Research Paper:

The Relationship Between Psychological Factors and Cognitive Function in Patients With Parkinson's Disease Who Have Chronic Fatigue

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Conflict of interest

The authors declared no conflict of interest.

ABSTRACT

Background and Objectives: Cognitive and psychological disorders are among the most debilitating complications of Parkinson's Disease (PD). Despite the high prevalence of these disorders in patients with PD and the important effect of psychological factors on cognitive factors in other neurological diseases, no study was found on the relationship between psychological factors and cognitive function in patients with PD who have chronic fatigue. The present study was conducted to investigate the relationship between psychological factors and cognitive function in patients with PD and chronic fatigue.

Methods: In the present cross-sectional study, a total of 73 patients with PD who had chronic fatigue were selected by non-random convenience sampling method from those visiting Tehran's rehabilitation centers in 2019. The following questionnaires were used: Fatigue Severity Scale (FSS) for fatigue, Beck's Depression Inventory for depression, Beck's Anxiety Inventory for anxiety, and Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) for cognitive function, as well as Unified Parkinson's Disease Rating Scale (UPDRS-III) and Pain Visual Analog Scale (Pain VAS).

Results: The regression models explained the cognitive function variance by a maximum of 1.43% in MMSE and 8.79% in MoCA. In all stepwise models of cognitive function, anxiety was the strongest predictor of cognitive function followed by age and UPDRS-III score.

Conclusion: The results of this study indicated that anxiety as the strongest predictor can affect cognitive function in patients with PD who have chronic fatigue. Hence, therapeutic interventions focusing on psychological factors may be particularly important for improving cognitive function in these patients.

Keywords: Anxiety, Depression, Cognition, Parkinson's disease, Fatigue

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↑ *What is "already known" in this topic:*

There is a high prevalence of psychological and cognitive disorders in Parkinson's disease patients and there is a important effect of psychological factors on cognitive factors in other neurological diseases. No information available about role of psychological factors on cognitive function in patients with Parkinson's disease who have chronic fatigue.

→ *What this article adds:*

The results of this study indicated that psychological disorders such as anxiety can affect cognitive function in patients with Parkinson's disease who have chronic fatigue.

Introduction

Parkinson's disease (PD) is a progressive and degenerative neurological disease. The incidence of PD varies from 10 to over 400 per 100,000 people globally, and 200 persons per 100,000 people in Iran. PD is associated with motor and non-motor defects. Nearly all patients with PD (95% to 100%) exhibit at least one of the non-motor symptoms that cause the most performance-reducing features of PD [1-5]. The non-motor symptoms of PD include cognitive dysfunction and psychological disorders. Fatigue has been reported in over two-thirds of the patients with PD and is considered by most as one of the most incapable symptoms [6].

Chronic Fatigue Syndrome (CSF) is a complex and debilitating disorder. Fatigue is considered chronic if it lasts for over six months, and can present with common symptoms, including malaise, muscle pain, memory loss, reduced concentration, insomnia, chest pain, dizziness, night sweat, weight loss, and psychological problems, such as depression, irritability, and anxiety. Its incidence in the general adult population has been estimated at 0.7% to 2.8%. Twice as many women suffer from CFS as men [7, 8]. One of the key signs in CSF is cognitive disorders (50% to 85% of patients) that have a significant role in their social and occupational function.

Cognitive disorders are manifested as difficulty in concentration, attention, memory, finding words, slow information processing, mental slowness, and burnout [9]. Cognitive disorders in PD range from mild cognitive disorders to dementia. Impairment in cognitive factors, such as visuospatial/executive, memory, attention, abstraction, and spatial and temporal awareness variables make it difficult for a person to perform occupational and social functions, new and complex tasks, and gradually everyday tasks [1]. In demographic studies, 23.5% to 55% of patients exhibit mild cognitive impairment in the early stages of PD [10]. Several interrelated cognitive disorders are observed in these patients, including psychological symptoms [11-17], the most common of which are depression and anxiety (with prevalence rates of 58% and 49%, respectively) and stress [18-20].

Anxiety is defined as an often-unrealistic worry, which is excessive and persistent [20]. Anxiety causes a destructive state of mental inhibition, reduces mental output in the intelligence quotient test, impairs focus and memory, and diminishes cognitive and executive function [11, 12].

Depression is a mood disorder [7]. Depression affects information acquisition, retention, retrieval, executive functions of working memory, attention function, and time estimation [13, 14-16].

Stress is defined as any stimulus disrupting the natural balance of the body by changing vital functions. According to Lazarus and Folkman Theory (1984), one of the main psychosocial aspects of stress is its effect on memory and concentration. Stress disrupts mental functions mostly by diverting attention [17].

