Heliyon 9 (2023) e18081

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Clinical characteristics and reaction to dopaminergic treatment of drug-naïve patients with Parkinson's disease in central China: A cross sectional study

Weiqi Zeng [a,b,1], Yukai Wang [a,1], Ling Liu [b,1], Yi Wu [b], Yu Xu [b], Heng Zhai [b], Xiaoman Yang [b], Xuebing Cao [b,**], Yan Xu [b,*]

[a] Department of Neurology, The First People's Hospital of Foshan, Foshan, Guangdong, China
[b] Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

ARTICLE INFO

Keywords:
Drug-naïve
Parkinson's disease
Clinical characteristics
Acute levodopa challenge test

ABSTRACT

Background: The symptoms of early Parkinson's disease (PD) are complex and hidden. The aim of this study is to explore and summarize the characteristics of the symptoms of drug naïve patients with PD.

Objectives: and Methods Drug-naïve patients with PD and age-matched healthy controls were recruited from the outpatient clinic of Wuhan Union Hospital. The motor and non-motor symptoms were evaluated for further analysis using Unified Parkinson's Disease Rating Scale (UPDRS) I, II, and III; Sniffin' Sticks Screening 12 test; Mini-Mental State Exam (MMSE); Montreal Cognitive Assessment (MoCA); Hamilton Anxiety Scale (HAMA); and Hamilton Depression Scale (HAMD) scores. The acute levodopa challenge test (ALCT) was adopted to assess the reaction to dopaminergic treatment.

Results: We recruited 80 drug-naïve patients with PD and 40 age-matched healthy controls (HCs). Approximately 53.7% of the patients were females. The mean onset age was 59.96 ± 10.40 years. The mean UPDRS I, II, and III were 2.01 ± 1.90, 6.18 ± 3.68, and 26.13 ± 12.09, respectively. Compared with HCs, PD patients had lower scores in MMSE and MoCA; and higher scores in HAMA and HAMD ($p < 0.05$). In ALCT, 54 patients showed good responses to levodopa while 26 patients did not. The mean improvement rate of UPDRS III was 34.09% at 120 min.

Conclusion: The motor symptoms of patients with early PD were mild but virous. They also suffered from different non-motor symptoms. In ALCT, about two thirds of patients (54/80) with early PD showed good response to levodopa. Among four aspects of motor symptoms, bradykinesia reacted best to ALCT, while axial symptoms were the worst.

1. Introduction

Parkinson's disease (PD) is the most prevalent neurodegenerative disease second to Alzheimer's disease. PD is a progressive disease

* Corresponding author.
** Corresponding author.
E-mail addresses: caoxuebing@126.com (X. Cao), xuyanwxf@126.com (Y. Xu).
[1] These authors have contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2023.e18081
Received 27 November 2022; Received in revised form 11 May 2023; Accepted 6 July 2023
Available online 7 July 2023

characterized by motor symptoms of static tremors, myotonia, and bradykinesia [1]. In addition, patients often suffer from a series of non-motor symptoms (NMS) such as anosmia, constipation, depression, and rapid eye movement sleep behavior disorder [2]. NMS lack specificity and often appear in the prodromal stage of the disease. Dopamine replacement therapy with levodopa is the major pharmacotherapy for PD [3]. The diagnosis of PD depends on the occurrence of motor symptoms but they are sometimes hidden, atypical and diverse in early PD, which renders the diagnosis of early PD difficult.

It was reported that the prevalence of PD is positively correlated with ages, having a percentage of 0.64% in Asia, which is lower than that in the western countries [4]. An epidemiological study in China revealed that the prevalence among people over 65 years old is 1.7% with an estimated number of 1.7 million cases. Among the confirmed patients, more than 50% did not receive formal treatment [5]. Improving the detection and diagnosis rates of PD will help to improve the quality of life and prognosis of patients [6].

The purpose of this study was to explore and summarize the characteristics of the motor symptoms and NMS in addition to investigating the reaction of drug-naïve patients with PD to dopaminergic treatment in Central China.

2. Participants and methods

2.1. Participants and clinical assessment

Patients diagnosed with possible PD were recruited as the "PD group" from the outpatient Department of Neurology at the Union Hospital Affiliated to Tongji Medical College of Wuhan Huazhong University of Science and Technology, one of the largest hospitals in Central China between January 2020 and July 2021. All participants with PD were evaluated by experienced neurologists before enrollment to ensure that they met the enrollment conditions of this study. Forty age-matched healthy individuals were recruited as the healthy control (HC) group from the neuropsychiatric examination center of the same hospital.

