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Cognitive and affective disturbances in patients with Parkinson's disease: Perspectives for classifying of motor/neuropsychiatric subtypes

Anastasiia D. Shkodina [a,b,1], Kateryna A. Tarianyk [a,1], Dmytro I. Boiko [c], Mehrukh Zehravi [d,1], Shamima Akter [e], Ghulam Md. Ashraf [f,g], Md. Habibur Rahman [h,i,*]

[a] Department of Neurological Diseases with Neurosurgery and Medical Genetics, Poltava State Medical University, Poltava, Ukraine
[b] Neurological Department, Municipal Enterprise "1 City Clinical Hospital of Poltava City Council", Poltava, Ukraine
[c] Department of Psychiatry, Narcology and Medical Psychology, Poltava State Medical University, Poltava, Ukraine
[d] Department of Clinical Pharmacy Girls Section, Prince Sattam Bin Abdul Aziz University, Alkharj, 11942, Saudi Arabia
[e] Department of Bioinformatics and Computational Biology, George Mason University, Fairfax, VA 22030, USA
[f] Pre-Clinical Research Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah 21589, Saudi Arabia
[g] Department of Medical Laboratory Sciences, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah 21589, Saudi Arabia
[h] Department of Pharmacy, Southeast University, Banani, Dhaka 1213, Bangladesh
[i] Department of Global Medical Science, Wonju College of Medicine, Yonsei University, Seoul 26426, Gangwon-do, Republic of Korea

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ABSTRACT

Parkinson's disease (PD) is a neurological disorder, related to rigidity, bradykinesia, and resting tremors, among other motor symptoms. It is noticed in the increasing frequency of neuropsychiatric disorders, which may be also caused by non-motor symptoms of PD. Treatment of PD is usually based on the classification of motor subtypes; however, it remains unclear whether motor subtypes have differences in the severity of psychiatric symptoms. It determines the importance of discovering possible neuropsychiatric subtypes of PD. We conducted a clinical study, which included group 1 - patients with postural instability and gait disorders dominant (PIGD) subtype, group 2 - patients with tremor dominant (TD) and indeterminate subtypes (non-PIGD), and group 3 - people who did not have CNS damage. We used the Montreal Cognitive Assessment, Russified 20-point version of the Toronto Alexithymia Scale, State-Trait Anxiety Inventory, and Beck Depression Inventory for assessment of the mental status. It was the first time that neuropsychiatric subtypes of PD had been investigated based on the condition of cognition and mood. Cluster analysis gave us the possibility to classify our patients by the following subtype: affective-cognitive PIGD, anxious PIGD, affective-cognitive non-PIGD, and non-PIGD without psychiatric symptoms. This indicates a closed link between psychiatric and motor symptoms, which can be used for the improved treatment of PD.

1. Introduction

One of the leading causes of disability in the world is diseases of the nervous system, in particular neurodegenerative diseases. Parkinson's disease (PD) develops due to the degeneration of neurons in the pars compacta of the substantia nigra, which causes the development of the classic triad of motor symptoms such as tremor, bradykinesia, and muscle rigidity [1]. However, an equally important component of PD is non-motor symptoms, which include psychiatric, autonomic, and sensory symptoms, cardiovascular, and gastrointestinal disorders, disorders of the genitourinary system, sleep, and circadian rhythm disorders [2,3]. Recent studies indicate that psychiatric symptoms occur in 70–89% of PD cases and have a huge impact on both the quality of life of patients and health care systems [4]. Table 1 analysis of mood disorders levels in PD patients.

Mood disorders are associated with impairments in neurotransmitter transmission in the late stages of the disease, but their role remains important in the early stages when it appears as a result of significant psycho-emotional stress. Its association with motor fluctuations creates additional challenges in disease management [5]. Alexithymia, which is described as difficulty in identifying and describing feelings, occurs in the general population with a frequency of 9–17%. It leads to decreased

* Corresponding author at: Department of Pharmacy, Southeast University, Banani, Dhaka 1213, Bangladesh.
E-mail address: pharmacisthabib@gmail.com (Md.H. Rahman).
[1] Authors equally contributed this work.

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Table 1
Analysis of mood disorders levels in PD patients.