None of the existing studies have investigated the effect of psychological factors on cognitive function in patients with PD and chronic fatigue. Lack of studies on the existence and extent of the effect of psychological symptoms on cognitive symptoms in patients with PD and chronic fatigue explains the need for conducting this study.

Materials and Methods

In the present cross-sectional study, the sample size was determined with 80% power and 5% error. A total of 73 patients with PD and chronic fatigue were selected by non-random convenience method from 150 patients visiting Tehran rehabilitation centers. This study was conducted during the first eight months of 2019. The study inclusion criteria were: Chronic fatigue based on Fatigue Severity Scale (FSS), the appropriate level of cognitive function (i.e. MMSE≥21), and lack of other neuropsychological disorders, such as stroke and orthopedic or rheumatic disorders. Exclusion criteria were lack of patient cooperation during the tests, consuming red meat or vitamin B6 or B complex up 12 hours before the tests, which prevents the successful effect of levodopa. All participants signed a written consent form.

A demographic questionnaire was used to record demographic and clinical details, including gender, age, the more affected side, dominant hand, and date of diagnosis of PD. Demographic /clinical details cannot predict chronic fatigue, depression, stress, or anxiety in patients with PD. Therefore, the following questionnaires were used in the present study: Fatigue Severity Scale (FSS), cognitive tests, including Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MCA), Beck's Anxiety Inventory (BAI), and Beck's Depression Inventory (BDI), Unified Parkinson's Disease Rating Scale-Part III (UPDRS-III), and Pain Visual Analog Scale (VAS).

Data collection

Procedures

The tests were performed in a quiet room with adequate ventilation and adequate lighting from 8 am to 12 pm. All scales were taken randomly.

Demographics questionnaire

This form was given to the subjects to collect demographic data, including age, gender, and education.

Mini-Mental State Examination (MMSE)

MMSE was first published by Folstein in 1975 for assessing cognitive status in older adults and can assess orientation, short-term memory, reading, writing, calculation, observation and drawing, and connection between one object or image with another. This test takes a little time to complete and is quickly scored, and can be conducted by any rehabilitation team member. It has a total score of 30 points, and scores≤23 indicate cognitive impairment. This test has a satisfactory validity (Cronbach's alpha=0.78), with 90% sensitivity and 84% specificity at a cut-off point of 21 [21].

Unified Parkinson's Disease Rating Scale (UPDRS)

This scale was first published in 1987 by Fahn and Elton. This scale has been translated into Persian by Maryam Norouzian and has been used to assess PD patients. It specifically assesses the functional level in patients with PD in four parts: behavior and mood, daily living skills, complications of therapy, and motor skills. Part I (mind, mood, and behavior) includes four items: intellectual impairment, thought disorder, depression, and motivation. All items are scored from zero (normal) to four (severely affected), with a total score of 147, where higher scores indicate greater functional impairment. The motor section of UPDRS was used in the present study. The test-retest reliability of this scale was performed by Sidroff et al. in Pennsylvania, America (2000), and a reliability of 92% was reported [22].

Hoehn and Yahr Scale

This scale was developed by Hoehen & Yahr (1967) and is highly used as a clinical tool to classify the motor function of patients with PD. This tool provides a common pattern of motor impairment progression in PD patients and divides motor function into five levels. Progress in the stages of this scale is correlated with motor function deficiency, reduced quality of life, and lack of dopaminergic neurons in the images taken from the brain [23].

Montreal Cognitive Assessment (MOCA)

MOCA was developed by Nasreddine et al. (2005) to determine mild cognitive impairment. MOCA has a high sensitivity in the diagnosis of mild cognitive impairment (90%) and Alzheimer's disease (100%). The reliability of this test was determined with Cronbach's alpha of 92% and IC of 83%. It has a cut-off point of 24. This one-page test has a maximum score of 30 points and is completed in less than 15 minutes. This test assesses eight cognitive domains through different skills, with scores as follows: normal older adult≥26; mild cognitive impairment=26, and Alzheimer's<26. The highest score is 30. One point is added to the total score of people with less than 12 years' education [24, 25].

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Beck's Depression Inventory (BDI)

BDI was standardized in Iran in 2005 by Ghasemzadeh and is now widely used to assess depression in normal people and those with psychological problems. It consists of 21 items associated with different symptoms, and the subject is asked to rate the severity of these symptoms compared to the previous two weeks according to a 4-point scale from 0-3. Items assess feeling weak, failure, feeling of guilt, irritability, sleep disturbance, and loss of appetite. This is a self-assessment test, with a total score varying from 0-63. Scores 0-13 are considered as "the least depression", 14-19 as "mild", 20-28 as "moderate", and 29-63 as "severe depression" [26].

