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Temporal Change of Cognitive Decline in Alzheimer's Disease: The Results of Turquoise Alzheimer's Working Group

Alzheimer Hastalığındaki Bilişsel Kayıpların Zamansal Değişimi: Turkuaz Alzheimer Çalışma Grubu Sonuçları

Nilgün Çınar[1], Şevki Şahin[1], Miraç Ayşen Çakmak[1], Sibel Karşıdağ[1], Taç Grubu[2]

[1]Maltepe University Faculty of Medicine, Department of Neurology, İstanbul, Turkey
[2]Turquoise Alzheimer's Working Group (TAC)

Summary

Objective: The aim of the present study was to evaluate the temporal characteristics of the cognitive decline in Alzheimer's Disease (AD). For this reason, the factorial analysis of Mini-Mental State Examination (MMSE) was used in first visit and six months after.

Materials and Methods: In this multicenter, longitudinal study, the data of 268 (152 mild, 116 moderate) cases obtained from the 'Turquoise Alzheimer Working Group' in Turkey, was evaluated. The patients who were diagnosed with probable AD according to the DSM-IV criteria were included in the study. Disability was assessed by means of global deterioration scale. The MMSE, which has 7 components (time orientation, spatial orientation, immediate memory, attention/concentration, delayed recall, language, and constructional praxis) was applied to all patients at the initial visit (baseline) and 6 months after.

Results: The baseline evaluation revealed a significant correlation between orientation and attention subscales in the mild AD group. At the second evaluation of mild AD group and at both evaluations of moderate AD group, there were stronger correlations among all subscales.

Subscales of time orientation, attention/concentration and immediate memory had higher factor loading in the first evaluation in mild AD group. Subscales of delayed recall and language were more significant in second evaluation. Subscale of spatial orientation was added in moderate AD group in both evaluation periods.

Conclusion: Factor analysis of MMSE subscales varied according to the stage and duration of the disease. Generally, disturbances in attention and orientation might be the first findings in AD groups. When assessing AD cases, the properties of subscales in MMSE should be considered. (Turkish Journal of Neurology 2014; 20:39-44)

Key Words: Alzheimer's disease, Mini-Mental State Examination, factor analysis

Özet

Amaç: Bu çalışmada Alzheimer hastalığında (AH) görülen bilişsel kayıpların zamansal değişiminin gösterilmesi amaçlanmıştır. Bunun için, ilk vizitte ve 6 ay sonra yapılan Mini-Mental Durum Değerlendirmesinin (MMDD) faktöryel analizinden yararlanılmıştır.

Gereç ve Yöntem: Turkuaz Alzheimer Çalışma (TAÇ) Grubu tarafından çok merkezli olarak kayıtları tutulan, DSM-IV'e göre olası AH tanısı almış 268 (152 hafif, 116 orta) olguya ait veriler uzamsal olarak değerlendirilmiştir. Özürlülük düzeyi, Global Bozulma Ölçeği ile belirlenmiştir. Faktör analizi için MMDD testinin 7 alt ölçeği (yer ve zaman oryantasyonu, anlık ve uzak bellek, lisan, dikkat/konsantrasyon, konstrüksiyonel praksi) ilk başvuru ve 6 ay sonrasında değerlendirilmiştir.

Bulgular: İlk değerlendirmede, hafif AH grubunda, dikkat ve oryantasyon alt ölçekleri arasında anlamlı ilişki saptanmıştır. Hafif AH grubunun ikinci değerlendirmesi ile orta AH grubunun ilk ve ikinci değerlendirmelerinde, tüm alt ölçekler arasında belirgin ilişki saptanmıştır. Hafif AH grubunda, ilk değerlendirmede zaman oryantasyonu, dikkat/konsantrasyon ve yakın bellek alt ölçekleri, yüksek faktöriyel yüke sahip bulunmuştur. İkinci değerlendirmede, uzak bellek ve dili değerlendiren alt ölçeklerin önemi artmıştır. Orta AH grubunda, her iki değerlendirmede, yer oryantasyonu yüksek faktörlü alt ölçekler arasına eklenmiştir.

