Neurology Asia 2021; 26(1) : 85 – 93

Evaluation of cognitive functions in idiopathic Parkinson's disease and multiple system atrophy

Melike Batum, Ayşın Kısabay Ak, Mehmet Semih Arı, Deniz Selçuki

Celal Bayar University Medical School, Hafsa Sultan Hospital, Department of Neurology, Manisa, Turkey.

Abstract

Background & Objective: Cognitive impairment is one of the non-motor symptoms impairing life quality in idiopathic Parkinson's disease (PD) and multiple system atrophy (MSA). In our study, both groups' possible cognitive impairments were evaluated and compared, and the relationship between cognitive profile and motor, non-motor scores, and disease duration was evaluated. *Methods:* Fifty two PD, 18 MSA, 30 healthy controls were included in the study. Demographic information, scores of Unified Parkinson's Disease Rating Scale (UPDRS), Parkinson's Disease Questionnaire (PDQ), Addenbrooke's Cognitive Examination-Revised (ACE-R), and Frontal Assessment Battery (FAB) tests were recorded. In addition to the ACE-R test's total scores, sub-scores measuring attention-orientation, memory, verbal fluency, language, and visual-spatial abilities were also evaluated. *Results:* There was no difference between the groups in age, gender, years of education, and levodopa dose in treatment ($p > 0.05$). In the inter-group comparison, FAB, ACE-R total, ACE-R sub-scores and PDQ values were significantly different ($p < 0.05$). Significant impairment was found in FAB, ACE-R total, memory, verbal fluency, speaking, and PDQ scores in PD and in all tests in MSA compared to the control group ($p < 0.05$). All tests except memory were more impaired in the MSA group than the PD group. The motor scores in PD showed a strong correlation with FAB, ACE-R total, visual-spatial abilities, speaking, and PDQ scores, whereas motor scores in MSA only correlated poorly with PDQ scores. *Conclusion:* MSA progressing with multi-systemic involvement showed worse cognitive performance than PD in executive functions and visual-spatial functions, regardless of the disease duration.

Keywords: Idiopathic Parkinson's disease, multiple system atrophy, cognition, quality of life

INTRODUCTION

Idiopathic Parkinson's Disease (PD) is characterized by bradykinesia, rigidity, resting tremor, and postural instability.[1] Apart from motor symptoms, non-motor symptoms, including cognitive impairment, occur frequently.[2] Cognitive impairment is generally seen in PD at a rate of approximately 40% during the disease process.[3,4] While only minimal cognitive impairment is detected in some of the PDs, it appears as severe dementia in others.

Multiple system atrophy (MSA) is a sporadic neurodegenerative disease characterized by cerebellar ataxia, parkinsonism, and autonomic failure.[5] In MSA, cognitive impairment measured by neuropsychological batteries and disrupting daily life activities were detected at a rate of 12%, while autopsy studies showed that this rate could reach up to 32%.[6,7]

When the neuropathology of the diseases is examined, PD and MSA have similar pathologies from the synucleinopathy group.[5] In PD, Lewy body pathology containing alpha-synuclein begins anatomically from the medulla oblongata (stage 1). As the disease progresses, it spreads to pons in stage 2, mesencephalon in stage 3, substantia nigra in stage 4, limbic areas in stage 4 and neocortical regions in stage 5 and 6.[8] MSA has a pathology consisting of widespread neuronal loss and atrophy, including striatonigral, olivopontocerebellar, autonomic and corticospinal pathways.[5,9]

Although more researches on cognitive disorders in PD are conducted[10–16], there are few studies on cognitive disorders in atypical parkinsonism syndromes.[17–24] Since cognitive impairment is a symptom that increases morbidity, impairs quality of life in both PD and atypical

Address correspondence to: Dr. Melike Batum, Celal Bayar University Medical School, Hafsa Sultan Hospital, Department of Neurology, Manisa, Turkey. E-mail: drmelikeyaman@hotmail.com

Date of Submission: 23 October 2020; Date of Acceptance: 16 January 2021

parkinsonism syndromes such as MSA, and is vital in early diagnosis and treatment, this issue has become particularly important for further studies.

Frontal Assessment Battery (FAB) is one of the tests used to evaluate frontal lobe functions (conceptualization, mental flexibility, programming, susceptibility to interference, inhibitory control, environmental autonomy). In contrast, Addenbrooke's Cognitive Examination-Revised (ACE-R) is used to evaluate executive functions and visual-spatial abilities (attention-orientation, memory, verbal fluency, language, visual-spatial abilities).