Beck's Anxiety Inventory (BAI)

BAI was standardized in Iran by Kaviani (2008) and contains 21 items, in which anxiety symptoms are distinctive from depression. It is rated from 0 (not at all) to 3 (severe). Fourteen items reflect physical symptoms (e.g. trembling hands) and seven items indicate thoughts/feelings (e.g. fear of death). Total score varies from 0 to 63, with scores 0-7 indicating as "minimum", 8-15 as "mild", 16-25 as "moderate" and as 26-63 "severe anxiety" (McDowell & Newell, 1996) [27].

Fatigue Severity Scale (FSS)

FSS was designed and psychometrically assessed by Krupp et al. (1989) to assess the severity of fatigue in patients with multiple sclerosis and lupus. This 9-item questionnaire was derived from the 28-item fatigue scale. Score one is considered as a completely opposite opinion to the question and score seven is considered as a completely agreeable opinion. An overall score of four or higher indicates a significant effect of fatigue on a person's life. Acceptable validity and reliability of the Persian version of FSS have been reported by Azimian et al. (2013) (Cronbach's alpha=0.96) [28].

Pain Visual Analog Scale (Pain VAS)

VAS is a one-dimensional measure of the severity of pain used in various adult populations. Pain VAS consists of a horizontal or vertical line of 10 cm (100 mm), on which, zero indicates no pain and 10 indicates the highest pain imaginable. The subject is asked to indicate their pain score at the moment or in the last 24 hours on the line. VAS was developed in psychology to assess well-being. The validity and reliability of VAS have been confirmed in various studies [29].

The Ethics Committee of the Iran University of Medical Sciences confirmed the study (IR.IUMS.REC. 1398. 895). All participants read the consent form and agreed.

Statistical analysis

Data were analyzed by SPSS software v. 22 using Pearson's correlation test, Spearman's Correlation coefficient, and multivariate regression.

Results

A total of 73 patients with PD and chronic fatigue (23 women/50 men) took part in the present study. Their mean (standard deviation) age was 64.70±9.21 years and the mean (standard deviation) time since diagnosis of PD was 7.99±5.28 years. This study lasted 10 months.

Participants' demographic and clinical details are shown in Table 1. The results showed that cognitive function had no significant correlation with gender, Hoehn & Yahr scale, Edinburgh, more affected side, education, time since diagnosis, or pain (p-value > 0.05), but it had a significant correlation with anxiety predictors, age, and UPDRS-III (p-value < 0.05) (Table 2).

The regression models explained a maximum of 43.1% of the cognitive function variance in MMSE and 79.8% in MOCA. In all stepwise models of cognitive function (MoCA and MMSE), anxiety was the strongest predictor followed by age (years), and UPDRS-III (based on MoCA). Anxiety was the strongest predictor of cognitive function in all stepwise models, followed by age and UPDRS-III (Table 3).

Discussion

The present study investigated the relationship between psychological factors and cognitive function in patients with PD and chronic fatigue. The results showed that anxiety measured with BAI was the strongest predictor of cognitive function, followed by age (years) as the second factor and then UPDRS-III score. This result suggests the need for specifically considering the predictive role of psychological factors to improve cognitive function in patients with PD who have chronic fatigue.

Despite the high prevalence of cognitive and psychological disorders in patients with PD and the important role of psychological factors on cognitive function in other neurological diseases [11-17], no study was found on the relationship between psychological factors and cognitive function in patients with PD who have chronic

Table 1. Demographic information and outcomes of the participant

Characteristics	Mean±SD/Number	95% Confidence Interval
Sex (female/male)	23/50	-
Hoen and Yahr (1/2/3/4)	11/24/38/0	-
Edinburgh Inventory (right/left/both)	56/11/6/0	-
More affect side (nothing/right/left/both)	0/34/39/0	-
Education (ZD/D/FD/FL/DR)	18/12/6/18/19/0	-
Times since diagnosis of Parkinson's disease (year)	7.99±5.27	6.77-9.20
Age (y)	64.70±9.21	62.59-66.81
Pain (score)	4.86±2.35	4.32-5.40
UPDRS III (score)	17.36±9.46	15.20-19.52
Beck anxiety (score)	13.22±11.16	10.66-15.78
Beck depression (score)	14.48±9.55	12.29-16.67
MMSE (score)	27.07±4.36	26.07-28.07
MOCA (score)	25.70±4.72	24.62-26.78
FSS (score)	5±0	5-5