Sonuç: MMDD'nin faktöriyel analizi, hastalığın evresine ve süresine göre değişim gösterebilmektedir. Dikkat ve oryantasyondaki bozukluklar, AH olgularında saptanan ilk bulgular olmuştur. AH olguları, MMDD ile değerlendirilirken alt ölçeklerin bu özellikleri göz önünde bulundurulmalıdır. (Türk Nöroloji Dergisi 2014; 20:39-44)

Anahtar Kelimeler: Alzheimer, Mini-Mental Durum Değerlendirme, faktör analizi

Address for Correspondence/Yazışma Adresi: Şevki Şahin MD, Maltepe University Faculty of Medicine, Department of Neurology, İstanbul, Turkey
Gsm: +90 532 654 77 01 E-mail: drsahin@gmail.com
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Introduction

Alzheimer's disease (AD), the leading cause of dementia in the elderly, is characterized by an insidious onset and slow deterioration of cognitive function, functional ability (e.g., daily living activities), behavior and mood (1,2). While the prevalence of AD is 5%-10% in individuals over 65 years of age, it reaches 40% in those over 85 years of age (3).

Mini-Mental State Examination (MMSE) was developed by Folstein et al. in 1975 (4). In order to investigate the neural correlates of cognitive deficits, MMSE and certain neuro-imaging methods have been combined in many studies. Even though MMSE is a simple cognitive screening instrument, these studies revealed more reliable results (4-6). Mini-Mental State Examination is comprised of 11 items for five dimensions of cognitive functions such as orientation to time and place, immediate and short-term recall, attention, language functions, and constructional ability (7-9). These subscales deteriorate in parallel with progression of dementia (10).

Factor analysis may provide information about the relationship among cognitive subscales of MMSE. In the past, factor analysis has been used in several neuro-muscular diseases such as the examination of the internal consistency of functional rating scale in amyotrophic lateral sclerosis (11,12). It has been also used for the evaluation of the relationship between clinical findings and neurophysiological abnormalities in diabetic polyneuropathy (13).

The factorial structure of the MMSE was first laid out by Fillenbaum et al. (14). Several other investigators evaluated the factorial structure of the MMSE in different stages of dementia, but there is no detailed data about the changes in factorial structure of the MMSE in follow-up period (15-17).

In this study, we aimed to investigate the changes in MMSE subscales in the first and second (6 months later) evaluations of AD patients from different parts of the country whose data were collected in one database.

Materials and Method

Participants

The data was collected from the Turquoise Alzheimer's Working Group (TAC) which included 22 centers. The diagnosis of probable AD was made according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria (18). Mild and moderate AD patients were included to the study. The stages of AD patients were determined according to Global Deterioration Scale (GDS score: 3 or 4: mild; 5: moderate) as previously described (19,20).

Mini-Mental State Examination (MMSE)

In the present study, the scores of MMSE of AD patients were evaluated at the initial (baseline) visit and 6-months later. Mini-Mental State Examination has 2 versions; MMSE,validated for Turkish-speaking people with 5 years or more formal education and MMSE for people with less than 5 years of education (21). Mini-Mental State Examination consists of 7 subscales. These subscales and their maximum scores according to the number of correct answers are as follows: time orientation (5 points), spatial orientation (5 points), attention/concentration (5 points), immediate memory (3 points), delayed recall (3 points), language (8 points) and constructional praxis (1 point). For a better evaluation of cognitive functions, only educated patients were included in the study.

Factor Analysis

Data were stored and processed using SPSS 16 software. Parameters were established from the mean scores of MMSE subscales. Numerical variables of normal distribution were expressed as mean±SD. The Student t-test was performed to compare MMSE subscales in mild and moderate dementia groups. The significance level was set as $p=0.05$.

Factor analysis was performed to assess the factorial structure of the MMSE in both mild and moderate probable AD groups. Thus, a smaller set of independent factors (clusters) according to the basic underlying relationship among variables could be identified. In the same group, factor analysis of MMSE was repeated 6 months later. Factor analysis was initiated by the extraction of subscales of MMSE using principal component analysis. Principal component analysis is a linear transformation of a set of partially correlated and uncorrelated subscales of MMSE. The data set was arranged according to progressively decreasing contribution to total variance. Factor analysis identified two or three factors which were established by MMSE subscales. Factor coefficients of parameters greater than 0.6 were considered as high value, parameters between 0.3-0.59 were considered to be medium value. In the present analysis, factors with eigenvalues greater than 1 were retained. To determine whether the common factor model was appropriate, Kaiser's measure of sampling adequacy (MSA) was used. Values of MSA<0.5 were not considered acceptable. We also evaluated the internal consistency of the total scale and subscales by using alpha coefficients.