In this study, besides evaluating both disease groups' possible cognitive effects, a comparison was also made. Besides, the relationship between cognitive profile and motor and non-motor scores in both PD and MSA was evaluated.

METHODS

Fifty-two clinically probable or possible diagnosis of PD[25,26], 18 MSA[27] followed up in the Movement Disorders Outpatient Clinic of Celal Bayar University Department of Neurology and 30 healthy controls were included in our study between March 2019-March 2020. Those with Alzheimer's dementia, vascular dementia, normal pressure hydrocephalus, or secondary parkinsonism, those using drugs (such as anticholinergics, benzodiazepines) that could affect cognition, seizures, stroke, and head trauma were not included in the study. Besides, those who were found to have moderate and severe depression with the geriatric depression scale were excluded from the study. The control group was chosen from the relatives of the patients who were similar in age and gender. A written informed consent form was obtained from all the patients and the control group.

Demographic information of all patients, Unified Parkinson's Disease Rating Scale (UPDRS) scores (part III as motor score, and UPDRS part I as non-motor score), the Parkinson's Disease Questionnaire (PDQ) scale score that evaluates the quality of life, scores of Addenbrooke's Cognitive Examination-Revised (ACE-R) and Frontal Assessment Battery (FAB) tests used to evaluate cognitive functions were recorded. Sub-scores of the ACE-R test, measuring both total and attention-orientation, memory, verbal fluency, speaking, and visual and spatial abilities, were also assessed.

Addenbrooke's Cognitive Examination-Revised (ACE-R)

The ACE-R, which evaluates frontal executive functions and visual-spatial abilities with a total score of 100 points, consists of 26 items in five sub-sections: attention-orientation, memory, verbal fluency, language, and visual-spatial abilities. Test scores of 86 and below was considered indicative for cognitive impairment. The validity and reliability study for its use in PD was conducted by Reyes *et al*. in 2009. As a result of this study, it was found that the sensitivity in diagnosis of dementia was 92%, and the selectivity was 90% when the cut-off value of 83 was taken.[28] Its validity and reliability study in Turkey was performed by Mıhçı *et al*. in 2011.[29]

Frontal Assessment Battery (FAB)

Frontal assessment battery (FAB) is a simple, easy-to-apply, short (approximately 10 minutes) bedside test developed to measure frontal lobe functions.[30] FAB has six items, and each item has 0-3 points. A higher score means better performance. FAB consists of six subtests, such as similarities (conceptualization), word fluency (mental flexibility), motor series (programming), conflicting instructions (susceptibility to interference), do-not-do (inhibitory control), capture behavior (environmental autonomy). Its validity and reliability study in Turkey was performed by Yener *et al*. in 2008 and showed high reliability (for internal consistency α=0.72) and high validity results (Spearman's Rho=0.72).[31]

Parkinson Disease Questionnaire (PDQ)

The Parkinson's Disease Questionnaire (PDQ-39) scale is a quality of life scale developed by Peto *et al*. in 1995, translated into many languages and validated in different languages.[32] It contains 39 items in eight different areas consisting of mobility, daily living activities, emotional state, stigma, social support, cognition, communication, and physical discomfort. The scale evaluates the effect of Parkinson's disease on quality of life in the last month. Each question is scored between 0 and 4 (0: never, 1: rarely, 2: sometimes, 3: mostly, 4: always). A high score in total indicates a deterioration in the quality of life. A validity and reliability study in our country was conducted by Kayapınar *et al*. in 2018 and showed high reliability score after existing thirteenth question (α=0.78). Also the test had high validity index (α=0.95).[33]

Statistical analysis

We used the IBM SPSS version 23 statistics program (SPSS, Chicago, IL, USA) to evaluate the data analysis. The mean, standard deviation, median, minimum and maximum values of variables were presented, and normality of distribution was evaluated using the Kolmogorov–Smirnov test. Paired comparisons of independent groups were performed using Mann-Whitney U and multiple comparisons with Kruskal-Wallis test methods. Crosstables were prepared in categorical variables, and distribution differences of groups were tested by the Chi-Square method. The relationship between disease duration, UPDRS part III as motor score, and UPDRS part I as non-motor score, and the results of cognitive tests and quality of life test was evaluated with the Pearson Correlation test. In all statistical comparison tests, the first type of error margin was determined as α: 0.05, and two-tailed was tested. If the "p" value was less than 0.05, the difference between the groups was considered statistically significant.

