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The relationship between cognition and the non-cognitive clinical findings in Turkish patients with Parkinson's disease

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ABSTRACT

The study intended to examine the relationship between cognition and the clinical features at the onset of Parkinson disease (PD) in Turkish patients. Fifty patients were included and their cognitive status was evaluated by using the Turkish version of the Montreal Cognitive Assessment (MoCA-TR) test. Clinical findings were obtained by using all of the subparts of the Unified Parkinson's Disease Rating Scale (UPDRS). Disease severity was measured using the Hoehn and Yahr staging scale, and the Schwab-England Activities of Daily Living scale was used to assess the patients' disability. Bivariate correlation analysis was conducted to examine the demographic factors, disease duration, presenting motor symptoms (tremor or bradykinesia) and laterality (right or left), and the unique contributions of the UPDRS subscores to cognitive dysfunction on the MoCA-TR. This study carried out among PD patients revealed that, 36% (18/50) had cognitive impairment (score of<21) on the MoCA-TR. Significant correlations were observed between cognitive impairment on the MoCA-TR and age, education level, subjective memory complaints, and the UPDRS I and II subscores and total score; whereas the age at disease onset, type of clinical presentation, and laterality of motor symptoms were not associated with cognitive dysfunction.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder characterized by tremor, bradykinesia, rigidity, postural instability, and gait dysfunction (Fahn and Jankovic, 2010). The clinical presentation of these motor symptoms can vary, and different subtypes of PD onset have been described, such as the 'hypokinetic-rigid' and 'tremor-predominant' forms. The presence of postural instability and gait dysfunction complicate the disease (Jankovic et al, 1990; Reijnders et al., 2009; Fahn and Jankovic, 2010). PD typically begins with unilateral motor symptoms, and the side of the body in which the motor symptoms initially begin generally remains more affected (Lee et al., 1995; Amick et al., 2006).

Cognitive dysfunction is common in PD and can range from mild impairment to frank dementia. The estimated prevalence of dementia in PD, as defined by neuropsychological testing, is 37-44%. PD patients with mild cognitive impairment have a high risk of ultimately developing dementia (Emre, 2003; Aarsland et al., 2005). These cognitive problems can result in a reduced quality of life and increased economic and psychological burdens on the family (Schrag et al., 2000). It has been suggested that the various motor presentations, laterality and severity of symptoms in PD, age of disease onset, and disease duration are also characterized by different risks and severities of specific non-motor symptoms, such as cognitive deterioration and psychiatric disorders.

This study examined the relationship between cognitive dysfunction and the phenotypes, laterality and clinical findings of the disease in Turkish patients with PD.

2. Materials and methods

Fifty patients presenting the clinical diagnostic criteria for idiopathic PD were recruited from a movement disorders outpatient clinic. Their ages ranged from 40-80 years, and they were followed regularly. Demographic and clinical features were recorded. The patients with PD were divided into two groups according to their initial motor symptoms: tremor-predominant and hypokinetic-rigid forms. The presence of postural instability and gait dysfunction were recorded. Lateralization of motor symptom onset (left or right) was determined by the side on which the symptoms first occurred. Disease severity was measured using the Hoehn and Yahr (HY) scale (scores ranging from 1 to 5, with higher scores indicating greater disease severity) and the daily living activities of the patients were rated on the Schwab-England Activities of Daily Living scale (SE-ADL) (Hoehn and Yahr, 1967; Schwab and England, 1969). The PD patients underwent standardized clinic evaluations using the Unified Parkinson's Disease Rating Scale (UPDRS) parts I (mental dysfunction and mood), II (activities of daily living), III (motor section), IV-A (dyskinesia), B (motor fluctuations), and C (others), and total score (Fahn and Elton, 1987). Patients were encouraged to take their regularly scheduled PD medications during the study visit so that they would be evaluated in their on-state. Dopaminergic medication was recorded as the L-dopa equivalent daily dose (LEDD, mg/day) (Tomlinson et al, 2010). Patients were excluded to the study if they had a history of stroke, brain damage, psychiatric co-morbidity, such as moderate to severe depression equal to or greater than a score of 17 on the Beck Depression Inventory, presence of impulse control disorder behaviors, psychosis, recent delirium, alcohol or drug addiction, mental retardation, or brain surgery for PD or any other reason. Patients with severe visual or hearing impairment and less than a five years of education were also excluded.

