Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2021;46(1):233-239
DOI: 10.17826/cumj.794256

ARAŞTIRMA / RESEARCH

Cognitive profile in early stage Parkinson disease

Erken evre Parkinson hastalığında kognitif profil

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Cukurova Medical Journal 2021;46(1):233-239

Abstract

Purpose: Parkinson's disease (PD) is a neurodegenerative disorder characterized by both motor and nonmotor symptoms mainly due to striatal dopamine deficiency. Cognitive dysfunction is one of nonmotor symptoms. The purpose of this study is to determine the cognitive dysfunction with practical screening tests and to investigate relationship between cognitive dysfunction and clinical severity in early stage of PD (EPD)

Materials and Methods: EPD patients and healthy control group were included into the study. Mını mental state examination (MMSE), digit span (DS), clock drawing (CD), verbal and visual memory tests were applied to all cases. Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn & Yahr Staging (H&Y) tests were performed to EPD patients. Correlation of neurocognitive tests with UPDRS and H&Y scores were examined in EPD patients.

Results: There were 30 EPD patients (11 female/19 male) and 20 healthy controls (10 female/10 male). There was a significant difference only in CD test between EPD and healthy controls. EPD with H&Y stage 1. group had higher score on backward DS, CD, and visual memory tests than EPD with H&Y stage 2. Verbal memory test scores had negatively correlated with UPDRS scores.

Conclusion: The first impaired test was CD in EPD compared to control group. Other cognitive tests (backward DS, verbal and visual memory tests) were also impaired with increasing severity of disease. MMSE was not different from the control group and did not change with increasing severity of disease. MMSE alone is not enough for evaluating of EPD, other cognitive tests have to be used.

Keywords:. Parkinson, MMSE, clock drawing, digit span, memory

Öz

Amaç: Parkinson hastalığı (PH); striatal dopamin eksikliğine bağlı gelişen motor ve nonmotor semptomlarla karakterize nörodejeneratif bir hastalıktır. Kognitif disfonksiyon PH'ın nonmotor bulgularından biridir. Bu çalışmada erken evre Parkinson hastalığında (EPH) kognitif disfonksiyonların pratik tarama testleri ile belirlenmesi ve kognitif disfonksiyonun EPH'ın klinik şiddeti ile ilişkisinin saptanması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya erken evre Parkinson hastaları ve sağlıklı kontrol grubu alınmıştır. Olgulara mini mental durum değerlendirmesi (MMSE), sayı menzili (SM), saat çizme (SÇ), sözel ve görsel bellek testleri uygulanmıştır. Parkinson hastalarının kognitif durumları ile Unified Parkinson's Disease Rating Scale (UPDRS) ve Hoehn & Yahr (H&Y) skorlarının ilişkisi incelenmiştir.

Bulgular: 30 Parkinson hastası (11 kadın/19 erkek) ve 20 sağlıklı (10 kadın/10 erkek) kontrol çalışmaya alınmıştır. Sadece saat çizme testinde PH ve sağlıklı kontrol grubu arasında istatistiksel olarak anlamlı fark gözlenmiştir. H&Y skoru 1 olan olguların H&Y skoru 2 olan olgulara göre görsel bellek, saat çizme ve sayı menzili test skorları daha yüksek saptanmıştır. Sözel bellek test skorlarıyla UPDRS skorları arasında negatif korelasyon gözlenmiştir.

Sonuç: Sağlıklı kontrol grubu ile karşılaştırıldığında EPH'da tek etkilenen kognitif test saat çizme testi olmuştur. Sayı menzili, saat çizme, sözel ve görsel bellek testleri ise hastalığın şiddetinin artmasıyla bozulma göstermiştir. MMSE control grubuna gore farklı olmadığı gibi hastalığın şiddeti ile de farklılık göstermemiştir. Bu durum erken evre Parkinson hastalarını değerlendirirken MMSE'nin yeterli olmadığını, diğer kognitif testlerden de yararlanmak gerektiğini göstermiştir.