Mood disorder	Groups Group 1 (n = 38)	Group 2 (n = 26)	Group 3 (n = 30)	p-value
Alexithymia	60.21 ± 2.81	56.11 ± 2.79	42.36 ± 2.99	0.001
Depression	17.76 ± 1.46	14.73 ± 1.79	11.87 ± 1.56	0.038
State anxiety	45.87 ± 1.71	41.27 ± 2.23	31.17 ± 2.83	0.029
Trait anxiety	51.09 ± 1.46	44.62 ± 2.34	30.87 ± 1.45	<0.001

emotional regulation and the ability to cope with stress [6]. It has been reported that in patients with PD, alexithymia is a predictor of cognitive impairment and may be associated with the severity of mood disorders [7]. Cognitive decline is one of the most debilitating non-motor symptoms of PD. The rapid progression of cognitive impairment in the early stages of PD has been associated with mood disorders, in particular depression and anxiety [8].

Given the importance of non-motor symptoms in the treatment of PD, attempts have been made over the years to define the non-motor or motor/non-motor subtypes of PD. The non-motor subtypes are expected to be dynamic and may change throughout the disease [9]. Despite a large amount of data on attempts to integrate non-motor symptoms into the structure of PD phenotype classification, mood disorders, and cognitive impairments are used with the least demand. Treatment of PD is usually based on the classification of motor subtypes; however, it remains unclear whether motor subtypes have differences in the severity of psychiatric symptoms. It determines the importance of discovering possible neuropsychiatric subtypes of PD. Therefore, the aim of our study aimed to differences between en cognitive and affective disorders in different motor subtypes of PD and to discover possible neuropsychiatric subtypes of PD.

2. Materials and methods

2.1. Inclusion and exclusion criteria

We conducted a clinical retrospective study on the Poltava Regional Clinical Hospital from 2020-to 2021, which included 64 patients with PD and 30 people in the control group. Criteria for inclusion in the study were clinically confirmed PD with Hoen and Yahr stage<4, disease duration more than 1 year, age from 18 to 89 years, and treatment with levodopa therapy. Exclusion criteria: concomitant severe somatic or mental diseases, over 90 years, secondary parkinsonism due to drugs, vascular lesions, tumors and trauma, special MRI-signs, which are typical for atypical parkinsonism (dementia with Lewy bodies, progressive supranuclear palsy, corticobasal degeneration and multisystem atrophy) [10–12], following clinical signs: unequivocal cerebellar abnormalities or cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia, downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades, probable behavioral variant frontotemporal dementia or primary progressive aphasia, parkinsonian features restricted to the lower limbs for more than 3 years, absence of observable response to high-dose levodopa despite at least moderate severity of disease, rapid progression of gait impairment requiring regular use of wheelchair, severe autonomic failure or bulbar dysfunction within 5 years of onset, complete absence of progression of motor symptoms or signs over 5 or more years unless stability is related to treatment, inspiratory respiratory dysfunction, more than 1 falls per year because of impaired balance within 3 years of onset, disproportionate anterocollis or contractures of hand or feet within the first 10 years, absence of any of the common nonmotor features of disease despite 5 year disease duration, otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response) [13–15].

2.2. Grouping

PD was verified according to the recommendations of the International Society of Motor Disorders and Parkinson's Disease [16]. Parkinson's syndrome was initially confirmed, with bradykinesia and tremor at rest and/or muscle rigidity. Clinically confirmed PD was determined in the absence of absolute exclusion criteria, at least 2 auxiliary criteria, and in the absence of "red flags". The Unified Parkinson Disease Rating Scale (UPDRS) was used to assess the severity of the clinical condition of patients with PD.

The motor subtype of PD was determined by the method of Jankovich and Stebbins [17], which consists of the calculation of the subtype index (SI) according to the UPDRS rating (1):

$$Subtype\ index\ = \frac{question\ No16\ +\ \Sigma questions\ No20-21 \div 8}{\Sigma questions\ No13-15\ +\ \Sigma questions\ No29-30 \div 5} \quad (1)$$

SI > 1.5 corresponds to the TD subtype, SI from 1.0 to 1.5 –an indeterminate subtype of PD, and SI < 1.0 –PIGD subtype. According to the recommendations, patients with indeterminate subtypes and subtypes with a predominance of tremors were grouped into one group, whose patients did not show a predominance of postural instability and gait disorders [18].

The examined patients were divided into 3 groups according to the motor subtype of PD:

group 1 (n = 38 people) - patients with PIGD subtype;
group 2 (n = 26 people) - patients with non-PIGD (TD and indeterminate) subtypes;
control group (n = 30 people) - relatively healthy people who did not have CNS damage.

