

Depression as a Prodromal Marker and Dementia as a Terminal Symptom in Parkinson's Disease

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Introduction: In our study, we aimed to examine the relationship between depression and dementia, which are the most common prodromal and terminal symptoms in Parkinson's disease.

Materials and Methods: Patients with Parkinson's disease who presented to the Neurology outpatient clinic were evaluated on selected from October 2020 and February 2021. A total of 87 patients with Hoehn and Yahr stage 1-4 were included in the study. Of the Parkinson's patients, 37 were female and 50 were male. Hamilton Depression Rating Scale for depression and Mini-Mental Test score was used for dementia.

Results: The duration of the disease did not make a significant difference between the sexes in depression and dementia. In contrast to dementia in the descriptive statistics according to the H-Y stage, depression is observed at all stages of Hoehn and Yahr. In Parkinson's disease, dementia is more common in advanced-stage patients, which is associated with the course of the disease. According to the HAM-D scale, the mean depression values were 21 in male patients and 19 in female patients. Mean dementia in men and women was 22 according to the MMSE scale.

Conclusion: Depression and dementia are important determinants of the poor health-related quality of life in Parkinson's disease. Patients should be provided with the best treatment via a multidisciplinary team.

Keywords: Parkinson disease, depression, dementia

Introduction

Idiopathic Parkinson's disease (PD) is the second most common neurodegenerative geriatrics disease after Alzheimer's disease (AD) and affects more than 1% of the elderly population in the world. The causative factors, symptoms, and signs of the disease are different in geriatric PD. Multiple pathology and polypharmacy are

common in this age group. It is a different age group in terms of psychological, cognitive, socioeconomic, familial, and community health. PD is a progressive neurodegenerative disease manifested by bradykinesia, resting tremor, rigidity, and postural disorder. Degeneration of the neurons in the substantia nigra and the

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presence of Lewy bodies in their cytoplasm, as well as dopaminergic loss, constitute the classical pathology of the disease. There is evidence that alpha-synuclein pathology can spread along the neuronal pathways. This supports that PD is a multiorgan proteinopathy. Motor symptoms are explained by pathology of the dopaminergic system. However, both dopaminergic and non-dopaminergic neurotransmitters are believed to be involved in non-motor symptoms (NMS) (1-3).

It is an important need that has not been met so far. Neuroimaging studies can provide targets for new treatments for early motor involvement and NMS. Some different and new results in the genetic spectrum of PD may contribute to the treatment. Indeed, NMS predominate the clinical presentation of advanced Parkinson's disease. They can cause serious discomfort, disability, and impaired quality of life. NMS is usually poorly recognized and is inadequately treated. NMS may occur in the early and late stages of PD. For example, as in the case of depression, these symptoms can be potentially useful biomarkers for the disease (4-6).

The prevalence of significant depression in patients with PD is considered to be 35%. Depression begins at an early age and nascent stage of PD. It affects the quality of life of the patient and is often permanent. In patients with PD, changes occur in dopaminergic, noradrenergic, and serotonergic systems. Primary degeneration of dopaminergic mesocortical and mesolimbic neurons was observed in PD patients with depression. Noradrenaline metabolite 3-methoxy-4-hydro phenyl glycol levels in the cerebrospinal fluids (CSF) are decreased. In the autopsy study, 5-hydroxy tryptamine increased, indicating serotonergic

neuronal cell loss in the dorsal raphe nucleus. In another study, both cortisol and IL-6 levels were lower in the CSF of patients with PD and major depression (3,7,8).

In PD, the prevalence of dementia was reported to be quite variable. The average prevalence is estimated to be 30%. Dementia can reduce survival in PD patients since its prevalence increases with age. The pathology underlying dementia in PD is still controversial. Many clinicopathological studies suggest that three types of pathology can cause dementia in PD: Lewy-body degeneration in cortical and limbic structures, random AD type pathology in cortical and limbic structures, and pathology in subcortical structures. All these pathologies can cause cognitive impairment in PD (9-11).

We aimed to examine depression, which, we may say, is the most common prodromal marker in PD and dementia, which is a terminal symptom. We wanted to draw attention to the relationship of depression and dementia with age, sex, duration of disease, and stages of the disease as well as the degrees of these parameters.

