total	64	6083.538	-		
Mini-Mental State Exam	Between groups	2	276.385	138.193	4.046	0.028
	Within groups	29	990.583	34.158		
	Total	31	1266.969	-		

SD: Standard deviation, MS: Mean square, F: Wlch's F ratio, df: Degree of freedom, WMS: Wechsler Memory Scale, WAIS-R: Wechsler Adult Intelligence Scale-Revised Form

The Öktem Verbal Memory Processes Test can distinguish many parameters related to memory (14). The first of these parameters is immediate memory, the second is the process of learning or acquiring knowledge and the third is the process of memory and recall. Recall is evaluated in two ways: delayed free recall and delayed cued recall. In our study, the two sub-parameters identified to have a possible role in distinguishing patients with MCI and mild dementia were the total learning and delayed free recall scores.

When assessing total learning, the interviewer reads 15 words 10 times and asks the patient to recall the words each time. The score is calculated by taking the sum of the words at the end of each repeat. It evaluates the processes of maintaining attention and short-term memory. Patients with MCI were found to be able to remember significantly more words in this area compared to patients with mild dementia (and also those with moderate dementia). This suggests that attention is maintained in MCI patients and that they have little difficulty in learning compared to individuals with dementia. The delayed free recall section evaluates long-term memory. It depends on recalling the initial 15 words, that were spoken in the prior step, after a duration of 45 minutes. Patients with MCI were found to recall a significantly higher number of words than those with mild dementia, which suggests that long-term memory functions are preserved in MCI patients.

These tests evaluate frontal lobe and temporal lobe functions. Earlier studies have reported significant differences between MCI and Alzheimer's disease in terms of frontal lobe functions (31-33). Results of the present study support these conclusions. However, contrastingly Yagi et al. (34) reported that they found no significant difference between these two groups in terms of frontal lobe function.

Quantitative analysis of clock drawing is a very widely used method to assess cognitive functions. It is considered to be an ideal screening test that is independent of culture, language and education. The results of this test pertain to various cognitive skills; therefore, it is utilized to evaluate cognitive skills in a comprehensive manner. Many areas, such as planning, visual, memory, visual-spatial skills, motor planning and application, digital memory, abstract thinking and concentration, are evaluated (35-37). Umidi et al. (38) evaluated MMSE and clock-drawing test in MCI and dementia in comparison to healthy subjects. Both parameters were normal in healthy controls; MMSE was normal and clock drawing was disrupted in MCI; and both parameters were abnormal in cases with dementia. In another study, Beber et al. (39) applied clock-drawing test in two ways (free drawing and the incomplete copy method) for patients with MCI and dementia and healthy controls. They reported a significant difference between all groups with free drawing. In our study, we found that clock-drawing test was distinctive between moderate dementia and MCI patients -similar to Umidi et al. (38). The contradictory results in Beber's study may be due to the inclusion of patients at different stages of cognitive decline.

Apart from the significant difference in age (lower in the MCI group), there are also some other limitations to discuss. Firstly, this work was conducted in a retrospective manner with a single point of measurement. Therefore, the absence of patients' longitudinal analyses (with regard to time since the development of symptoms triggering hospital application) and lack of cognitive progression data are important limitations. Secondly, although all patients that underwent the analyzed tests were included in the study, there is probability of baseline differences (or biases) related to the identification of tests that were applied to each patient. Besides, other types of dementia (vascular, frontotemporal etc.) could not be included in the study due to very low patient numbers. In addition, subjects were not separated with regard to amnestic or non-amnestic MCI. Finally, the absence of a geriatric depression scale to assess whether depression was effective on neurocognitive tests was also another significant limitation.

Conclusion

To conclude, we believe that the total learning and delayed free recall scores of the Öktem Verbal Memory Processes Test can guide in the discrimination of MCI from mild dementia. After appropriate training, these tests can be administered by all clinicians and the early examination and diagnosis of MCI and mild dementia may be possible. The results of this study must be supported by future research with increased patient numbers. It is also critical to note that future studies on this topic should strive to assess whether linguistic, cultural and education-related differences among subjects can affect the results of cognitive

assessment via the Öktem Verbal Memory Processes Test.

Ethics

Ethics Committee Approval: The study plan was approved by the Ethics Committee of the Aydın Adnan Menderes University Faculty of Medicine on 07.06.2018, with the protocol number 2018/1417.

Informed Consent: Written informed consent was not obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.Ş., Design: Y.B.Ş., Supervision: Y.B.Ş., Fundings: A.Ş., Materials: A.Ş., Y.B.Ş., Data Collection or Processing: A.Ş., Y.B.Ş., S.Ö., Analysis or Interpretation: A.Ş., Literature Search: Y.B.Ş., Writing: A.Ş., Critical Review: Y.B.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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