The study was performed from January 2020 to March 2021. The study was conducted by the principles of Good Clinical Practice (ICH E2 (R6) GCP) and the Helsinki Declaration of the World Medical Organization. All patients provided informed consent to participate in the study. Group 1 consisted of 20 women (52.6%) and 18 men (47.4%), group 2 of 13 women (50%) and 13 men (50%), and the control group of 16 women (53.3%) and 14 men (46.7%). The mean age of patients in group 1 was 63.40 ± 1.48 years, in group 2–63.88 ± 1.69 years, and in the control − 59.9 ± 1.56 years, and corresponded in all cases to the elderly. No significant gender and age differences were found between the groups (p = 0.719 for sex and p = 0.167 for age). The overall score on the UPDRS scale in group 1 was 48.79 ± 3.23, and in group 2–46.31 ± 3.52, which had no statistically significant differences (p = 0.856). Therefore, the age, sex, and clinical severity of patients can be excluded from the confounders. During the visit of the patient, neurological status was examined. Patients were interviewed with psychometric scales.

2.3. Cognitive impairments measurement

Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), which is considered the most sensitive for screening of cognitive impairment in people with Parkinson's disease. In general, the maximum score is 30, while scoreless than 26 points is corresponding to the presence of cognitive impairment [19].

2.4. Severity of alexithymia measurement

We chose alexithymia to assess emotional disorders/ It was studied using a Russified 20-point version of the Toronto alexithymia Scale (TAS-20R). We have analyzed the total level and severity of alexithymia, which is estimated as a high level of over 61 points, elevated over 51 points, and normal 50 points or less. We have also rated components of alexithymia, such as "difficulty identifying feelings" (DIF), "difficulty describing feelings" (DDF), and externally oriented thinking (EOT) [6].

2.5. Level of anxiety measurement

The level of anxiety was assessed by the State-Trait Anxiety Inventory (STAI). It consists of 40 questions divided into 2 blocks, the first of which is responsible for trait anxiety, and the second - for the state [20]. A separate amount of points is calculated for each block, which can vary from 20 to 80 points, whereby a larger amount corresponds to a higher intensity of anxiety. It is considered that < 30 points is a low level of anxiety, 31–45 points – moderate, and greater than 45 points – high [21].

2.6. Level of depression measurement

Beck Depression Inventory (BDI-I) was used in the study to measurement of depression level. It consists of 21 statements that the level of compliance with their experiences the patient evaluates on a scale from 0 to 3. The total score may be from 0 to 63 points and 0–13 is no symptoms of depression, 14–19 is mild depression, 20–28 is moderate, and 29–63 is a severe depressive syndrome [22].

2.7. Statistical analysis

Microsoft Statistical Excel 2019 software (Microsoft Corp., USA), EZR Statistics v.1.13, and IBM SPSS Statistic 26.0 (IBM Corp., USA) were used for statistical analysis of the obtained results. The normality of the distribution was evaluated according to the Shapiro-Wilk test. Quantitative data were presented as arithmetic mean (M) and standard error (σ) or as medians (Me) with an interquartile (Q1-Q3) range. One-factor analysis of variance (ANOVA) with Sheffie's correction or Kruskal-Wallis criterium with Still-Dwass test, the Yates-corrected and $\chi 2$ test were used. We conducted a two-stage cluster analysis with 8 input variables and 64 observations by Ward's clustering method. The degree of significance of clustering variables was determined by calculating ANOVA. The critical p-value was 0.05.

3. Results and discussion

The MoCA scale score was 24.47 ± 0.56 in group 1, 24.01 ± 0.57 in group 2, and 27.83 ± 0.39 in the control group. In the group of healthy individuals, the level of cognitive functions was significantly higher compared to both subtypes of PD ($p < 0.001$). In group 1 there were 24 (63.2%) people with cognitive decline, in group 2–14 (53.8%) people, and in the control – 5 (16.7%) people. Thus, the control group was less likely to show signs of cognitive impairment compared to persons with PD ($\chi 2 = 18.39$, $df = 2$, $p < 0.001$). It should be noted that with a higher frequency of detection of cognitive decline in the PIGD motor subtype of PD, their severity on the MoCA scale remains the same in both. The mean age of onset was 59.32 ± 2.48 years in group 1 and 57.81 ± 3.17 years in group 2. People with later onset of PD were reported to develop dementia faster [23], but no statistically significant differences were found between groups in the age of onset.