The inclusion criteria for the PD group were patients who: (1) were diagnosed with clinically probable PD according to the 2015 Movement Disorder Society (MDS) clinical diagnostic criteria for PD [7]; and (2) did not receive prior *anti*-PD medications (including levodopa, dopamine antagonists, catechol-*O*-methyl transferase inhibitors, or monoamine oxidase-B inhibitors). The exclusion criterion for both groups, PD and HC groups, was the presence of any primary neurological diseases (such as stroke, encephalitis, or brain tumor), other than PD.

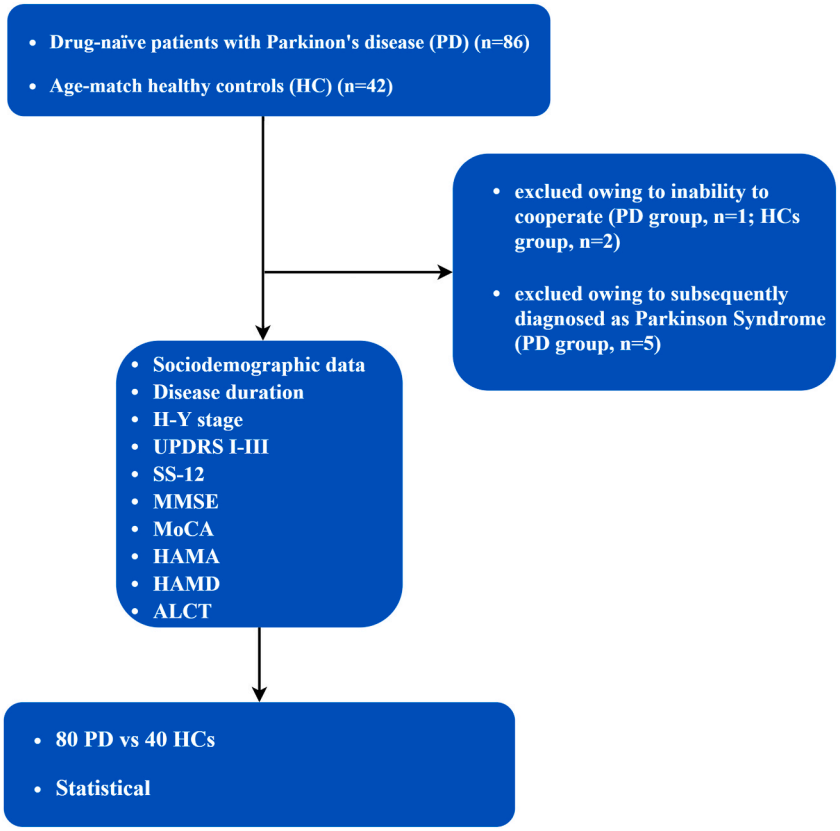

Fig. 1. Flow diagram of the study. Abbreviations: PD, Parkinson's disease; HCs, healthy controls; UPDRS, Unified Parkinson's Disease Rating Scale; SS-12, Sniffin' Sticks Screening 12 test; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MMSE, Mini-Mental State Exam; MoCA, Montreal Cognitive Assessment; ALCT, acute levodopa challenge test.

The motor symptoms were independently evaluated by two experienced neurologists using part I, II, and III of the Chinese versions of the Unified Parkinson's Disease Rating Scale 3.0 (UPDRS 3.0) and Hoehn-Yahr (H–Y) stage. The Sniffin' Sticks Screening 12 test [8] (SS-12) was used to examine the olfactory function. The Chinese version of Mini-Mental State Exam (MMSE), Montreal Cognitive Assessment (MoCA), Hamilton Anxiety Scale (HAMA), and Hamilton Depression Scale-24 (HAMD) were used to measure the general cognitive and psychomotor abilities of the participants. The whole procedure of the study is shown in Fig. 1.