Table 2. Correlations between predictors and outcomes (psychological factor and cognitive function) (n=73)

Predictors	No. (%)/ Outcomes	
	MMSE (score)	MOCA (score)
Sex (female/male)	0.158 (0.182)	0.125 (0.291)
Hoen and Yahr (1/2/3/4)	-0.109 (0.358)	-0.096 (0.419)
Edinburgh (right/left/both)	-0.157 (0.183)	-0.210 (0.074)
More affected side (nothing/right/left/both)	-0.067 (0.572)	-0.204 (0.084)
Education (ZD/D/FD/FL/DR)	0.238∗ (0.043)	0.233∗ (0.047)
Times since Parkinson (y)	0.213 (0.071)	0.034 (0.776)
Age (y)	-0.215 (0.067)	-0.368∗ (0.001)
Pain (score)	-0.277∗ (0.018)	-0.090 (0.45)
UPDRS III (score)	-0.117 (0.323)	-0.350∗ (0.002)
Beck anxiety (score)	-0.407∗ (0.00)	-0.839∗ (0.00)
Beck depression (score)	-0.347∗ (0.003)	-0.606∗ (0.00)

UPDRS: Unified Parkinson's Disease Rating Scale; MMSE: Mini-Mental State Examination; MOCA: Montreal Cognitive Assessment; FSS: Fatigue Severity Scale.

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Table 3. A summary of stepwise multiple regression analyses for cognitive function

Cognitive Outcomes	Predictors/ Models	R² (%)	R² change (%)	P
MMSE (score)	Model 1: Beck Anxiety	43.1	43.1	0.00
MOCA (score)	Model 1: Beck Anxiety	75.0	75.0	0.00
	Model 2: Beck Anxiety+Age	78.0	3.0	0.003
	Model 3: Beck Anxiety+Age+ UPDRS III	79.8	1.8	0.02

fatigue. According to the results of the present study, anxiety was the best predictor of cognitive function. Foster et al. (2010) demonstrated that anxiety affects the working memory in patients with PD [30]. Kathrine et al. (2010) also reported that anxiety was associated with cognitive function in patients with PD, but they found no association between depression and cognitive function. Nadeeka (2017) demonstrated a positive association between anxiety and cognitive impairment in PD, in particular, memory deficits but did not demonstrate an association between depression and cognitive impairment in general or in relation to a specific subtype of PD [31]. Paul (2010) proved that PD patients with left hemi-body involvement with heightened anxiety exhibited worse working memory than their counterparts [32].

Contrary to our study, Starkstein (1993) demonstrated that depression was associated with a long duration of illness and more severe cognitive and physical impairments; anxiety was not associated with greater impairment. This opposite result may be due to the small population of their study [33]. In this study, depression was not a predictor of cognitive factors, this is because women are more likely than men to receive a clinical diagnosis of depression and also usually score higher in BDI. Current findings suggest that anxiety is a better predictor of cognitive impairment than depression. Anxiety dysregulates the function of the pituitary-adrenal axis [34].

Chronic dysregulation of adrenal gland function and catecholamine can cause hippocampal damage that has a key role in cognitive function, including working memory and attention [35]. Besides, anxiety may cause neurochemical changes, such as dopamine depletion in the nigrostriatal region and cell loss in serotonergic and noradrenergic segments of the brainstem nucleus. Moreover, empirical studies have shown that damage to dopaminergic neurons can cause cognitive impairment [36]. Neurochemical mechanisms of impaired cognitive function in chronic fatigue syndrome and anxiety disorders affect common cerebral regions, including the parietal cortex containing hippocampal and basal ganglia (where

dopamine is produced) as well as the damaged region in PD. Therefore, anxiety in patients with PD and chronic fatigue exacerbates the likelihood of cognitive function impairment [37, 38].

Another predictor of cognitive function was age. The strength of low-frequency waves (7 Hz), such as delta and theta linearly reduces with aging. Previous studies have shown a significant relationship between the strength of delta and theta waves and cognitive function. Since delta and theta waves are normally impaired in older participants, this impairment disrupts perception speed, working memory, and the process of cognitive control, which led to a significant relationship between age and cognitive function in the present study [39]. Le Bon et al. reported that the strength of the delta wave reduces in patients with chronic fatigue [40]. Since the reduction in the strength of delta and theta waves that happens with aging impairs cognitive function, aging exacerbates impairments of cognitive function in patients with PD and chronic fatigue.