It was reported that the PIGD subtype is associated with a greater deficit of attention and cognitive function compared to the TD subtype of PD [24]. At the same time akinetic rigidity form of PD, which is supposed to a similar to the PIGD subtype, has accompanied more severe cognitive, and mood disorders and functional connectivity in the fronto-insular and frontal-parietal cortex [25].

The emotional condition was studied by analyzing the level of alexithymia, depression, and anxiety, which is shown in the tab. 1. It was found that PD patients have a higher level of these mood disorders than the control group.

Therefore, in group 1 there was an elevated level of alexithymia in 10 (26.3%) and high in 19 (50.0%) people, in group 2 13 (50.0%) had an elevated level, and 7 (26.9%) %) had high one, while in the control group 10 (33.3%) had an elevated level, and only 3 (10.0%) had a high level. It was found that in people with PD alexithymia is found almost 2 times more often than in the general population ($\chi 2 = 18.01$, $df = 4$, $p = 0.001$). No significant differences between motor subtypes were found.

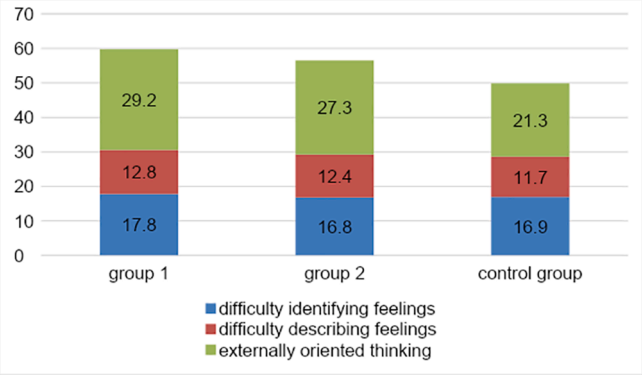

Fig. 1. Alexithymia subcomponents by TAS-20R in patients with different motor subtypes of Parkinson's disease and control group.

Table 2
Levels' distribution of affective disorders levels in PD patients.

Disorder	Level	Groups Group 1 (n = 38)	Group 2 (n = 26)	Group 3 (n = 30)	p-value
Trait anxiety	Low	0 (0%)	5 (19.2%)	16 (53.3%)	<0.001
	Moderate	9 (23.7%)	6 (23.1%)	9 (16.7%)	
	High	29 (76.3%)	15 (27.7%)	5 (31.9%)	
State anxiety	Low	3 (7.9%)	6 (23.1%)	13 (43.3%)	0.029
	Moderate	14 (36.8%)	7 (26.9%)	10 (33.3%)	
	High	21 (55.3%)	13 (50.0%)	7 (23.3%)	
Depression	Absence	12 (33.3%)	26 (34.6%)	18 (60.0%)	<0.001
	Mild	7 (18.4%)	7 (26.9%)	4 (13.3%)	
	Moderate	8 (21.1%)	8 (30.8%)	7 (23.3%)	
	Severe	11 (28.9%)	2 (7.7%)	1 (3.3%)	

The distribution of the mean values of the components of alexithymia is presented in Fig. 1. We can observe the absence of statistically significant differences between the groups in terms of DDF and DIF. However, EOT was significantly higher in groups 1 ($p = 0.007$) and 2 ($p = 0.011$) compared to the control group.

There is conflicting evidence as to whether alexithymia is secondary or primary to PD. However, it is known that it occurs about twice as often as in healthy people, which confirms our results [26]. Alexithymia has been reported to be associated with other mood disorders and cognitive impairment. However, there are insufficient data on neurobiological changes accompanying the development of PD that could explain this observation [27].

We demonstrate the distribution of levels of affective disorders among our patients in tab.2. Statistically significant differences in distribution indicate a greater predisposition of group 1 to severe trait anxiety and group 2 to moderate compared with the control group ($\chi 2 = 33.50$, $df = 4$, $p < 0.001$) and prevalence of high levels of state anxiety in patients with PD compared with the control group ($\chi 2 = 13.71$, $df = 4$, $p = 0.008$).

Trait anxiety in de novo PD patients is considered a risk factor for impulse control disorders [28]. At the same time, state anxiety can be a predictor of cognitive impairment in PD [29]. Although there is no report of an association between anxiety level and motor subtype of PD [30], we assume that our results may differ due to different measurement tools.