The drug-naïve participants were grouped according to their response to dopaminergic therapy. The reactivity was determined by the acute levodopa challenge test (ALCT) which was conducted in the morning. Domperidone (10 mg) was prescribed 30 min before L-dopa to minimize the probable side effects. Drug-naïve participants were in the fasting state and 250 mg L-dopa (soluble preparation; Madopar LT, Roche Pharma AG, Basel, Switzerland) was prescribed. The UPDRS part III (motor section) was performed by two experienced physicians independently before L-dopa administration and, 30, 60, 90, and 120 min after L-dopa administration. All the assessments at the different time intervals were video recorded for re-evaluation.

2.2. Data processing

2.2.1. Database establishment

We used EpiData 3.1 to manage all clinical raw data. The private information (such as ID numbers and addresses) is not recorded in the database to protect the privacy of the participants.

2.2.2. Data post-processing

2.2.2.1. UPDRS. The score items were divided into tremor score (T) and akinetic-rigid score (AR) parentheses [9]. T was the sum of the average of items 16 and 20–26 and AR was the sum of the average of item 5, 7, 12–25, 18, 19, and 27–44. The T mainly reflects the tremor in the participants' daily life and physical examination, while the AR reflects the non-tremor movement disorders such as speech, swallowing, turning over in bed, falling, frozen gait, walking, facial expression, bradykinesia, fine movement, posture, gait, and stability in the participants' daily life activities.

2.2.2.2. MMSE. According to the contents of the scale items, the items were divided into 8 dimensions: orientation, short-term memory, attention and calculation, delayed recall, naming, language, visuospatial, and executive dimensions. The scoring rate of each dimension was calculated according to the actual score/expected score $\times$ 100 (%).

2.2.2.3. MoCA. According to the contents of the scale items, the items were divided into 8 dimensions: visuospatial and executive, naming, memory, attention, language, abstraction, delayed recall, and orientation. The scoring rate of each dimension was calculated according to the actual score/expected score $\times$ 100 (%).

2.2.2.4. HAMA. According to the total score, the anxiety status of the participants was graded into five levels: no anxiety (score $\leq$6 points), possible anxiety (7 points $\leq$ score $<$ 14 points), positive anxiety (14 points $\leq$ score $<$ 21 points), obvious anxiety (21 points $\leq$ score $<$ 29 points) and severe anxiety (score $\geq$29 points). According to the symptoms, the items were divided into two dimensions: somatic anxiety and psychic anxiety.

2.2.2.5. HAMD-24. According to the total score, the depression status of the participants was classified into four levels: no depression (score $<$ 8), mild depression (8 $\leq$ score $<$ 19), moderate depression (20 $\leq$ score $<$ 34), and severe depression (score $\geq$35) [10,11]. According to the contents of the scale items, the items were divided into 8 dimensions: anxiety & somatization, weight, cognitive dysfunction, diurnal variation, retardation, sleep disorders, and despair.

2.2.2.6. ALCT. According to each item of UPDRS III, the scores were divided into four sub-scores: tremor sub-score (items 20 and 21), rigidity sub-score (item 22), bradykinesia sub-score (items 23–26), and axial sub-score (items 18, 19, and 27–31) [12]. The improvement rates at each timepoint were calculated. According to the rate of improvement at 120 min, patients were divided into two subgroups: levodopa good response group ($\geq$30%) and levodopa poor response group ($<$30%) [7].

2.2.3. Statistical analysis

SPSS 23.0 was used for statistical analysis. An independent sample Student's *t*-test was used to evaluate the statistical significance of the clinical data between the PD and HC groups ($\alpha = 0.05$).

3. Results

3.1. Sociodemographic and clinical data

A total of 80 participants in the PD group and 40 in the HC group were included in this study. All participants completed the process as required and achieved reliable results.

The sociodemographic and clinical data of the two groups are shown in Table 1. There were no significant statistical differences in

age, gender and educational year between the PD and HC groups. However, there were significant statistical differences in the scores of cognitive scales (MMSE, MoCA) and depression and anxiety scale (HAMA, HAMD) between the two groups ($p < 0.05$), indicating that the participants in the PD group have obvious cognitive impairment and higher level of depression and anxiety compared with those in the HC group.

The first symptoms of PD are shown in Fig. 2a. The mean score of UPDRS I, II, and III in the PD group were 2.01 ± 1.90, 6.18 ± 3.68, and 26.13 ± 12.09, respectively. The mean T score was 0.55 ± 0.47 and the mean AR score was 0.95 ± 0.47, while the mean T/AR was 0.81 ± 0.95. Detailed scores of UPDRS are shown in supplementary Table 1.