Anahtar kelimeler: Parkinson, MMSE, bellek, saat çizme, sayı menzili

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Geliş tarihi/Received: 13.09.2020 Kabul tarihi/Accepted: 24.12.2020 Çevrimiçi yayın/Published online: 15.01.2021

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting approximately 1% of individuals over 60 years old[1]. Neuropathology underlying PD is not confined to nigrostriatal system, it extends to brainstem, olphactor nucleus, hypothalamus, some parts of limbic system and neocortex, as well as peripheral autonomic nervous system[2]. Although PD is characterized as a movement disorder, non-motor symptoms are reported too[3], one of non-motor symptoms is cognitive dysfunction. Cognitive impairments are observed in PD from mild cognitive impairment to severe dementia. Dementia is a clinical condition arising due to cognitive loss, which affects the daily activities[4], it leads to an increase in patient care burden and cost[5]. Therefore, early detection of cognitive dysfunction in PD must be considerable. If the course of PD can be slowed down with treatment, it will be reduced the possible care and financial burden.

Cognitive impairment in attention, visuospatial functions and executive functions are early and prominent features of PD[6]. The previous studies on cognitive tests in early Parkinson disease (EPD) were conflicting. While in one study forward digit span was preserved, backward digit span was affected[6], in another study reported no impairment in either forward or backward digit span[7]. Usually detailed neuropsychological tests must be made for detecting cognitive dysfunction in PD, unfortunately the time we can allocate to outpatients is limited in our country. Therefore, we need to practical cognitive screening tests.

In our study; we aimed to evaluate whether practical tests are useful in assessing cognition in early Parkinson disease (EPD), to determine the relationship between cognitive dysfunction and clinical severity of EPD.

MATERIALS AND METHODS

Patients with EPD who admitted to outpatient clinic of Neurology department in Cukurova University between 2015-2017 years and healthy controls were included to study. Inclusion Criteria were to be diagnosed with Parkinson's disease by a movement disorder specialist according to "United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria"[8], early parkinson disease was defined as the onset of disease ≤5 years, to be graduated from primary school, and to be fluent in Turkish.

Exclusion criteria were being educated less than 5 years reason of they can not adapt to cognitive tests, cases with a diagnosis of dementia according to DSM-4, subjects with conditions that can affect cognition (psychiatric diseases, obstructive sleep apnea syndrome, stroke, diabetes mellitus, hypertension, mental retardation), using drug which may affect cognition (anticholinergic, antiepileptic, antipsychotic, antidepressant), having abnormal imaging and/or laboratory tests (Brain Magnetic Resonance Imaging, Liver, Kidney and Thyroid Function Tests, Vitamin B12 and Folate Levels).

The study was performed in accordance with the ethical guidelines. Approval was received from the ethics committee on Faculty of Medicine, Cukurova University (Approval no: 02.05.2013/19/7), and written informed consent was obtained from all subjects.

Procedure

The following neurocognitive tests were performed in about 30 minutes by a behavioral neurologist in a quiet room, only patients were taken inside, their relatives were taken outside.

Mını mental state examination (MMSE)

A valid and reliable 30 item brief cognitive screening test that assesses select constructs including orientation, attention, memory, and the ability to respond to verbal and written commands. Scores less than or equal to 23 on this measure are indicative of significant cognitive impairment, whereas scores greater than or equal to 24 suggest that individuals are more cognitively intact[9,10].

Digit Span test (DS)

It is a widely used neuropsychological measure, known as a test of attention and working memory. The DS consists of forward recall part and backward recall part for digit sequences. Each part is considered to assess somewhat different cognitive processes. The DS was presented beginning with a length of 3 in forward or 2 in backward. In the DS forward, the participant had to listen to a digit span that keep to the speed of one digit per second and repeat it forward. In the DS backward, the participant had to listen and repeat span backward. Two trials were presented at each length. Test was halted when participant failed to either trial at equal digit length[11].

Clock drawing (CD)

This test is used for screening as a measure of spatial dysfunction and neglect. Doing the test requires verbal understanding, memory and spatially coded knowledge in addition to constructive skills. The subject is presented with a white paper with the instructions to draw a clock. and also the subject is asked to draw the hands at a fixed time, often 10 past 11[12].

Verbal memory test (The Five-Word Test)

The words were ball, book, dress, blue and falcon. Subjects were told to read them aloud and that they should remember the five words and be able to recall them later. The participants were asked to recall the words. When a word was not recalled, the examiner gave the semantic category as a clue to elicit retrieval. The number of items retrieved after free and first clued recalls was recorded. An interference task lasting 4 to 5 minutes was given before the second part of the test[13].