A significant predisposition of persons of group 1 to severe depression was found in comparison with group 2 and the control group ($\chi 2 = 14.29$, $df = 6$, $p = 0.027$). Depression is a common psychiatric symptom of PD which does not change during disease progression [31]. By the way, the effect of depression on gait and gait variability has been reported, which may be associated with the PIGD subtype of PD [32].

Table 3
Final centers of neuropsychiatric clusters of Parkinson's disease.

Symptom	Cluster				p-value
	1	2	3	4	
Tremor dominance	0.17	0.42	0.27	0.80	<0.001*
PIGD dominance	0.83	0.47	0.73	0.10	<0.001*
Intermediate motor variant	0.00	0.11	0.00	0.10	0.203
State anxiety	2.50	2.63	2.73	1.3	0.002*
Trait anxiety	2.75	2.95	2.73	1.5	0.004*
Depression	0.42	2.95	2.73	1.5	0.009*
Alexithymia	1.54	0.37	1.82	1.10	0.108
Cognitive impairment	0.50	0.79	0.82	0.50	0.016*

Note. *-p < 0.05, statistically significant parameter according to the results of ANOVA.

We conducted a two-stage cluster analysis of data from individuals with PD to determine the most appropriate number of groups into which the study group of patients can be divided by the centers of the final clusters shown in Table 2. Table 3 shows that the PIGD subtype has an association with clusters 1 and 3 when the TD subtype has it with clusters 2 and 4. High levels of state and trait anxiety are linked to clusters 1, 2, and 3, while cluster 4 has its low levels. The high level of depression and cognitive impairments are associated with clusters 2 and 3.

We found that the most optimal number of clusters is 4. This model describes the population well because the degree of connectivity and distribution of clusters was greater than 0.5. To further assess the factors that determine the distribution of variables were clustered by the method of k-variables (k = 4). According to cluster analysis, we can identify the following neuropsychiatric clusters of patients with PD who have psychiatric manifestations, which are described in Table 4:

type 1 (cluster 1) – PIGD with moderate anxiety (n = 15) or anxious PIGD;
type 2 (cluster 2)–PIGD with anxiety, depression, and cognitive impairments (n = 22) or affective-cognitive PIGD;
type 3 (cluster 3)–non-PIGD with anxiety, depression, and cognitive impairments (n = 16) or affective-cognitive non-PIGD;
type 4 (cluster 4)– non-PIGD without anxiety, depression, or cognitive impairments (n = 11) or non-PIGD without psychiatric symptoms.

Our results indicate the possibility of identifying close links between motor subtypes and psychiatric manifestations, as shown in Fig. 2 and demonstrate new possibilities for typing PD with considering non-motor symptoms.

It should be considered that our study was limited to psychiatric symptoms and a small number of patients. The authors believe that similar multidimensional relationships should be investigated in the future. The localization of aggregation-prone proteins, such as b-amyloid and α-synuclein might play role in the link between psychiatric signs and motor features in PD patients and need more studies for a better understanding of neuropathology [23,33]. Numerous studies have attempted to develop an optimal classification that could combine motor and non-motor symptoms. In particular, two recent studies received 6 clusters that differed in their heterogeneity [9,34]. Our results may differ because of include only affective and cognitive disturbances. Furthermore, it is proposed to include laboratory biomarkers in the variables of the classification of subtypes of PD, in particular the cytokine profile [35] and the concentration of metabolites that may be predictors of the course of PD and influence mood and cognition [36].

The results obtained can improve the understanding of the stages and process of development of psychiatric disorders in PD, and as a result, improve the treatment strategy through the joint work of a multidisciplinary team, including neurologists and psychotherapists.

4. Concluding remarks

It was discovered that the PIGD subtype of PD is accompanied by more frequent cognitive decline and depression. Alexithymia has a vaster prevalence among Parkinson disease's patients than in healthy people without significant differences between motor subtypes. The