Results

The mean age was 71.6±10 years of total 268 patients (male/female ratio: 152/178). The mean MMSE subscales and their percent distribution in the mild and moderate AD patients with demographic data were presented in Table 1.

Factor Analysis

Mild Alzheimer's Disease Group

There were significant correlations between time orientation and spatial orientation as well as attention/concentration at the first evaluation (Table 2). The correlation analysis of the second evaluation showed relationships among all sub-scales (Table 3).

Three factors were identified by principal component analysis in the mild dementia group explaining 55% of the variance in MMSE scores at the first evaluation. The first, second and third factor explained 23% (time orientation and attention/concentration), 17% and 15% (immediate memory) of the variance, respectively. Factor coefficients of parameters greater than 0.6 and others were shown in Table 4.

In the second evaluation, three factors explaining 64% of the variance were identified by analysis. The first, second and third factor explained 28% (immediate memory and language), 21% (time orientation) and 15% (time orientation and delayed recall) of the variance, respectively. At the second evaluation, 3% of the mild AD patients progressed to moderate AD. They were excluded from statistical analyses (Table 4).

Moderate Alzheimer's Disease Group

In the correlation analyses, there were significant correlations among the subscales of MMSE, both at the first and second evaluations (Table 5,6).

Two factors explaining 52% of the variance in MMSE scores were identified by factorial analysis in the moderate AD group at the baseline evaluation (Table 6). The first factor explaining 28% of the variance consisted of time and spatial orientation. The second factor explaining 24% of the variance consisted of immediate memory and delayed recall subscales.

Three factors explaining 66% of the variance were identified at the second evaluation of MMSE subscales in moderate dementia group. The first factor explaining 34% of the variance was noted as time orientation, spatial orientation, immediate memory and language subscales. The second factor explained 16% of the variance. The third factor explaining 15% of the variance consisted of delayed recall (Table 7). At the second evaluation there were no changes in the stage of AD cases.

Table 1. Demographic parameters and scores of MMSE subscales in mild to moderate AD patients at the first and-second evaluations.

	Mild AD	Moderate AD	p
Age (years)	73.8±8	72.9±9	0.4
Education (years)	8.6±3.9	7.8±3.6	0.03*
Time orientation			
1st evaluation	2.9±1.5	1.4±1	<0.0001*
2nd evaluation	2.2±1.6	1.1±1	<0.0001*
Spatial orientation			
1st evaluation	3.8±0.9	2.8±1.1	<0.0001*
2nd evaluation	3.5±1.1	2.3±1.3	<0.0001*
Attention/concentration			
1st evaluation	3.8±1.6	0.9±1	<0.0001*
2nd evaluation	2.9±1.1	0.8±1	<0.0001*
Immediate memory			
1st evaluation	2.9±0.4	2.7±0.5	0.1
2nd evaluation	2.8±0.5	2.3±1	<0.0001*
Delayed recall			
1st evaluation	2.9±0.4	2.7±0.5	0.1
2nd evaluation	2.8±0.5	2.3±1	<0.0001*
Language			
1st evaluation	7.3±0.8	5.9±1.4	<0.0001*
2nd evaluation	7±1.4	5.4±2.2	<0.0001*
Constructional praxis			
1st evaluation	0.7±0.4	0.4±0.2	<0.0001*
2nd evaluation	0.6±0.4	0.2±0.1	<0.0001*
MMSE			
1st evaluation	22.4±2	14.3±2	<0.0001*
2nd evaluation	20±4	12.8±5	<0.0001*

*p<0.001.