Materials and Methods

The data of this study were collected from consecutive Parkinson's patients who presented to the neurology outpatient clinic of the University. Patients with PD were evaluated on selected days from October 2020 and February 2021. In total, 87 patients between the ages of 29 and 88 were included in the study. Of the Parkinson's patients, 37 were female and 50 were male. The patients were evaluated according to the Hoehn and Yahr (HY) scale used for PD. Patients from stages 1-4 on the HY scale were accepted. Neurological examination of the patients was conducted by experienced neurologists. All the patients were receiving

dopaminergic treatment. The majority of our patients consisted of patients with akinetic-rigid PD and, predominantly, bradykinesia. Almost all the patients were using dopamine agonists and levodopa. The study was conducted prospectively.

Motor and non-motor symptoms and medical histories of the patients were investigated. Mini-Mental Test (MMSE), which can be easily and quickly performed in a clinical setting as a simple and universal scale was performed. The relationship of the stages of the dementia process in Parkinson's disease and the HY scale in Parkinson's disease with MMSE was investigated. Hamilton Depression Rating Scale (HAM-D) was used for depression. The MMSE cut-off score of 25 or less is recommended, according to movement disorders Association. We have To determine dementia, we accepted the value of 25 as the cut-off point according to the MMSE. According to the HAM-D scale for depression, a score greater than 23 was evaluated as very severe, 19–22 severe, 14–18 moderate, 8–13 mild, and less than 7 as normal. The relationship of the use of levodopa and dopamine agonists with depression and dementia was investigated.

Standard protocol approvals, records, and consents were obtained from all participants. The present study was approved by the ethics committee of the University Training and Research Hospital (with the decision dated 2020/07-19). Questions of the survey were asked to the patients by neurologists via face-to-face interview. Spouses of the patients were asked to assist where necessary.

Patients suffering from Alzheimer's dementia and those with a history of stroke, head trauma, drug-induced parkinsonism, vascular parkinsonism, atrophy, progressive supranuclear

palsy, or atypical forms of parkinsonism such as corticobasal degeneration, were excluded.

Statistical Analysis

In the study, an independent t-test was used to compare the sexes in terms of HAM-D, MMSE, and Disease Duration parameters. Pearson's correlation was applied to determine the relationship between the parameters. In addition, a one-way analysis of variance was used to compare disease duration, age, HAM-D, and MMSE parameters in terms of HY. Duncan's multiple comparison was performed to determine the stages found to be important as a result of variance analysis. The necessary statistical analyses were performed using SPSS statistical software package.

Results

In the study, it was found that disease duration did not make a significant difference between the sexes in depression. The difference between the sexes in terms of the HAM-D parameter was found to be insignificant ($p > 0.05$). In addition, it was observed that the duration of the disease did not make any difference between genders in dementia. As a result of the independent t-test, the difference between the genders in terms of MMSE and disease duration was found to be insignificant ($p > 0.05$). However, the average HAM-D value was higher in male patients. The mean depression was 21 in male patients and 19 in female patients. The mean dementia was found to be 22 in men and women. Descriptive statistics of HAM-D, MMSE, and disease duration parameters by sex are given in Table 1 and the Pearson's correlation matrix for all patients in Table 2.

In the descriptive statistics of the HAM-D parameter according to HY stage, depression is observed in all stages of HY, unlike in the case of dementia. In particular, that depression was

similar to stage 4 even in HY stage 1 indicates that depression may be a prodromal symptom. As a result of the independent one-way analysis of variance, the difference between 4 different HY levels in terms of HAM-D was statistically significant ($p < 0.01$). As a result of the Duncan test, HY 1 and HY 2, as well as HY 3 and HY 4 levels, were similar.

Table 1. Distribution of HAM-D, MMSE, and disease duration by gender

Parameter	Gender	N	Mean	Std. Error
D. Duration	Male	50	6.24	0.3818
	Female	37	5.919	0.4198
Age	Male	50	68.34	1.4083
	Female	37	69.027	1.1167
HAM-D	Male	50	21.62	0.6508
	Female	37	19.568	0.6432
MMSE	Male	50	22.3	0.4231
	Female	37	22.108	0.5267

In PD, dementia is more common in advanced-stage patients, which is associated with the course of the disease. In terms of MMSE, the difference between the HY stages was found to be statistically significant. ($p < 0.01$). As a result of the Duncan test, HY stage 4 caused the difference.