Visual memory test (Three Shapes Test); subjects were initially asked to copy three shapes on a sheet of paper and were not forewarned to remember them. After the stimuli were copied, the sheet was removed and the subject was immediately asked to reproduce all three shapes (Incidental Recall). And than delayed recall was tested after 5 minutes[14].

Parkinson disease evaluation

The clinical tests for PD patients were also applied by a movement disorder specialist. The first one was Unified Parkinson's Disease Rating Scale motor scores (UPDRS) which evaluates motor signs of PD[15]. The second one was Hoehn & Yahr Staging (H&Y) stages clinic of PD[16].

Cognitive data of two groups (EPD-Control) were compared. Correlation between neurocognitive tests scores and UPDRS/H&Y scores were examined. Patients were divided into three groups according to therapies depending on severity of PD:

1. MAO-B inhibitor; First-step therapy
2. MAO-B inhibitor and dopamine agonist (DA); Second-step therapy
3. L-Dopa or polytherapy with L-Dopa; Third-step therapy

Relationships between treatment groups and neurocognitive tests were also analysed.

Statistical analyis

All analyses were performed using SPSS 20 statistical software package (IBM SPSS Statistics). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum where appropriate. For comparison of continuous variables measured at basal and control visit, paired samples t-test or Wilcoxon Signed Rank test was used depending on whether the statistical hypotheses were fulfilled or not. To evaluate the correlations between basal measurements, Pearson Correlation Coefficient or Spearman Rank Correlation Coefficient was used depending on whether the statistical hypotheses were fulfilled or not. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

After 50 PD patients were evaluated, 30 PD patients (11 female, 19 male) were included to study. Twenty PD patients were excluded from study, they had diabetes mellitus (n:6), hypertension (n:4), late stage of PD (n:4), depression (n:3), history of using antiepileptic (n:2) and stroke (n:1). Also 20 healthy controls (10 female, 10 male) were included to study. Duration of disease was 29.42 ± 16.88 (3-60) months, mean UPDRS score was 12.62 ± 4.90 (5-22), and H & Y score was 1.69 ± 0.54 (1-3) in EPD group. There was no significant difference in demographic data between EPD and healthy controls (Table 1). There was a significant difference in clock drawing test (CD) between EPD and healthy controls (p: 0.03) (Table 1).

Bradykinesia was the onset symptom in 18 (60%) and resting tremor in 12 (40%) patients. Neurocognitive profile did not differ significantly according to the onset symptoms in our patient group. Fourteen patients (47%) were in H&Y stage 1, fifteen patients (50%) in H&Y stage 2 and one patient (3%) in stage 3. Patients with H&Y stage 1 had higher score on backward digit span, clock drawing, and especially visual memory tests than H&Y stage 2 (Table 2).

Verbal memory test negatively correlated with UPDRS scores; clock drawing and visual memory negatively correlated with H&Y scores. Both forward and backward digit spans showed negative correlation with treatment groups (Table 3, Table 4).

Table 1. Comparisons of cases with Parkinson's disease and control group

	Parkinson Disease (n:30)	Control (n:20)	p
Gender (Male/Female)	11/19	10/10	0.38
Age (years)	59.27±9.48 (43-81)	56.00±8.03 (43-72)	0.23
Duration of Parkinson Disease (months)	29.42±16.88 (3-60)	-	-
Education (years)	9.12±3.87 (5-15)	8.21±3.19 (5-15)	0.41
UPDRS *	12.62±4.90 (5-22)	-	-
Hoehn-Yahr	1.69±0.54 (1-3)	-	-
MMSE**	28.96±1.24 (25-30)	28.68±1.5 (24-30)	0.55
Forward Digit Span	5.31±0.97 (4-7)	5.53±1.26 (4-7)	0.54
Backward Digit Span	3.00±1.13 (0-6)	3.26±1.04 (2-5)	0.48
CD †	8.50±2.15 (3-10)	9.74±0.65 (8-10)	0.03*
Verbal M(FR) ‡	2.88±1.77 (0-5)	3.84±1.38 (0-5)	0.16
Verbal M(CR) §	4.15±1.59 (0-5)	4.53±1.02 (1-5)	0.78
Visual M(FR) ¶	2.50±0.70 (0-3)	2.68±0.47 (2-3)	0.58

*Unified Parkinson's Disease Rating Scale motor scores, **Mini mental state examination, † Clock Drawing, ‡ Verbal Memory (Free Recall), § Verbal Memory (Recall With Clue), ¶ Visual Memory (Free Recall)