RESULTS

Seventy patients (52 PD, 18 MSA) and 30 healthy controls were included in the study. Demographic characteristics are summarized in Table 1. No significant difference was observed between the groups (PD, MSA, control) when looking at age, gender, and education duration (p=0.104, p=0.177, p=0.189, respectively).

Total UPDRS score, motor score (UPDRS-III score), non-motor score (UPDRS-I score), and levodopa equivalent dose (LEDD) of the PD and MSA patient groups were calculated and recorded. Motor scores were significantly higher in the MSA group than the two groups (PD, MSA), but when the UPDRS total score, non-motor scores, and LEDD were compared, no significant difference was observed between the two groups. The duration of the disease was found to be significantly higher in the PD group (Table 1).

In comparison between groups (PD, MSA, and control groups), FAB, ACE-R total, and ACE-R sub-scores and PDQ values were found to be significantly different (Table 2).

The values obtained by comparing the cognitive tests of the patient-control groups (PD -control, MSA-control) and patient groups (PD-MSA) in paired groups are given in Table 3.

In our study, the correlation was evaluated

Table 1: Demographic and clinical characteristics of PD, MSA patient groups and control subjects

	PD (n=52)	MSA (n=18)	Control (n=30)	p value
Age (years)	65.10±9.81 (30-80)	63.78±8.30 (50-78)	61.80±5.74 (51-70)	0.104
Gender				
Female	15	8	16	0.177
Male	35	10	14	
Education duration (years)				
≤ 5 years	31	9	13	0.189
>5 years	19	9	17	
UPDRS Total	52.87±32 (12-144)	62.78±19.30 (33-100)		0.076
Motor score	36.33±24.64 (7-93)	50.06±16.47 (26-79)		**0.010**
Non-motor score	16.54±11.58 (2-51)	12.72±5.50 (6-27)		0.439
LEDD	583.69±267.95 (100-1225)	657.82±354.78 (200-1164)		0.433
Disease duration (months)	77±56 (6-240)	28±16 (3-72)		**<0.001**

PD Idiopathic Parkinson's disease, MSA: Multiple system atrophy, UPDRS: Unified Parkinson's Disease Rating Scale, LEDD: levodopa equivalent dose

Table 2: Comparison of cognitive battery and quality of life values between groups (PD, MSA, and control groups)

	PD (n=52)	MSA(n=18)	Control (n=30)	p value
FAB	10.52±3.62(4-18)	7.67±1.19(6-10)	12.27±1.60(10-16)	**<0.001**
ACE-R Total	59.23±14.25(25-86)	46.78±10.03(25-64)	68.80±3.71(62-75)	**<0.001**
Attention-orientation	15.46±2.53(7-20)	13.50±3.24(7-19)	16.03±1.33(14-18)	**0.021**
Memory	10.08±3.98(3-19)	7.94±1.80(4-11)	11.20±1.32(9-14)	**<0.001**
Verbal fluency	6.63±3.32(2-18)	4±2.09(2-9)	9.60±1.59(7-14)	**<0.001**
Language	16.02±4.66(7-25)	12.50±3.22(6-18)	18.93±1.83(16-22)	**<0.001**
Visual and spatial ability	11.35±3.56(3-16)	9.44±3.35(3-14)	13.03±1.99(9-16)	**0.002**
PDQ	60.21±27.24(5-114)	83.56±16.30(50-110)	32.60±7.11(21-51)	**<0.001**

PD: Idiopathic Parkinson's disease, MSA: Multiple system atrophy, FAB: Frontal Assessment Battery, ACE-R Addenbrooke's Cognitive Examination-Revised, PDQ: Parkinson Disease Questionnaire. For ACE-R and FAB tests a higher score means better performance. For PDQ a high score in total indicates a deterioration in the quality of life.