The Turkish version of the Montreal Cognitive Assessment (MoCA-TR) was performed in all patients by the same neurologist, regardless of their motor or cognitive status. The MoCA-TR has been validated in PD in Turkey (Ozdilek and Kenangil, 2014). The MoCA is a 10-min test that briefly evaluates the following seven cognitive domains on one page: The visuospatial and executive functions, naming, attention, language, abstraction, delayed recall, and orientation. To correct for education effects found in the original study, an additional point was given to subjects with 12 or less years of education (Nasreddine et al., 2005). The scores of the MoCA-TR ranged from 0 to 30, with higher scores indicating better cognition and scores below 21 indicating cognitive impairment in the Turkish PD population (Ozdilek and Kenangil, 2014).

The study protocol was approved by the Institutional Review Board, and informed written consent was obtained from all subjects.

Statistical analyses

All statistical analyses were performed using the Number Cruncher Statistical System (NCSS) 2007 and Power Analysis and Sample Size (PASS) 2008 statistical software (NCSS, Kaysville, UT, USA). We compared the cognitively impaired and unimpaired groups in terms of demographic (e.g., age, education, etc.), clinical (e.g., age at PD onset, PD duration, etc.), and motor characteristics (e.g., UPDRS total and subscale scores), including the MoCA-TR scores. We used parametric statistics (independent sample t-test) to

Table 1. Demographic and clinical features of Parkinson's disease patients with (score < 21) and without (score ≥ 21) cognitive dysfunction evaluated by the MoCA-TR

Variables		MoCA-TR score < 21 (n=18) Mean ± S.D. (median)	MoCA-TR score ≥ 21 (n=32) Mean ± S.D. (median)	*P*-value
Age (years)		65.28±8.50 (66.50)	59.06±9.45 (59.00)	[a]0.030*
Education (years)		6.78±3.28 (5.00)	9.59±4.04 (9.00)	[a]0.010*
Disease duration (years)		6.39±3.65 (5.50)	5.56±3.88 (5.00)	[a]0.388
HY score		2.17±0.79 (2.00)	1.97±0.82 (2.00)	[a]0.409
LEDD (mg/day)		599.17±200.47 (600.00)	791.72±377.69 (800.00)	[a]0.099
UPDRS-I score		3.28±1.81 (3.00)	1.59±1.41 (1.00)	[a]0.001**
UPDRS-II score		11.39±8.06 (10.00)	7.06±3.83 (8.00)	[a]0.038*
UPDRS-III score		14.06±9.05 (12.50)	9.59±5.09 (9.50)	0.096
UPDRS-IV score		3.06±3.33 (2.00)	2.19±2.83 (1.00)	0.422
UPDRS total score		31.78±18.10 (28.00)	20.44±9.70 (17.00)	[a]0.012*
		n (%)	**n (%)**	
Gender	**Male**	10 (55.6)	24 (75.0)	[b]0.272
	Female	8 (44.4)	8 (25.0)	
Predominant motor subtype	**Tremor**	12 (66.7)	23 (71.9)	[b]0.949
	Bradykinesia	6 (33.3)	9 (28.1)	
Side of tremor (n=35)	**Left**	5 (41.7)	11 (47.8)	[b]1.000
	Right	7 (58.3)	12 (52.2)	
Side of bradykinesia (n=15)	**Left**	2 (33.3)	3 (33.3)	[c]1.000
	Right	4 (66.7)	6 (66.7)	
Presence of postural instability		7 (38.9)	10 (31.2)	[b]0.813
Subjective memory complaints		12 (66.7)	11 (34.4)	[b]0.049*

[a]Mann-Whitney U-test; [b]Yates' continuity correction test; [c]Fisher's exact test; *p<0.05; **p<0.01
MoCA-TR: Turkish version of the Montreal cognitive assessment; **SD:** Standard deviation; **HY:** Hoehn and Yahr scale; **LEDD:** L-dopa equivalent daily dose; **UPDRS:** Unified Parkinson's disease rating scale

compare groups for continuous variables when the data were distributed normally and nonparametric statistics (Mann-Whitney U-test) when the data followed a non-normative distribution. The chi-square test was used to compare categorical variables. In all analyses, $P<0.05$ was taken to indicate statistical significance.

3. Results

The cohort had mean age of 61.3±9.5 years, education period of 8.5±3.9 (range 5-17) years, PD duration of 5.8±3.7 (range 2-18) years, HY score of 2, total UPDRS score of 24.5±14.2, and LEDD of 722.4±336.0 mg/day. Males comprised 68% of the PD patients (34/50). The 50 study subjects included 35 patients with tremor-dominant (70%) and 15 with bradykinesia-dominant (30%) forms. Seventeen patients (34%) had gait and postural dysfunction. The patients were distributed equally in the first, second, and third stages of the HY scale. Eight patients had a family history. Twenty-three patients (46%) had subjective memory complaints.