Table 2. Comparison of neurocognitive data according to Hoehn & Yahr stage

	Stage 1 (n:14)	Stage 2-3 (n:16)	p
Gender (Male/Female)	6/8	5/11	0.92
Age (years)	57.56±6.36 (43-65)	60.75±10.94 (45-81)	0.85
Duration* (months)	28.00±14.69 (12-48)	28.31±17.18 (3-60)	0.84
Education (years)	10.44±4.72 (5-15)	8.25±3.31 (5-15)	0.24
UPDRS	9.00±2.12 (6-12)	14.31±4.99 (5-22)	0.006*
MMSE**	29.44±0.72 (28-30)	28.63±1.40 (25-30)	0.18
Forward †	5.78±0.97 (4-7)	5.00±0.89 (4-7)	0.07
Backward‡	3.67±1.32 (2-6)	2.63±0.88 (0-4)	0.048*
CD§	9.78±0.66 (8-10)	7.69±2.38 (3-10)	0.018*
Verbal M(FR)¶	3.44±1.66 (0-5)	2.62±1.85 (0-5)	0.23
Verbal M(CR)§§	4.78±0.44 (4-5)	3.75±1.91 (0-5)	0.32
Visual M(FR)***	3.00±0.00 (3-3)	2.19±0.75 (0-3)	0.002*

*Duration of Parkinson Disease, ** Mini mental state examination, † Forward Digit Span, ‡ Backward Digit Span, § Clock Drawing, ¶ Verbal Memory (Free Recall), §§ Verbal Memory (Recall With Clue), *** Visual Memory (Free Recall)

Table 3. Correlation between neurocognitive and demographic values of Parkinson's disease

	Age	Education	Duration	UPDRS	Hoehn-Yahr	Treatment Groups
MMSE**	0.27	0.049* r;0.390	0.12	0.28	0.33	0.54
Forward†	0.57	0.025* r;0.437	0.84	0.68	0.14	0.013* r;-0.478
Backward¶	0.48	0.001>* r;0.674	0.48	0.09	0.07	0.036* r;-0.413
Clock§	0.10	0.32	0.90	0.34	0.045* r;-0.396	0.35
Verbal M (FR) ††	0.001* r;-0.611	0.82	0.69	0.017* r;-0.465	0.20	0.79
Verbal M (CR) ‡	0.001* r;-0.574	0.74	0.67	0.044* r;-0.398	0.46	0.88
Visual M (FR) §§	0.39	0.22	0.45	0.23	0.005* r;-0.529	0.91
UPDRS	0.04* r;0.408	0.86	0.80	-	0.003* r;0.552	0.12
Hoehn-Yahr	0.91	0.36	0.57	0.003* r;0.552	-	0.03* r;0.421

**Mini mental state examination, † Forward Digit Span, ¶ Backward Digit Span, § Clock Drawing, ††Verbal Memory (Free Recall), ‡ Verbal Memory (Recall With Clue), §§ Visual Memory (Free Recall)

Table 4. Comparison of neurocognitive data according to treatment

Treatment	MMSE**	Clock§	Forward†	Backward ¶	Verbal M ††	Verbal M ‡	Visual M §§
R (n:10)	28,83±0,75 (28-30)	9,33±1,03 (8-10)	5,50±1,04 (4-7)	3,33±0,51 (3-4)	2,83±1,16 (1-4)	4,33±1,21 (2-5)	2,50±0,54 (2-3)
P+R (n:11)	28,82±1,6 (25-30)	8,64±2,61 (3-10)	5,64±0,92 (4-7)	3,09±1,64 (0-6)	3,00±1,73 (0-5)	4,36±1,28 (1-5)	2,45±0,93 (0-3)
M+P+R (n:9)	29,22±1,09 (27-30)	7,78±2,04 (5-10)	4,78±0,83 (4-6)	2,67±0,5 (2-3)	2,78±2,27 (0-5)	3,78±2,16 (0-5)	2,56±0,52 (2-3)
p	0,57	0,26	0,13	0,26	0,91	0,89	0,93

M; Madopar, **P**; Pramipexol, **R**; Rasajilin , **Mini mental state examination, † Forward Digit Span, ¶ Backward Digit Span, § Clock Drawing, ††Verbal Memory (Free Recall), ‡ Verbal Memory (Recall With Clue), §§ Visual Memory (Free Recall)

DISCUSSION

Deficits in visuospatial and executive functions are observed in PD[16,17]. Several earlier studies demonstrated that clock drawing test which evaluates executive functions and visuospatial abilities has been effected in PD[19,20,21]. Consistent with literature clock drawing test scores of PD patients were lower than healthy controls in our study. The difference in clock drawing test was prominent only in patients with H&Y stage 2 and 3. Patients with H&Y stage 1 had similar scores to the control group. It shows that severity of disease affects cognition more than duration of disease.

