Assessment of Cognitive Dysfunction in Hemodialysis Patients By the Mini Mental Test and the Clock Drawing Test

Hemodiyaliz Hastalarında Kognitif Disfonksiyonun Kısa Mental Muayene ve Saat Çizme Testi ile Değerlendirilmesi

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ABSTRACT

OBJECTIVE: Our aim was to assess cognitive dysfunction, which is common in hemodialysis patients and difficult to diagnose, by an easily applicable test, the Mini Mental State Examination and Clock Drawing Test.

MATERIAL and METHODS: Two hundred and sixty six (266, 88.37%) dialysis patients that were followed-up at the Nephrology Clinic of Bursa Specialty Training and Research Hospital and private dialysis centers, and 35 (11.63%) healthy control individuals were involved in our study. Mini Mental State Examination and Clock Drawing Test were applied by a neurologist to the subjects. MMSE and CDT scores of the patients were compared with the control group.

RESULTS: Patient and control groups were similar in terms of age, gender, diabetes, and smoking. The rate of hypertension was significantly higher in the dialysis group. Mini Mental State Examination and Clock Drawing Test success rates were significantly higher in the control group. Orientation, attention and language modalities evaluated in the MMSE were observed to be significantly lower in the hemodialysis group. A statistically significant inverse correlation was found between registration memory and recall scores in MMSE, and urea.

CONCLUSION: Cognitive performances of hemodialysis patients must be monitored closely. The relationship between record memory and recall scores and urea suggests that uremic toxins may affect memory functions negatively. In addition, cognitive performance can be monitored by Clock Drawing Test in these patients.

KEY WORDS: Hemodialysis, Clock Drawing Test, Cognitive dysfunction

ÖZ

AMAÇ: Hemodiyaliz hastalarında sık görülebilen ve tanı almakta zorlanılan kognitif disfonksiyonun kolay uygulanabilir bir test olan kısa mental muayene ve saat çizme testi ile değerlendirmeyi amaçladık.

GEREÇ ve YÖNTEMLER: Çalışmaya Bursa Yüksek İhtisas Eğitim Araştırma Hastanesi Nefroloji kliniğinde ve özel diyaliz merkezlerinde takipli olan 266 (%88,37) diyaliz hastası ve 35 (%11,63) sağlıklı kontrol grubu alındı. Hastalar bir nöroloji uzmanı tarafınca değerlendirilip, kısa mental muayene ve saat çizme testi uygulandı. Hastaların kısa mental muayene ve saat çizme testi skorları kontrol grubu ile karşılaştırıldı.

BULGULAR: Hasta ve kontrol grubu arasında yaş, cinsiyet, diyabet ve sigara kullanımı açısından fark yoktu. Hipertansiyon görülme oranı diyaliz grubunda anlamlı olarak daha yüksekti. Kısa mental muayene ve saat çizme başarı oranları kontrol grubunda anlamlı olarak daha yüksekti. Kısa mental muayene de değerlendirilen yönelim, dikkat ve lisan modalitelerinde hemodiyaliz grubunda anlamlı derecede düşük olduğu gözlendi. Kısa mental muayenede kayıt hafızası ve hatırlama puanları ile üre arasında negatif yönde anlamlı korelasyon mevcuttu.

SONUÇ: Hemodiyaliz hastalarında kognitif fonksiyonlar yakın takip edilmelidir. Kognitif fonksiyonlar kısa mental muayene yanında saat çizme testi ile de güvenle takip edilebilir. Kayıt hafızası ve hatırlama puanları ile üre arasındaki ilişki, üremik toksinlerin bellek fonksiyonlarını negatif yönde etkileyebileceğini düşündürmektedir.