Table 3: Paired group comparison-cognitive battery and quality of life (PDQ) scale values of the PD, MSA and control group

	Compared Groups Disease/Test score				p-value
FAB	**PD**	10.52±3.62(4-18)	**Control**	12.27±1.60(10-16)	**0.008**
	MSA	7.67±1.19(6-10)	**Control**	12.27±1.60(10-16)	**<0.001**
	PD	10.52±3.62(4-18)	**MSA**	7.67±1.19(6-10)	**0.002**
ACE-R TOP	**PD**	59.23±14.25(25-86)	**Control**	68.80±3.71(62-75)	**<0.001**
	MSA	46.78±10.03(25-64)	**Control**	68.80±3.71(62-75)	**<0.001**
	PD	59.23±14.25(25-86)	**MSA**	46.78±10.03(25-64)	**0.001**
Attention-orientation	**PD**	15.46±2.53(7-20)	**Control**	16.03±1.33(14-18)	0.482
	MSA	13.50±3.24(7-19)	**Control**	16.03±1.33(14-18)	**<0.001**
	PD	15.46±2.53(7-20)	**MSA**	13.50±3.24(7-19)	**0.024**
Memory	**PD**	10.08±3.98(3-19)	**Control**	11.20±1.32(9-14)	**0.006**
	MSA	7.94±1.80(4-11)	**Control**	11.20±1.32(9-14)	**<0.001**
	PD	10.08±3.98(3-19)	**MSA**	7.94±1.80(4-11)	0.072
Verbal fluency	**PD**	6.63±3.32(2-18)	**Control**	9.60±1.59(7-14)	**<0.001**
	MSA	4±2.09(2-9)	**Control**	9.60±1.59(7-14)	**<0.001**
	PD	6.63±3.32(2-18)	**MSA**	4±2.09(2-9)	**0.001**
Language	**PD**	16.02±4.66(7-25)	**Control**	18.93±1.83(16-22)	**0.001**
	MSA	12.50±3.22(6-18)	**Control**	18.93±1.83(16-22)	**<0.001**
	PD	16.02±4.66(7-25)	**MSA**	12.50±3.22(6-18)	**0.008**
Visual and spatial ability	**PD**	11.35±3.56(3-16)	**Control**	13.03±1.99(9-16)	0.064
	MSA	9.44±3.35(3-14)	**Control**	13.03±1.99(9-16)	**<0.001**
	PD	11.35±3.56(3-16)	**MSA**	9.44±3.35(3-14)	**0.032**
PDQ	**PD**	60.21±27.24(5-114)	**Control**	32.60±7.11(21-51)	**<0.001**
	MSA	83.56±16.30(50-110)	**Control**	32.60±7.11(21-51)	**<0.001**
	PD	60.21±27.24(5-114)	**MSA**	83.56±16.30(50-110)	**0.001**

PD: Idiopathic Parkinson's disease, MSA: Multiple system atrophy, FAB: Frontal Assessment Battery, ACE-R Addenbrooke's Cognitive Examination-Revised, PDQ: Parkinson Disease Questionnaire. For ACE-R and FAB tests a higher score means better performance. For PDQ a high score in total indicates a deterioration in the quality of life.

between disease duration, UPDRS motor and non-motor scores, cognitive tests, and quality of life for each disease group (Table 4).

A weak correlation was found between disease duration and PDQ score in the PD group.

A strong correlation was found between motor and FAB scores, ACE-R total and visual and spatial abilities, speaking scores, and PDQ scores, which are subgroups of ACE-R, and weak correlation with the attention-orientation score.

In the non-motor score, the FAB, ACE-R total showed a strong correlation with memory, speaking scores, and PDQ scores from the subgroup of ACE-R, and weak correlation with visual and spatial ability score (Table 4).

In the MSA group, while the disease duration and motor score were weakly correlated with the PDQ score, the non-motor score was not correlated with any test (Table 4).

DISCUSSION

Although not included in the diagnostic criteria in PD and MSA, cognitive impairment, one of the non-motor findings, is a critical finding that impairs the quality of life.[1,2] In studies conducted in both groups, defects in frontal lobe functions responsible for functions such as attention, executive function, memory, and speaking, draw attention.[4,17,34–38] In addition to the early diagnosis of these disorders and their treatment regulation, it is also important to know similar and different cognitive features in both diseases.

Based on this theory, the affected cognitive areas were evaluated by comparing the PD and MSA groups in this study. Besides, the effect of cognitive tests on the duration of disease, correlation with motor and non-motor signs, and quality of life was also investigated.