In the present study, the third predictor of cognitive function was PD-induced motor impairment that was measured using UPDRS-III. Previous studies have reported that the motor circuit is involved in cognitive functioning, which helps improve cognitive function by producing dopamine. Moreover, motor activities improve cognitive function by increasing dopamine production in the brain. Neurochemical mechanisms in chronic fatigue and motor defect and activities in impaired cognitive indicators are caused by dopamine reduction in the brain [37, 38, 41, 42]. Hence, motor damage in patients with PD who have chronic fatigue exacerbates the impairment of cognitive function.

The present study is the first to investigate the relationship between psychological factors and cognitive function in patients with PD who had chronic fatigue. The clinical outcome of this finding is that impairment in psychological factors, such as anxiety and stress in patients with PD and chronic fatigue can affect cognitive

factors, including problems in focusing and attention, memory, difficulty in finding words, reduced speed of information processing, and mental exhaustion and sluggishness. Therefore, the therapeutic role of psychological factors should be considered to improve cognitive factors in patients with PD and chronic fatigue.

Conclusion

The results of this study indicated that psychological disorders, such as anxiety can affect cognitive function in patients with PD who have chronic fatigue. Hence, therapeutic interventions focusing on psychological factors may be particularly important for improving cognitive function in these patients.

Ethical Considerations

Compliance with ethical guidelines

The Ethics Committee of the Iran University of Medical Sciences confirmed the study (IR.IUMS.REC. 1398. 895). All participants read the consent form and agreed.

Authors' contributions

Conceptualization: Laleh Lajevardi, Farahnaz Farhanginasab; Methodology: Ghorban taghizadeh, Laleh Lajevardi; Investigation: Farahnaz Farhanginasab; Writing-Review & editining: Farahnaz Farhanginasab, Laleh Lajevardi.

Conflict of interest

No conflicts of interests were reported by the authors.

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مقاله پژوهشی

رابطه بین عوامل روانشناختی و عملکرد شناختی در بیماران مبتلا به پارکینسون دارای خستگی مزمن

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چکیده

مقدمه اختلالات شناختی و روانی یکی از ناتوان کننده ترین عوارض بیماری پارکینسون است. با وجود شیوع بالای این اختلالات در بیماران مبتلا به پارکینسون و تأثیر مهم عوامل روانی بر عوامل شناختی در سایر بیماری های عصبی، هیچ مطالعه ای در مورد ارتباط عوامل روانی و عملکرد شناختی در بیماران مبتلا به بیماری پارکینسون که خستگی مزمن دارند، یافت نشد. مطالعه حاضر (۲۰۱۹) به منظور بررسی ارتباط عوامل روانشناختی و عملکرد شناختی در بیماران مبتلا به بیماری پارکینسون که خستگی مزمن دارند انجام شد.

مواد و روش ها در این مطالعه همبستگی حاضر، در مجموع ۷۳ بیمار مبتلا به بیماری پارکینسون که دچار خستگی مزمن بودند به روش نمونه گیری غیر تصادفی از مراجعه کنندگان به مراکز توانبخشی تهران (۲۰۱۹) انتخاب شدند. پرسشنامه های زیر مورد استفاده قرار گرفت: مقیاس شدت خستگی (FSS) برای خستگی، پرسشنامه افسردگی بک برای افسردگی، پرسشنامه اضطراب بک برای اضطراب و معاینه حالت روانی کوچک (MMSE) و ارزیابی شناختی مونترال (MOCA) برای عملکرد شناختی و همچنین مقیاس درجه بندی بیماری پارکینسون (UPDRS-III) و مقیاس آنالوگ بصری درد (Pain VAS).

یافته ها یافته ها: مدلهای رگرسیونی واریانس عملکرد شناختی را حداکثر در ۱,۴۳٪ در MMSE و ۸,۷۹٪ در MoCA توضیح دادند. در همه مدل های مرحله ای عملکرد شناختی، اضطراب قوی ترین پیش بینی کننده عملکرد شناختی بود که بعد از آن سن و سپس نمره UPDRS-III تعیین شد.

نتیجه گیری نتیجه گیری: نتایج این مطالعه نشان داد که اضطراب به عنوان قوی ترین پیش بینی کننده می تواند بر عملکرد شناختی در بیماران مبتلا به بیماری پارکینسون که خستگی مزمن دارند تأثیر بگذارد. بنابراین، مداخلات درمانی با تمرکز بر عوامل روانی ممکن است برای بهبود عملکرد شناختی در این بیماران اهمیت ویژه ای داشته باشد

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