ANAHTAR SÖZCÜKLER: Hemodiyaliz, Saat Çizme Testi, Kognitif disfonksiyon

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INTRODUCTION

Cognitive dysfunction is more common in patients with Chronic Renal Failure (CRF) compared to the healthy population due to uremic toxins, increased oxidative stress, anemia, and vascular pathologies. Deterioration in cognitive function may affect the patient's morbidity and mortality due to the need for diet restrictions, multiple-drug use with a narrow therapeutic index, and the need for self-monitoring of blood glucose, that may not be achieved in cognitively impaired patients, in the majority of patients (1). It has been reported that the prevalence of cognitive dysfunction is between 30-60% in end-stage renal disease (ESRD) patients. Cognitive dysfunction increases at each stage of CRF compared to the normal population and becomes more severe with the progress of disease stage (2). Despite the incidence of cognitive dysfunction in CRF patients, and its negative effects on morbidity and mortality, it might be ignored in this patient group due to other major pathologies. A very small portion of these patients are diagnosed with cognitive dysfunction and receive treatment. The screening of dementia is evaluated with various neurophysiological tests and among them Mini-Mental State Examination (MMSE) and clock drawing test (CDT) are most commonly used (2,3).

When screening of dementia is evaluated by MMSE and CDT together, the sensitivity and specificity of the diagnosis increases (4).

Contribution of anemia to cognitive dysfunction is not clear in this patient group due to several factors in the etiopathogenesis. Although there are studies that have reported the positive effects of erythropoetin (EPO) treatment, some studies reported no efficacy (5,6,7). Patients that receive replacement treatment with the diagnosis of ESRD must be closely monitored in terms of cognitive functions along with the accompanying medical pathologies. In our study, our aim was to assess cognitive function of patients that receive hemodialysis treatment by means of easily-applicable MMSE and CDT and to assess the effect of EPO treatment on cognitive functions.

MATERIAL and METHODS

Two hundred and sixty six (266, 88.37%)dialysis patients without dementia symptoms who were followed-up at the Nephrology Clinic of Bursa Specialty Training and Research Hospital and private dialysis centers, and 35 (11.63%) healthy controls were included in our study. Patients were divided into 2 groups based on whether they received erythropoietin or not during the last 3 months. Urea, Kt/V (dialysis efficiency), creatinine, albumin, iron, hemoglobin, calcium, phosphorus, and parathormone values of the patients were recorded.

Patients were evaluated by a neurologist, and the MMSE and CDT tests were applied. MMSE and CDT scores of patients and biochemical parameters were compared with the control group.

MMSE has been grouped under 5 main titles; orientation, registration memory, attention and calculation, recall, and language. It consists of 11 articles that are assessed over a total score of 30. Conventionally, scores between 24 and 30 are considered normal. Since it is a practical scale that can be applied in a short time, it is commonly used for screening of dementia. Turkish validity and reliability studies of the form that is used by trained individuals have been conducted by Güngen et al.(8). CDT is a scale used to evaluate many different cognitive functions such as visual spatial functions, executive functions, memory and attention. Sensitivity and specificity of CDT were found to be 85% and 85% respectively in screening of cognitive impairment and correlated with MMSE test for early detection of cognitive functions (9).

Cangöz et al.(10) conducted a standardization study on people above the age of 50 in our country. The participants were asked to draw a clock, write the numbers on the drawing in their correct places, and draw the time as ten past eleven (11:10). The four points method (0-4 points) was preferred in the scoring of CDT. In the four points method, the scoring was made as follows: A circle/square/rectangle drawn as an enclosed space =1 Point, Placement of numbers in their right locations and positions =1 Point, Inclusion of all 12 numbers (completeness) =1 Point, Placement of hour and minute hands in their right positions (11:10) =1 Point. The highest point was 4, and the lowest was 0. Patients with a history of stroke, diagnosed with psychosis or severe depression not included in to the study Education levels of patients grouped as primary school, secondary school and higher education. Illiterate patients and controls not included.

All participants signed an informed consent. The study was approved by the local ethics committee in Bursa Specialty Training and Research Hospital and was conducted in accordance with the Declaration of Helsinki.

RESULTS

There was no difference between patient and control groups in terms of age and gender. Mean MMSE score was 29 (min-max=26-30), and 27 (min-max=10-30) in the control and hemodialysis group respectively (p <0,001).

A significant impairment was observed in all assessments of CDT as well as the total score in the hemodialysis group as compared to the control group (p <0,001). MMSE total score, and orientation, language, and attention and calculation scores were significantly low in the hemodialysis group as compared to control group (Table I).