The relationship between the disease duration parameter and the HY stages is that all stages are affected differently, but advanced stage patients are affected more. The difference between 4 different HY levels in terms of disease duration was found to be statistically significant ($p < 0.01$). As a result of the Duncan test, all HY levels were found to be different from each other.

Considering the descriptive statistics of the age parameter according to the HY stages, the majority of elderly patients consist of advanced-stage patients. The difference between 4 different HY levels in terms of age was found to be statistically significant ($p < 0.01$). As a result of the Duncan test, HY stage 4 caused the difference. Comparison of disease duration, age, HAM-D, and MMSE values in terms of HY is given in Table 3.

Considering the degrees of depression, according to HAM-D evaluation results in men, depression levels were found to be very severe in 22%, severe in 30%, moderate in 42%, and mild in 6% of men. In women, depression levels were found to be very severe in 31%, severe in 27%, moderate in 21.6%, and mild in 5.4% of

Table 2. Pearson's correlation matrix for all patients

		Age	Hamilton-D	MMSE	Duration
Age	Pearson's correlation	1	383	114	486
	p-value		000	293	000
	Number of patients	87	87	87	86
HAM-D	Pearson's correlation	383	1	029	552
	Sig. (2-tailed)	000		790	000
	Number of patients	87	87	87	86
MMSE	Pearson's correlation	114	029	1	137
	p-value	293	790		208
	Number of patients	87	87	87	86
D. Duration	Pearson's correlation	486	552	137	1
	p-value	000	000	208	
	Number of patients	86	86	86	86

*** Significant based on 0.01

the patients. Very severe depression was found at a mean rate of 32.2% in male and female patients. Very severe depression was more common in women.

Table 3. Comparison of disease duration, age, HAM-D, and MMSE values in terms of HY

H-Y Stages		N	Mean	Std. Error
D. Duration	Stage 1	19	3.421a	0.2993
	Stage 2	26	5,308b	0.3364
	Stage 3	23	7,043c	0.3849
	Stage 4	18	8,944d	0.5570
Age	Stage 1	19	65.789a	1.4175
	Stage 2	26	65.962a	1.7624
	Stage 3	24	68.625a	1.6614
	Stage 4	18	75,500b	1.9067
HAM-D	Stage 1	19	10.789a	1.1435
	Stage 2	26	14.885a	1.2629
	Stage 3	24	18,542b	1.0356
	Stage 4	18	22.667b	1.4841
MMSE	Stage 1	19	22.263a	0.4578
	Stage 2	26	21.962a	0.5697
	Stage 3	24	20.625a	0.7117
	Stage 4	18	25,111b	0.7041

The difference between those with different letters is significant, while the difference between the same lettered H-Y ones is statistically insignificant.

In dementia, according to MMSE, the values below 24, which we describe as severe dementia, were found at a rate of 16% in men and the rate of MMSE values above 24 were found to be 84%. In women, the rate of MMSE values below 24, which refers to severe dementia, was found to be 11%, while the rate of MMSE values above 24 was found to be 89.2%

Discussion

The hypothesis that depression develops before PD was investigated in various studies. In eight of the nine studies examined, a strong correlation was found between a history of depression and an increased risk of PD development. Current evidence shows that 10–15% of the patients are depressed at the

time of diagnosis. This relationship was found when researchers investigated the period of 2–5 years before the diagnosis of PD. This finding supports the hypothesis that depression is not a risk factor for the disease but a prodromal symptom. This may be the gold standard for making a psychiatric diagnosis in research studies. Mild depression is usually persistent in patients with PD and is a risk factor for moderate to severe depression (12,13).

A systematic examination of patients with PD found that 17% had major depression, 22% had minor depression, and 13% were dysthymic in population-based studies. Depression was slightly higher in female patients than in male patients. Comorbid anxiety was found in 50% of depressive patients with PD. Although suicide was reported rarely in PD, suicidal thoughts were reported to be present in about 11% of PD patients (3,13).

Depression is complicated in PD. Increased risk of depression was reported in first-degree relatives of patients with PD. It is considered to be more common in Gly2019 mutation carriers. There was a serious loss of striatal dopamine in patients with PD and depression. In the imaging studies, frontal hypoperfusion was observed in PD patients with depression. Compared with the glucose metabolism in the same region in healthy individuals without PD and depression, hypometabolism of glucose was reported at the beginning of the caudate nucleus and in the inferior orbital region of the frontal lobe in depressed individuals with PD (8,14,15).