When looking at neurotransmitters' functions in general, the dopaminergic system is held responsible for executive functions, cholinergic for memory impairment, adrenergic for sustained attention, and serotoninergic system for maintenance of mood.[39] However, the anatomical region where the neurotransmitter is deficient also leads to clinical cognitive differences and effects. For example, while dopamine deficiency in the putamen impairs motor functions, deficiency in the caudate nucleus can affect cognitive abilities.[40]

Dopamine efficiency in subcortical structures and acetylcholine deficiency in cortical structures are mainly responsible for cognitive impairment in PD. Dopaminergic deficiency causes deterioration in executive functions by disrupting the normal function of striatofrontal connections.[15]

Table 4: Correlations between motor, non-motor scores, and disease duration with cognitive tests and quality of life testing in patients with PD and MSA

PD		**FAB**	**ACE-R total**	**Attention-orientation**	**Memory**	**Verbal fluency**	**Language**	**Visual and spatial abilities**	**PDQ**
Duration of disease	*R*	-.246	-.128	-.025	-.059	-.098	-.134	-.174	.267
	p	.079	.367	.863	.679	.488	.344	.217	.055
Motor score	*R*	-.534**	-.417**	-.309*	-.231	-.075	-487**	-.361**	.700**
	p	.000	.002	.026	.099	.596	.000	.009	.000
Non-motor score	*R*	-.474**	-.418**	-.234	-.372**	-.249	-.359**	-.324*	.526**
	p	.000	.002	.095	.007	.075	.009	.019	.000
MSA		**FAB**	**ACE-R total**	**Attention-orientation**	**Memory**	**Verbal fluency**	**Language**	**Visual and spatial abilities**	**PDQ**
Duration of disease	*R*	.219	-.039	.119	-.202	.343	-.093	.398	.531*
	p	.383	.878	.639	.421	.164	.715	.102	.023
Motor score	*R*	-.297	-.279	-.115	-.030	-.082	-.465	.152	.543*
	p	.232	.263	.649	.907	.746	.052	.547	.020
Non-motor score	*R*	.075	-.053	.074	.100	-.303	-.101	.164	-.174
	p	.767	.833	.769	.694	.222	.689	.516	.491

PD: Idiopathic Parkinson's disease, MSA: Multiple system atrophy, FAB: Frontal Assessment Battery, ACE-R Addenbrooke's Cognitive Examination-Revised, PDQ: Parkinson Disease Questionnaire

In PD, there are limitations in executive functions, which are manifested by impairment in category creation, automatic response generation, planning, decision-making, and goal-oriented behavior managed by the prefrontal cortex.[4]

Speaking problems such as decreased verbal fluency and difficulty in producing syntactically complex words due to bradiphrenia are also part of the cognitive impairment in PD. Also, impairment in memory and visual-spatial functions is among other impaired cognitive disorders in PD.[34]

In our study, similar to the studies of Litvan and Hely[4,34], when comparing the PD patient group with the control group, a significant decrease was found in the FAB test score evaluating the frontal lobe functions and the scores of the memory, language, and verbal fluency categories, which are the subgroups of the ACE-R test. In association with these results, it was observed that executive dysfunction in the PD patient group complied with impaired memory, language, and verbal fluency.

In our study, in addition to the cognitive evaluation of the PD-control group, cognitive evaluation of the MSA-control group, in which a small number of studies were performed, was also performed.

Deterioration of attention and executive functions in the MSA patient group causes the striato-pallido-thalamocortical circuits to be affected and dopamine levels to decrease due to the decrease in frontostriatal processing speed. Impairment of non-executive functions such as memory, speaking, and visual-spatial abilities develop secondary to cortical-subcortical changes.[41,42]

Studies have shown that the MSA patient group is significantly affected in terms of memory, attention-orientation, visual-spatial abilities, and speaking.[16,32–35,40]

Our study found that the scores obtained from all of the FAB, ACE-R total, and ACE-R subcategories were significantly lower in the MSA group compared to the control group. The results revealed that almost all cognitive areas were affected, including frontal executive functions, memory, attention-orientation, speaking, verbal fluency, and visual-spatial ability performances. It is thought that the limitation in the motor functions of speaking may be related to the effects on the language and verbal fluency areas in MSA.[44]

Another issue where few studies have been conducted is comparing cognition between Parkinson plus syndromes (PPS) and PD. In this limited area in our study, a comparison was made in terms of cognition between MSA and PD, which is a subgroup of PPS.