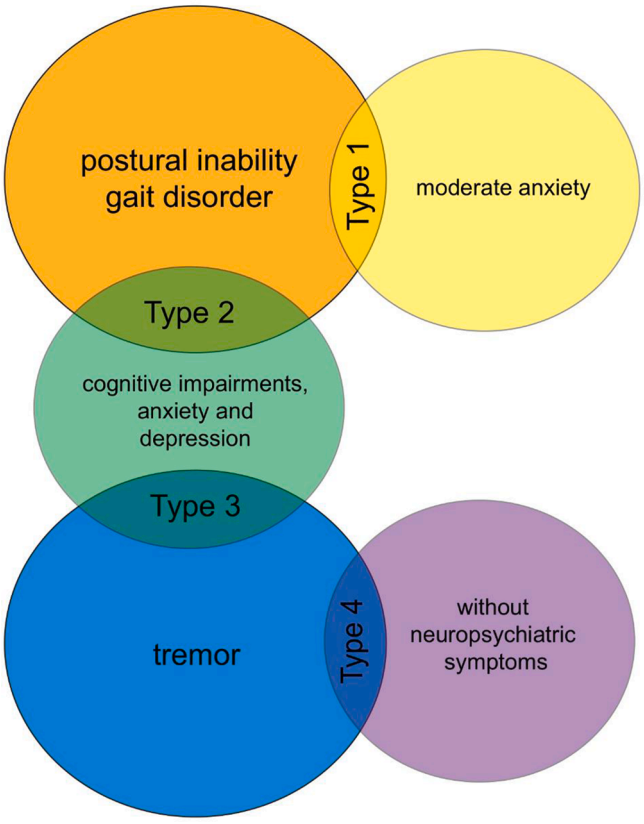

Fig. 2. The way of formation of proposed neuropsychiatric subtypes of Parkinson's disease.

Table 4
Characteristics of neuropsychiatric subtypes of Parkinson's disease.

Symptom	Neuropsychiatric subtype				p-value
	1 (n = 15)	2 (n = 22)	3 (n = 16)	4 (n = 11)	
Tremor dominance	0	0	13 (81.3%)	10 (90.9%)	<0.001*
PIGD dominance	15 (100%)	22 (100%)	0	1 (9.1%)	<0.001*
Intermediate motor variant	0	0	3 (18.7%)	0	0.224
State anxiety	39.0 (31.0–45.0)	50.5 (44.75–56.25)	49.5 (46.0–52.5)	29.0 (24.0–35.0)	<0.001*
Trait anxiety	49.0 (39.0–53.0)	55.5 (50.0–61.0)	52.5 (47.0–57.8)	31.0 (28.0–35.0)	<0.001*
Depression	11.0 (7.0–18.0)	19.0 (15.0–28.5)	18.5 (13.5–24.8)	14.0 (7.0–28.0)	0.014*
Alexithymia	59.0 (36.0–61.0)	64.5 (55.8–76.6)	56.5 (39.8–70.5)	59.0 (54.0–68.0)	0.107
Cognitive impairment	27.0 (26.0–28.0)	24.0 (22.0–25.0)	24.0 (22.0–25.0)	26.0 (22.0–28.0)	<0.001*

Note. *-p < 0.05, statistically significant parameter according to the Kruskal-Wallis criterium.

PIGD subtype is more inclined to anxiety compared to non-PIGD. It was the first time that neuropsychiatric subtypes of PD had been investigated based on the condition of cognition and mood. Cluster analysis gave us the possibility to classify our patients by the following subtype: affective-cognitive PIGD, anxious PIGD, affective-cognitive non-PIGD, and non-PIGD without psychiatric symptoms. This indicates a closed link between neuropsychiatric and motor symptoms, which can be used for the improved treatment of PD. An innovative approach could be implemented as out-patient as in in-patient treatment of PD. The organization of this process should consider involving psychotherapists and psychiatrists because of the high frequency of comorbid mental disorders.

It is interesting to suggest that the identification of these subtypes in clinical practice could contribute to the development of new approaches to the treatment of PD and the study of relationships between different symptoms of PD to fill gaps in knowledge of the pathophysiology of this disease.

5. Data Availability

Not applicable.

6. Code Availability

Not applicable.

7. Declarations

Ethical Approval
Not applicable.
Consent to Participate
Not applicable.
Consent for Publication
Not applicable.

CRediT authorship contribution statement

Anastasiia D. Shkodina: Conceptualization, Methodology, Supervision, Writing – original draft. **Kateryna A. Tarianyk:** Data curation, Writing – review & editing. **Dmytro I. Boiko:** Data curation, Writing – review & editing. **Mehrukh Zehravi:** Writing – review & editing. **Shamima Akter:** Writing – review & editing. **Ghulam Md. Ashraf:** Writing – review & editing. **Md. Habibur Rahman:** Conceptualization, Methodology, Supervision, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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