The previous studies on cognitive tests in EPD were conflicting. While in one study forward digit span was preserved, backward digit span was affected[6], in another study reported no impairment in either forward or backward digit span[7]. We found no difference regarding both forward and backward digit span tests between EPD and healthy controls. In previous studies the duration of disease was found longer than present study. Zgaljardic et al. 2006 reported that the disease duration was 4.9 years, while Dalrymple et al. reported 4.4 years[6,7]. In current study duration of disease was reported as 2.46 years, almost half time of the previous studies. It was showed that digit span can be preserved in EPD. In our study; patients with H&Y stage 2 had worse backward digit span, clock drawing, visual memory tests scores than patients with H&Y stage 1. These showed that

severity of disease affected cognition more than duration of disease.

While Whittington et. al (2006) reported that free recall verbal memory was impaired in EPD[22], we didn't find any differences in memory tests between PD and control groups in present study. Psychomotor retardation, memory and visuospatial impairment are expected in aging[11,23]. The study of Whittington et. al consisted older patients (mean age 68.24 years) than our study (mean age 59.27 years).

Although the underlying physiological mechanism was still unknown, cognitive loss was more prominent in patients with bradykinesia as the initial symptom rather than resting tremor in study of Hughes et al.[24]. We found no difference in neurocognitive tests regarding the onset symptom of PD. This discrepancy may be due to the duration of illness, which was found to be longer in the study of Hughes et al.[24]. There fore the onset symptom might still be a risk factor for PD, but not in EPD.

Negative correlations between cognitive tests (verbal and visual memory, clock drawing) and UPDRS/ H & Y scores were found in the present study. This findings show that cognitive functions were impaired with increasing severity of EPD.

The relationship between dopaminergic drugs and cognition has not been clearly identified yet. Although there are contradictory publications related to the impact of L-Dopa on cognition, Brown et. al. (1984) have demonstrated that PD patients in "on" period performed better in neurocognitive tests than "off" period [23]. This may indicate that L-dopa could have a positive impact on cognition. In our study, patients with L-dopa treatment (Group 3) had higher H & Y scores and relatively lower digit span test scores (Table 4). But patients with L-dopa treatment had more severe disease than other treatment groups. To evaluate the real effect of dopaminergic treatment on cognition must be given L-Dopa to same groups about severity, this is a limitation of current study. Other limitations of our study were numbers of subjects and variety of cognitive tests. Subsequently, studies with more detailed cognitive tests and more participants can be made.

This study showed that clock drawing test was firstly impacted in EPD. Clock drawing test must be used for evaluating cognition in EPD rapidly. And also memory and digit span tests were affected in EPD due to increasing severity of disease. MMSE was not impacted in EPD. We suggested that only MMSE was not enough for evaluating of EPD, other cognitive tests have to be used.

Yazar Katkıları: Çalışma konsepti/Tasarımı: ME, MD; Veri toplama: AE, ME; Veri analizi ve yorumlama: AE, MD; Yazı taslağı: AE; İçeriğin eleştirel incelenmesi: ME; Son onay ve sorumluluk: ME, AE, MD; Teknik ve malzeme desteği: ME; Süpervizyon: AE, MD; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Çukurova Üniversitesi Tıp Fakültesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulundan 02.05.2013 tarih ve 19/7 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.
Author Contributions: Concept/Design : ME, MD; Data acquisition: AE, ME; Data analysis and interpretation: AE, MD; Drafting manuscript: AE; Critical revision of manuscript: ME; Final approval and accountability: ME, AE, MD; Technical or material support: ME; Supervision: AE, MD; Securing funding (if available): n/a.
Ethical Approval: Ethical approval was obtained from Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee for this study. (With the date 6.3.2020 and the number 97/1).
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

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