Positively significant correlations were between total hours and calcium values (r=0.217; p=0.023), orientation score and creatinine (r=0.379; p=0.023), registration memory score and albumin (r=0.229; p=0.016), language score and creatinine (r=0.261; p=0.005) as well as language score and iron level (r=0.198; p=0.035). There were negatively significant

correlations between registration memory and urea (r= -0.184; p=0.047), and recall score and urea (r=-0.194; p=0.037). However after Bonferroni correction, no significant correlation was found between groups (α :0.0056) (Table II) Education levels of patients and control respectively were not different (Primary school: 71.4% vs. 74.3, secondary school: 14.8% vs. 17.1%, higher school: 5.2% vs. 8,6% p=0.795).

When those with and without erythropoietin intake in the dialysis group were compared, there was no significant difference in terms of total MMSE score and sub-scores (Table III).

Table I: Comparison of patient characteristics in patient and control groups.

Variable		**Control**	**Dialysis**	***p-value***
Age (year) [##]		49.69±13.25	54.78±15.33	0.062
Gender[&]	Female	20(57.14)	110 (41.51)	0.116
	Male	15 (42.86)	155 (58.49)	
Smokers[&]		12(34.29)	44 (22.68)	0.209
Hypertension [&]		10(28.57)	89(49.72)	**0.035**
Diabetes[&]		5(14.29)	62 (31.96)	0.070
CDT 1*		34 (97.14)	113(81.88)	**0.046**
CDT2		33 (94.29)	79 (60.31)	**<0.001**
CDT3		35 (100)	95 (72.52)	**<0.001**
CDT4		34 (97.14)	66 (47.83)	**<0.001**
Total hours		4 (2-4)	3 (0-4)	**<0.001**
Orientation		10(10-10)	10(0-10)	**0.002**
RM[#, **]		3(2-3)	3(0-3)	0.559
AC[#, †]		5(2-5)	5(0-7)	**0.008**
Recall[#]		3(2-3)	3(0-3)	0.124
Language[#]		9(7-9)	8.50(0-9)	**0.002**
MMSE[#, ‡]		29(26-30)	27(10-30)	**<0.001**

:** Clock Drawing Test , *:** registration memory, **†:** attention and calculation, **‡:** Mini Mental Test State Examination
Data has been provided as [#]median [minimum-maximum], [##]mean±standard deviation or [&]frequency (percentage) values.

Table II: Correlation between MMSE and CDT, and other patient characteristics in the dialysis group.

	MMSE*	**Total hours**	**Orientation**	**RM†**	**AC‡**	**Recall**	**Language**	
	p	**p**	**p**	**p**	**p**	**p**	**r**	**p**
Kt/V[§]	0.168	0.696	0.280	0.588	0.529	0.663	-	0.308
Urea	0.829	0.802	0.682	0.047	0.275	0.037	-	0.735
Creatinine	0.070	0.172	0.023	0.237	0.943	0.170	0.261	0.005
Alb[ll](mg/dL)	0.546	0.974	0.266	0.016	0.686	0.822	-	0.308
Iron	0.347	0.774	0.193	0.824	0.370	0.584	-	0.946
Hgb[¶]	0.386	0.851	0.398	0.411	0.251	0.927	0.198	0.035
Ca**	0.130	0.023	0.156	0.508	0.572	0.967	-	0.377
P[††]	0.305	0.875	0.930	0.810	0.596	0.717	-	0.590
PTH[‡‡]	0.164	0.739	0.294	0.078	0.230	0.659	-	0.998

:** Mental Test State Examination, **†:** registration memory, **‡:** attention and calculation, **§:** estimated dialysis efficiency, **ll:** Albumine, **¶:** Hemoglobin, *:** calcium, **††:** phosphorus, **‡‡:** parathormone, There were no significant correlations for Bonferroni corrected significance level (α*) 0.0056.

DISCUSSION

In our study, significant impairment was observed in all assessments of CDT as well as the total score in the dialysis group compared to the control group. MMSE total score, and orientation, language, and attention and calculation scores were significantly low in the hemodialysis group compared to control group. In a study conducted by Sehgal et al.(11), the MMSE test was applied to 336 dialysis patients and mild cognitive impairment was observed in 22% (MMSE18-23), and moderate and severe cognitive impairment was observed in 8% of the patients.