Discussion

Factor analysis is useful in reduction of multiple independent variables according to their relationships in data set (22). In our study, the cumulative variance of MMSE was 55% in mild AD group and 52% in moderate AD group. Six months later, the ratios increased to 64% and 66%, respectively. Time orientation, attention/concentration and immediate memory had higher factorial load in the first evaluation in mild AD group. Although attention/concentration had higher factorial load in first evaluation, it decreased in second evaluation. Also, the parameters including delayed recall and language, were added as essential parameters in second evaluation. In moderate AD group, time, spatial orientation, immediate recall and delayed memory had higher factor loadings in the first evaluation. At the second evaluation, language was added to these factors.

Factorial analysis of MMSE in patients with dementia was used in several studies. Mini Mental State Examination subscales were grouped into two or three factors explaining 44.5%-85% of the total variance in these studies (14-16). In each study, subscales which were grouped into the same factors were different. Fillenbaum et al. found that the first factor included attention/concentration, language and constructional praxis; the second factor comprised time-space orientation and delayed recall (14). Shigemori et al. noted three factors in dementia patients. The first factor was language, the second factor included spatial/time orientation and delayed recall and the third factor included praxis and attention/concentration (15). The results of these studies were in accordance with our findings of moderate AD group.

Table 2. Correlations of MMSE subscales at the first evaluation for mild AD patients.

Correlations	Time orientation	Spatial orientation	Immediate memory	Attention/ concentration	Delayed recall	Language	Constructional praxis
Time orientation	1	0.22**	-0.04	-0.31**	0.12	-0.05	-0.09
Spatial orientation		1	-0.10	-0.16	-0.003	-0.11	-0.05
Immediate memory			1	-0.03	0.02	-0.002	-0.11
Attention/concentration				1	-0.11	0.04	-0.03
Delayed recall					1	-0.30	-0.07
Language						1	0.07
Constructional praxis							1

(Weighted data *p<0.05; **p<0.001).

Brugnolo et al. found that time-spatial orientation, attention/concentration, delayed recall and constructional praxis clustered under the same factor but language and immediate memory clustered under different groups (16). The results of this study were also in line with our findings of mild AD group except for praxis.

Conclusion

Even though mild AD cases were assessed with MMSE in the early period, subscales of time orientation and attention/concentration were found to be important. As cognitive deficits progressed, subscales of delayed recall and language in the MMSE were becoming more

Table 3. Correlations of MMSE subscales at baseline for mild AD patients 6 months later

Correlations	Time orientation	Spatial orientation	Immediate memory	Attention/ concentration	Delayed recall	Language	Constructional praxis
Time orientation	1	0.39**	0.16*	-0.06	0.22**	0.07	-0.005
Spatial orientation		1	0.27**	-0.02	0.09	0.19	-0.02
Immediate memory			1	0.25**	0.08	0.49**	0.09
Attention/concentration				1	-0.01	0.25**	0.27**
Delayed recall					1	-0.14*	0.07
Language						1	0. 0.19*
Constructional praxis							1

Weighted data *p<0.05; **p<0.001

Table 4. Table shows 3 factors for each evaluation in factorial analyses of MMSE subscales in the mild AD group

MMSE Subtype Mild AD	1st evaluation			2nd evaluation		
	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3
Time orientation	0.66*	---	---	0.40	0.67*	0.82*
Spatial orientation	0.51	0.41	---	0.53	0.55	---
Attention/concentration	0.60*	---	---	0.46	0.52	---
Immediate memory	---	0.45	0.68*	0.77*	---	---
Delayed recall	0.49	0.55	---	---	0.45	0.72*
Language	0.47	0.51	0.43	0.72*	---	---
Constructional praxis	---	---	0.49	---	---	0.57
Initial Eigenvalues	1.628	1.214	1.092	1.948	1.489	1.093
Variance (%)	23	17	15	28	21	15
Cumulative variance (%)	23	40	55	28	49	64

*Factor coefficient >0.6

Table 5. Correlations of MMSE subscales at the first evaluation for moderate AD patients

Correlations	Time orientation	Spatial orientation	Immediate memory	Attention/ concentration	Delayed recall	Language	Constructional praxis
Time orientation	1	0.43**	-0.29**	-0.15	0.15	-0.27**	-0.09
Spatial orientation		1	-0.02	-0.28**	-0.21	-0,10	-0.21
Immediate memory			1	-0.16	-0.31**	0.20*	-0.05
Attention/concentration				1	-0.17	0.24*	0.20
Delayed recall					1	-0.06	0.14
Language						1	-0.06
Constructional praxis							1