Studies on clinical correlations of PD depression demonstrated various results. The age of onset, severity, duration, stage, or subtype of PD is inconsistently associated with the time of onset or severity of depressive attacks. The reported risk factors for PD depression predominantly

include female gender, previous history of neuropsychiatric comorbidities, psychiatric disorders, and akinetic-rigid type. However, some studies do not confirm these results. Therefore, the main risk factor appears to be the underlying disease process of PD. In addition, people with cerebrovascular disease, Alzheimer's disease, Lewy-body pathology, functional changes in limbic and subcortical circuits, hippocampal atrophy, neurogenesis and changes in neurotrophic factors, psychosocial factors, musculoskeletal pain, toxic stress, as well as anxious and pessimistic personalities were found to be affected more (3,13,15).

Venlafaxine, Pramipexole, and nortriptyline are agents with antidepressant effects in placebo-controlled clinical trials in patients with PD. Transcranial magnetic stimulation can heal the symptoms of depression. Pallidal stimulation is used more often than subthalamic stimulation in the treatment of patients with PD that accompanies psychiatric symptoms. People with PD develop a cyclical mood disorder, which leads to receiving increased amounts of dopaminergic therapy. This disorder, called hedonistic homeostatic dysregulation (HHD) syndrome, may also be associated with substance abuse and addiction (16,17).

Clinical features of PD dementia usually differ from Alzheimer's disease (AD). The severity of the 4 areas of dementia, i.e. cognitive functions, daily life activities, emotional symptoms, and other behavioral symptoms are rated with MMSE according to the observation of the patient and discussion with the caregiver. A small number of patients may present with memory impairment similar to that in AD. In PD patients with dementia, memory-related to all cortical functions is affected. In particular, working memory deteriorates, including long-

term memory, visual-spatial memory, and procedural learning. As noted in the literature, PD dementia is more common in an advanced stage, elderly, and male Parkinson's patients. The average period from the onset of Parkinson's to the development of dementia has been reported to be about 10 years. There may also be a pronounced correlation between the stage of the disease and the prevalence of dementia. Some studies have found that the prevalence in patients with and without dementia is similar in PD. Such studies were summarized in a recent review (9,14,18).

When the degeneration of brainstem nuclei, especially the medial part of substantia nigra using positron emission tomography and in-vivo imaging of cortical cholinergic function were compared with the controls, the average cortical acetylcholinesterase activity in patients with PD dementia was shown to be 20%. Based on the significant deficiencies in cholinergic markers in PD dementia, cholinesterase inhibitors were tried in the population (14,19,20).

Numerous cross-sectional and population-based studies were conducted, where prevalence values were calculated. In a study conducted in the general population, it was reported that the prevalence of dementia was 41% in patients with PD. The mean $\pm$ SD data for patients with PD were as follows when they first met the criteria for dementia: Age: 78.4 $\pm$ 5.7 years; Disease Duration: 13.8 $\pm$ 6.3 years; HY scale score: 3.8 $\pm$ 0.9; MMSE score: 17 $\pm$ 6.2, and Depression rating scale score: 10 $\pm$ 7.9 (9,12,19).

In some studies, it was noted that there was better intellectual functionality in patients with mild dementia who were taking levodopa. However, in most studies, it has been emphasized that mental disorders may occur associated with levodopa treatment. Our

interpretation about why dementia is now more common among elderly patients is that these patients live longer thanks to levodopa (19,20).

The main limitation of the study is the small number of sample cases and the absence of a single-centered and approved prodromal survey for evaluating NMS. Larger and multi-center studies need for further evaluation.

Conclusion

Depression and dementia are important predictors of poor health-related quality of life in Parkinson. While depression is seen in all stages of Y-H, dementia is more common in the last stages of Y-H. The presence of depression in PD may be a 'biomarker' representing neuronal degeneration of the brainstem. We routinely recommend that HAM-D should be performed to detect prodromal depression in newly diagnosed Parkinson, and MMSE should be performed in advanced patients.

Conflict of Interests

The authors declared no conflict of interest.

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