The mean MoCA-TR score was 21.9±4.5 (range 13-30) in the PD patients. Of the PD patients, 36% (18/50) had cognitive dysfunction on the MoCA-TR scale. Table 1 illustrates the demographics and clinical characteristics of the patients with normal and abnormal MoCA-TR scores. The mean MoCA-TR scores did not differ between the tremor-dominant and hypokinetic-rigid forms (21.9±4.4 and 21.9±5.0, respectively, P=0.979). In addition, we could not find any relationship between the mean MoCA-TR score and the laterality of tremor, bradykinesia, or postural instability (P=0.345, P=0.451, and P=0.639, respectively). Cognitive dysfunction on the MoCA-TR scale was significantly correlated with age (r=0.309, P=0.029), education level (r=-0.366, P=0.009), presence of subjective memory complaints (r=0.331, P=0.028), and the UPDRS I (r=0.466, P=0.001) and II (r=0.296, P=0.037) subscores and total score (r=0.357, P=0.011).

4. Discussion

This study examined the influence of demographic and clinical findings, age at disease onset, lateralization, type of motor symptoms, and the current clinical status for cognition evaluated using the MoCA-TR scale in PD patients. Our findings argue against a straightforward association between cognition and the type and laterality of the disease.

A few studies have investigated the relationships among disease age of onset, presenting motor symptoms, laterality of symptoms, and cognitive dysfunction. Although some studies found that the patients with a later onset of disease had worse cognitive functioning, others did not (Huber et al., 1991; Muslimovic et al., 2005; Oh et al., 2009). Literature reports that not only the dopaminergic system but also the other neurotransmitters systems contribute the symptoms of PD. Although motor symptoms like tremor and bradykinesia is likely to derive from primarily dopaminergic deficits in the striatum, nonmotor symptoms like cognitive dysfunction has been described to be associated with impairment in basal forebrain cholinergic projections to the cerebral cortex (Pillon et al., 2001). It was reported that patients presenting with bradykinesia and rigidity were more likely to have greater cognitive dysfunction than those with tremor as the main symptom (Zetusky and Jankovic, 1985; Huber et al., 1989; Iwasaki et al., 1989; Portin et al., 1989; Williams et al., 2007; Oh et al., 2009; Baumann et al., 2014). Katzen et al. (2006) reported similar results, i.e., the tremor-dominant patients performed better on overall cognitive function tests, including language, visuospatial function, execution function, and memory ability, than did the patients whose main symptom was bradykinesia.

There are also conflicting reports on the association of laterality of motor symptoms with cognitive impairment. Patients whose motor signs began on the left side of the body consistently performed worse on the battery of cognitive measures than did those with right-side onset (Tomer et al., 1993; Baumann et al., 2014). However, several studies found no significant difference in cognition between right- and left-predominant PD patients (Huber et al., 1989; Finali et al., 1995; St Clair et al., 1998). In recent studies, Baumann et al. (2014) and Williams et al. (2007) found a strong relationship of cognition with laterality and type of PD signs. They reported the least amount of cognitive dysfunction in the right-sided tremor-dominant type. In this study, we did not find any correlation between cognition assessed using the MOCA-TR scale and either the clinical phenotype or laterality. The cognition was not influenced by either the type of disease or laterality. We think that this might have resulted from the small sample size of our cohort.

In addition, this study showed that the current clinical status, including disease duration, the HY score, the SE-ADL score, and the presence of gait impairment, did not correlate with cognitive performance or dysfunction, which suggests that the cognitive impairment of PD is an independent clinical feature, rather than a secondary complication of motor dysfunction. Other studies reported that gait impairment was another predictor of the cognitive decline in PD. Patients with gait impairment were more likely to have cognitive impairment and dementia (Alves et al., 2006; Burn et al., 2006; Camicioli et al., 2007; Oh et al., 2009). In our study, cognition assessed by using the MoCA-TR was found to be correlated only with age, education level, subjective memory complaints, and motor performance as evaluated using the UPDRS I and II subscales and total score. Previously, a relationship among older age, low education level and cognitive decline was reported, which was confirmed in our study. Interestingly, age and low education level seem to have a combined, rather than additive, effect on the risk of cognitive dysfunction. There is evidence that age, but not age at onset or duration of disease, is the key risk factor for dementia in PD (Levy et al., 2000 Levy et al., 2002). There was also a negative relationship between education and cognitive dysfunction on the MoCA-TR.

In conclusion, we believe that subjective memory complaints in PD patients should be evaluated carefully in outpatient interviews and that the relationships of cognition with the laterality and predominant type at disease onset need further evaluation in larger groups.

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