In a study performed on 374 hemodialysis patient to examine memory, executive function and language, mild, moderate, and severe cognitive dysfunction were observed in 13.9%, 36.1%, and 37.3% of the patients, respectively. Normal cognitive function was observed in only 12.7% of patients, and a documented dementia history existed in only 2.9% of these patients. Correlation was found between the severity of cognitive dysfunction, and level of education, Kt/V ratio, and stroke history (12).

None of our patients has been diagnosed with dementia. Mean MMSE score was 26, and total was between 10 and 30.

Cognitive dysfunction was found to be correlated with the severity of renal failure not only in ESRD patients but also in patients who do not receive dialysis treatment. Such findings may support the hypothesis that uremic toxins have a role in the etiology and generally correlated with urea (13,14). However this is somewhat different in hemodialysis patients. In hemodialysis patients, malnutrition is characterized by low creatinine, low urea and low albumin (15). In our study positive correlation of albumin and creatinine with memory tests may support the observation that good nutritional status of patients may have positive effect on cognitive functions. Many studies have shown that CKD patients, especially ESRD patients are at increased risk of cognitive dysfunction and our results were consistent with this finding that some patients suffering from probable dementia.

Rogova et al. (16) have reported that cognitive dysfunction is more common in patients with advanced stage renal failure. A correlation has been shown between MMSE scores and the severity of renal failure. In the brain magnetic resonance (MR) of patients with cognitive dysfunction, focal changes, locariosis and lateral ventricular dilatation in 30%, 23.3%, and 50% of the patients respectively have been reported. Imaging studies make us think that cerebrovascular disease underlies the major factor for cognitive dysfunction in CRF.

Negatively significant correlations were found in our study between the registration memory score and urea as well as the recall score and urea. Small molecular weight toxins like urea may penetrate the blood-brain barrier and may cause cognitive impairment. The fact that transplantation reverses cognitive impairment constitutes strong evidence for the adverse effects of uremic toxins (17). Although hemodialysis clears many small solutes like urea and creatinine, large molecules cannot be cleared adequately by conventional hemodialysis. Large and middle weight molecules may contribute to cognitive impairment in these patients. Griva et al.(17) showed that cognitive functions as assessed by attention-concentration, psychomotor and memory ability improved significantly at the sixth month after successful transplantation. This data may explain reversibility of cognitive impairment which is prevalent in the dialysis population. Along with the MMSE test, we used the CDT which was not used in dialysis patients, yet has a high level of applicability and reliability, in our study.

In the study conducted by Fomin et al.(18), cognitive dysfunction was observed in 68% of 51 patients. Cognitive dysfunction and male gender, hyperhomocysteinaemia, anemia, abdominal obesity, left ventricular hypertrophy, and age were found to be associated. Such findings give rise to the thought that CV effects of the uremic toxins are parallel to the effects

Table III: Comparison of patients that take and didn't take erythropoietin in hemodialysis group.

	EPO(-)	EPO (+)	p-value
MMSE*	27 (10-30)	26 (12-30)	0.533
ORIEN†	10 (0-10)	10 (0-10)	0.920
RM‡	3 (0-3)	3 (0-3)	0.091
AC‡	5 (0-5)	5 (0-7)	0.192
RECALL	3 (0-3)	3 (0-3)	0.691
LANG‖	9 (0-9)	8.50 (0-9)	0.396
Hours	3 (0-4)	3 (0-4)	0.946

*: Standardized Mini Mental Test, †: Orientation, ‡: registration memory,
‡: attention and calculation, ‖: Language

on cognitive function. Cognitive functions might be impaired by vascular damage or associated with the direct effects of uremic toxins. Frequency and severity of cognitive dysfunction have been found to be associated with atherosclerotic lesions in the carotid artery (19).

Several studies have suggested that increased in hematocrit after EPO results in improved cognitive function in CRF, However negative effects of EPO treatment on CV outcome is a well known fact. For that reason, these results need to be interpreted with caution (20,21).

In our study, when those with and without EPO treatment were compared in the dialysis group, there was no significant difference between total MMSE score and sub-scores, and total hours.

In conclusion, the fact that MMSE and CDT revealed significantly lower performance in hemodialysis group as compared to the control group. Both tests can be applied together in the hemodialysis population. Cognitive performances of hemodialysis patients must be closely monitored. Similar cognitive performances between patients with and without EPO treatment suggested that EPO did not contribute to the cognitive processes.

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