In the PRIAMO study, it was shown that the *Mini-Mental State Examination* (MMSE) and FAB scores were lower in the patient group in which all of the PPS subgroups were evaluated compared to the PD group.[45] In another study, patients in the MSA group had worse scores in general cognitive evaluation than the PD group, especially in frontal function tests.[20] A study by Santangelo *et al*. revealed that MSA patients showed a similar cognitive performance to that of PD patients.[46]

In our study, when the PD and MSA groups were compared, the FAB and ACE-R tests' total scores were found to be significantly lower in the MSA group. When localization was performed with the tests we performed, it was observed that attention-orientation, verbal fluency, speaking, and visual and spatial abilities were among the most prominently affected areas in MSA.

In our study, when memory functions were evaluated separately, it was seen that there was a significant influence in both the PD and MSA groups compared to the controls. When the two disease groups were compared, it was found that the memory scores in the MSA group were lower, although not at a statistically significant level.

There is no study in the literature evaluating the association of motor scores with cognitive functions in MSA. In our study, the cognitive functions of patients diagnosed with early MSA were examined, and the relationship between UPDRS motor scores and cognitive functions was evaluated. Similar to the PD group, in the comparison of MSA and the control group, it was observed that all cognitive parameters were affected in different degrees because bradykinesia caused bradiphrenia. In our study, it was thought that bradykinesia-motor score was higher in the MSA group than in the PD group, and bradiphrenia may also be higher, and in this case, it may affect all cognitive functions. Considering the correlation between motor scale and cognitive tests in our study, it was seen that the most affected were in language functions, although it was not statistically significant. It was also thought that there might be impairment in verbal fluency functions due to attention and bradykinesia due to bradyphrenia. Impairment in the specified cognitive functions was determined by evaluating the FAB and ACE-R attention-orientation, verbal fluency, and language subgroups.

We think that cognitive dysfunction is more pronounced in MSA compared to PD due to the lack of dopamine, as well as multi-systemic

involvement affecting multiple neurotransmitters and frontal-subcortical disconnection in the foreground, similar to PD. Also, severe disability and bradykinesia due to high UPDRS motor scores may have affected the MSA patient group's test performance.

The reason why cognitive impairment is seen less in MSA compared to PD in clinical experience is that the disease is less evaluated in this respect. In studies, cognitive impairment in MSA is clinically defined at the rate of between 15-30%[17,47] and pathologically 14% in the first five years.[48] These studies suggest that cognitive impairment is a part of the disease in MSA, although it is not among the disease's diagnostic criteria. Unlike dementia in PD, where provisional criteria have been published[15], we have no equivalent for diagnosing dementia in either MSA.

Data on the relationship between disease duration and cognitive functions is not sufficient. In a study conducted with PD and MSA groups, patients were followed for an average of 15 months, and it was shown that executive, speaking, and visual-spatial abilities were not affected longitudinally.[44]

In our study, the disease's duration was found to be different from each other, with an average of 77 months in the PD group and 28 months in the MSA group. Since MSA has the characteristics of a disease with a higher neurodegeneration rate than PD, patients enrolled in the MSA group to complete cognition tests are the patients in an earlier period. When both disease groups were evaluated within their groups, no relationship was found between cognitive tests and disease duration.

As a result, frontal lobe functions and executive functions were impaired in memory, speaking and verbal fluency in PD compared to the control group, while in MSA, compared to the control group, impairments were found in frontal lobe functions and executive functions of memory, attention-orientation, language, verbal fluency, and visual and spatial ability performances. When the PD and MSA groups were compared, it was noted that especially attention-orientation, verbal fluency, speaking, and visual and spatial abilities were the most prominently affected areas in MSA compared to PD. MSA progressing with multi-systemic involvement showed worse cognitive performance than PD in both executive functions and visual-spatial functions, regardless of the disease duration. This study is the first study in Turkey to evaluate the cognition of PD and MSA patient groups and investigate their relationship with motor and non-motor UPDRS scores and disease duration.

The limitations of this study are the small number of cases and its cross-sectional planning. Prospectively designed studies consisting of larger case numbers may contribute more to determining the difference in cognitive functions.

DISCLOSURE

Ethical approval: All procedures performed in the studies involving human participants were in accordance with the ethical standards of the Celal Bayar University Medical Faculty Etic Committee (Approval Date: 14/11/2018 Approval Number: 20.478.486) and with Helsinki declaration (1964) and its later amendments or comparable ethical standards.