Weighted data *p<0.05; **p<0.001

Table 6. Correlations of MMSE subscales at the second evaluation for moderate AD patients

Correlations	Time orientation	Spatial orientation	Immediate memory	Attention/ concentration	Delayed recall	Language	Constructional praxis
Time orientation	1	0.51**	0.12	0.14	0.21*	0.31**	0.14
Spatial orientation		1	0.35**	0.09	0.08	0.41**	0.07
Immediate memory			1	0.18	-0.04	0.49**	0.20*
Attention/concentration				1	0.12	0.37**	0.29**
Delayed recall					1	0.08	0.09
Language						1	0.21*
Constructional praxis							1

Weighted data *p<0.05; **p<0.001

Table 7. Table shows two factors at the first evaluation. The second evaluation shows three factors in factorial analyses of MMSE subscales in moderate AD group

MMSE Subtype Moderate AD	1st evaluation		2nd evaluation		
	Factor 1	Factor 2	Factor 1	Factor 2	Factor 3
Time orientation	0.76*	---	0.62*	0.51	---
Spatial orientation	0.70*	---	0.69*	0.50	---
Immediate memory	---	0.69*	0.63*	---	0.47
Attention/concentration	0.54	0.47	0.51	0.53	---
Delayed recall	---	0.70*	---	0.38	0.78*
Language	0.55	---	0.78	---	---
Constructional praxis	---	0.48	0.44	0.53	---
Initial eigenvalues	1.826	1.661	2.409	1.161	1.093
Variance (%)	28	24	34	16	15
Cumulative variance (%)	26	52	34	50	66

*Factor coefficient >0.6

important. In moderate AD cases, deterioration in spatial orientation was more pronounced. Physicians should keep these properties of subscales in mind when assessing AD cases with the MMSE.

Turquoise Alzheimer's Working Group (TAC)

- Abdurrahman Akbaş
  Samsun Education and Research Hospital, İstanbul Turkey
- Özlem Erden Akı
  Hacettepe University School of Medicine, Ankara, Turkey
- Talip Asil
  Bezmialem Gureba University School of Medicine Foundation, İstanbul, Turkey
- Başar Bilgiç
  Çapa Medical Faculty of İstanbul University, İstanbul, Turkey
- Sultan Çağırıcı
  Bakirkoy Dr. Sadi Guest Education and Reserch Hospital, İstanbul, Turkey
- Serpil Demirci
  Süleyman Demirel University Faculty of Medicine, Isparta, Turkey
- Demet İlhan
  Eskişehir Yunus Emre State Hospital, Eskişehir, Turkey
- Pervin İşeri
  Kocaeli University Faculty of Medicine, Kocaeli, Turkey
- Hatice Mavioğlu
  Celal Bayar University School of Medicine, Manisa, Turkey
- İsmet Melek,
  Mustafa Kemal University Faculty of Medicine, Hatay, Turkey
- Senem Ertuğrul Mut
  Yakın Doğu University, Faculty of Medicine, Nicosia, Cyprus
- Dilek Necioğlu Örken
  Sisli Hamidiye Hospital, Pediatric Education and Research, İstanbul, Turkey
- Demet Özbabalık
  Eskisehir Osmangazi University Faculty of Medicine, Eskişehir, Turkey
- Aynur Özge
  Mersin University School of Medicine, Mersin, Turkey
- Ayça Özkul
  Adnan Menderes University School of Medicine, Aydın, Turkey
- Nazan Sakallı,
  Dr. Mazhar Osman Mental Health and Neurological Diseases, Psychiatrists and psychiatry, Training and Research Hospital, İstanbul, Turkey

- Yusuf Tamam,
  Dicle University Faculty of Medicine, Diyarbakır, Turkey
- İrem Taşkıran,
  Atatürk Training and Research Hospital, İzmir, Turkey
- Mehmet Yaman,
  Kocatepe University Faculty of Medicine, Afyon, Turkey
- Görsev Yener,
  Dokuz Eylul University Faculty of Medicine, İzmir, Turkey

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