Financial support: None

Conflict of interest: None

REFERENCES

1. Poewe W, Seppi K, Tanner CM, *et al*. Parkinson disease. *Nat Rev Dis Prim* 2017;3(1):17013.
2. Lim SY, Tan AH, Fox SH, Evans AH, Low SC. Integrating patient concerns into Parkinson's disease management. *Curr Neurol Neurosci Rep* 2017;17(1):3.
3. Aarsland D, Andersen K, Larsen JP, Lolk A. Prevalence and Characteristics of Dementia in Parkinson Disease. *Arch Neurol* 2003;60(3):387.
4. Litvan I, Goldman JG, Tröster AI, *et al*. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord* 2012;27(3):349-56.
5. Greene P. Progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy. *Contin Lifelong Learn Neurol* 2019;25(4):919-35.
6. Fiorenzato E, Weis L, Seppi K, *et al*. Brain structural profile of multiple system atrophy patients with cognitive impairment. *J Neural Transm* 2017;124(3):293-302.
7. Koga S, Parks A, Uitti RJ, *et al*. Profile of cognitive impairment and underlying pathology in multiple system atrophy. *Mov Disord*.2017;32(3):405-13.
8. Gispert S. Transgenic mice expressing mutant A53T human alpha-synuclein show neuronal dysfunction in the absence of aggregate formation. *Mol Cell Neurosci* 2003;24(2):419-29.
9. Ahmed Z, Asi YT, Sailer A, *et al*. The neuropathology, pathophysiology and genetics of multiple system atrophy. *Neuropathol Appl Neurobiol* 2012;38(1):4-24.
10. Aarsland D, Bronnick K, Williams-Gray C, *et al*. Mild cognitive impairment in Parkinson disease: A multicenter pooled analysis. *Neurology* 2010;75(12):1062-9.

11. Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *Lancet Neurol* 2010;9(12):1200-13.
12. Silbert LC, Kaye J. Neuroimaging and cognition in Parkinson's disease dementia. *Brain Pathol* 2010;20(3):646-53.
13. Aarsland D, Kvaløy JT, Andersen K, *et al*. The effect of age of onset of PD on risk of dementia. *J Neurol* 2007;254(1):38-45.
14. Goldman JG, Litvan I. Mild cognitive impairment in Parkinson's disease. *Minerva Med* 2011;102(6):441-59.
15. Emre M, Aarsland D, Brown R, *et al*. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord* 2007;22(12):1689-707.
16. Riedel O, Klotsche J, Spottke A, *et al*. Cognitive impairment in 873 patients with idiopathic Parkinson's disease. *J Neurol* 2008;255(2):255-64.
17. Brown RG, Lacomblez L, Landwehrmeyer BG, *et al*. Cognitive impairment in patients with multiple system atrophy and progressive supranuclear palsy. *Brain* 2010;133(8):2382-93.
18. Leiguarda R. Apraxia in Parkinson's disease, progressive supranuclear palsy, multiple system atrophy and neuroleptic-induced parkinsonism. *Brain* 1997;120(1):75-90.
19. Pillon B, Gouider-Khouja N, Deweer B, *et al*. Neuropsychological pattern of striatonigral degeneration: comparison with Parkinson's disease and progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry* 1995;58(2):174-9.
20. Kishore A, Krishnan S, Mathuranath P, Sarma S. Neuropsychological functions in progressive supranuclear palsy, multiple system atrophy and Parkinson's disease. *Neurol India* 2006;54(3):268.
21. Lange KW, Tucha O, Alders GL, *et al*. Differentiation of parkinsonian syndromes according to differences in executive functions. *J Neural Transm* 2003;110(9):983-95.
22. Monza D, Soliveri P, Radice D, *et al*. Cognitive dysfunction and impaired organization of complex motility in degenerative parkinsonian syndromes. *Arch Neurol* 1998;55(3):372.
23. Robbins TW, James M, Owen AM, *et al*. Cognitive deficits in progressive supranuclear palsy, Parkinson's disease, and multiple system atrophy in tests sensitive to frontal lobe dysfunction. *J Neurol Neurosurg Psychiatry* 1994;57(1):79-88.
24. Aarsland D, Litvan I, Larsen JP. Neuropsychiatric symptoms of patients with progressive supranuclear palsy and Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 2001;13(1):42-9.
25. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988;51(6):745-52.
26. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson ' s disease : a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55(3):181-4.
27. Gilman S, Wenning GK, Low PA, *et al*. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* 2008;71(9):670-6.
28. Reyes MA, Lloret SP, Gerscovich ER, Martin ME, Leiguarda R, Merello M. Addenbrooke's Cognitive Examination validation in Parkinson's disease. *Eur J Neurol* 2009;16(1):142-7.
29. Mihci E, Gurvit H, Bilgic B, *et al*. P1-158: Validation of the Turkish version of the Addenbrooke's cognitive examination in Turkey. *Alzheimer's Dement* 2011;7:S162-S162.
30. Uytdenhoef P, Depauw Y, Cambier J, Blum S, Jacquy J. Potentiels évoqués cognitifs dans le diagnostic de la démence sénile et de la démence de la maladie de Parkinson: intérêt de l'analyse multivariée. *Neurophysiol Clin Neurophysiol* 1991;21(5-6):439-47.
31. Gorsev Y. Validation and reliability of the Frontal Assessment Battery (FAB) in Turkish. *Front Hum Neurosci* 2008;2.
32. Peto V, Jenkinson C, Fitzpatrick R. PDQ-39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. *J Neurol* 1998;245(S1):S10-S14.
33. Kayapinar T. Parkinson hastaligi yasam kalitesi anketi. Published online 2018.
34. Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL. The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years. *Mov Disord* 2008;23(6):837-44.
35. Kao AW, Racine CA, Quitania LC, Kramer JH, Christine CW, Miller BL. Cognitive and Neuropsychiatric Profile of the Synucleinopathies. *Alzheimer Dis Assoc Disord* 2009;23(4):365-70.
36. Siri C, Duerr S, Canesi M, *et al*. A cross-sectional multicenter study of cognitive and behavioural features in multiple system atrophy patients of the parkinsonian and cerebellar type. *J Neural Transm*. 2013;120(4):613-8.
37. Kawai Y, Suenaga M, Takeda A, *et al*. Cognitive impairments in multiple system atrophy: MSA-C vs MSA-P. *Neurology*. 2008;70(Issue 16, Part 2):1390-6.
38. Auzou N, Dujardin K, Biundo R, *et al*. Diagnosing dementia in multiple system atrophy by applying Movement Disorder Society diagnostic criteria for Parkinson's disease dementia. *Parkinsonism Relat Disord* 2015;21(10):1273-7.
39. Calabresi P, Picconi B, Parnetti L, Di Filippo M. A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine–acetylcholine synaptic balance. *Lancet Neurol* 2006;5(11):974-83.
40. Zgaljardic DJ, Borod JC, Foldi NS, Mattis P. A review of the cognitive and behavioral sequelae of Parkinson's disease: Relationship to frontostriatal circuitry. *Cogn Behav Neurol* 2003;16(4):193-210.
41. Prakash KG, Bannur BM, Chavan MD, Saniya K, Kumar SS, Rajagopalan A. Neuroanatomical changes in Parkinson's disease in relation to cognition: An update. *J Adv Pharm Technol Res* 2016;7(4):123-6.
42. Fiorenzato E, Antonini A, Wenning G, Biundo R. Cognitive impairment in multiple system atrophy. *Mov Disord*. 2017;32(9):1338-9.

43. Stankovic I, Krismer F, Jesic A, *et al*. Cognitive impairment in multiple system atrophy: A position statement by the neuropsychology task force of the MDS multiple system atrophy (MODIMSA) study group. *Mov Disord* 2014;29(7):857-67.
44. Fiorenzato E, Antonini A, Camparini V, Weis L, Semenza C, Biundo R. Characteristics and progression of cognitive deficits in progressive supranuclear palsy vs. multiple system atrophy and Parkinson's disease. *J Neural Transm* 2019;126(11):1437-45.
45. Colosimo C, Morgante L, Antonini A, *et al*. Non-motor symptoms in atypical and secondary parkinsonism: the PRIAMO study. *J Neurol* 2010;257(1):5-14.
46. Santangelo G, Cuoco S, Pellecchia MT, Erro R, Barone P, Picillo M. Comparative cognitive and neuropsychiatric profiles between Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. *J Neurol*. 2018;265(11):2602-13.
47. Wenning GK. What clinical features are most useful to distinguish definite multiple system atrophy from Parkinson's disease? *J Neurol Neurosurg Psychiatry* 2000;68(4):434-40.
48. O'Sullivan SS, Massey LA, Williams DR, *et al*. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. *Brain* 2008;131(5):1362-72.