The results of the SS-12 are shown in Fig. 2b. The results of the dimensional analysis of MMSE and MoCA are shown in Fig. 2c and e, respectively.

The participants in the PD group had more obvious anxiety level (mean HAMA score = 11.26 ± 7.64) than did those in the HC group (mean HAMA score = 5.55 ± 4.5, $p < 0.001$). The grading results showed that 43% of the participants with PD had no anxiety, 20% had possible anxiety, 21% had definite anxiety, and 16% had obvious or serious anxiety. The dimensional analysis showed that psychic anxiety was more serious than somatic anxiety among the patients (Fig. 2d and g).

The participants in the PD group had a more significant level of depression (mean HAMD score = 12.48 ± 9.18) than did those in the HC group (mean HAMD score = 7.95 ± 6.00, $p < 0.01$). The grading results showed that 37% of the patients had no depression, 31% might have had depression, 19% had definite depression, and 13% had severe depression.

The dimensional analysis showed that the score of anxiety/somatization factor was the highest among depressed participants followed by retardation and despair. Among the participants with definite depression, the score of anxiety/somatization factor was the highest, followed by sleep disorder and despair (Fig. 2f and h).

3.2. Acute levodopa challenge test

According to the improvement rate at 2 h after medication, 54 patients showed good responses to levodopa (>30%) while 26 patients did not (<30%), Indicating that about two thirds (54/80) of patients with early PD showed good responses to levodopa. Therefore, the PD group was divided into two subgroups: good response group (54 patients) and poor response group (26 patients) for further analysis. The UPDRS III baseline scores were 26.03 ± 12.20 (all patients), 24.49 ± 11.51 (good response group), and 29.07 ± 13.13 (poor response group), while the mean scores at 120 min were 17.63 ± 10.22 (all patients), 14.28 ± 7.62 (good response group), 24.21 ± 11.54 (poor response group). Fig. 3 shows the changes in UPDRS III after levodopa intake of all PD patients (Fig. 3a), good response group (Fig. 3c) and poor response group (Fig. 3e).

Among the four sub-scores, the best response to levodopa was observed with the bradykinesia sub-score at 120 min and the worst was observed with the axial sub-score. Detailed changes are shown in Fig. 3b (all PD patients), Fig. 3d (good response group) and Fig. 3f (poor response group).

4. Discussion

This study included 80 patients with early PD in Central China. The average age of onset was 59.96 ± 10.4, which was consistent with what has been reported in similar studies (62 ± 10) [13]. We investigated the motor symptoms, NMS, and reactions to

Table 1
The sociodemographic and clinical data of PD and HC.

	PD (n = 80)		HC (n = 40)		p	t
	Mean	SD	Mean	SD		
Age (years old)	61.36	10.44	61.65	8.54	0.881	−0.15
Disease duration (months)	16.69	13.40	–	–		
Age at onset	59.96	10.40	–	–		
Gender (Male:Female)	37:43	–	21:19	–	0.522	0.642
Educational Years	8.77	4.20	8.88	4.42	0.904	−0.12
UPDRS I	2.01	1.90	–	–		
UPDRS II	6.18	3.68	–	–		
UPDRS III	26.13	12.09	–	–		
H–Y stage	1.58	0.61	–	–		
Tremor score (T)	0.55	0.47	–	–		
Akinetic-Rigid score (AR)	0.95	0.47	–	–		
T/AR	0.81	0.95	–	–		
self-perceptive olfactory[a]	48:31:1	–	–	–		
Actual olfactory[a]	3:39:38	–	–	–		
MMSE	24.28	4.01	25.98	2.95	0.019	−2.38
MoCA	18.33	5.80	23.68	4.49	<0.001	−5.11
HAMA	11.26	7.64	5.55	4.5	<0.001	4.36
HAMD	12.48	9.18	7.95	6	0.006	2.82

Abbreviations: PD, Parkinson's disease; HC, healthy controls; UPDRS, Unified Parkinson's Disease Rating Scale; H–Y stage, Hoehn-Yahr Stage; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MMSE, Mini-Mental State Exam; MoCA, Montreal Cognitive Assessment.

[a] data is shown as euosmia: hyposmia: anosmia.

Fig. 2. The clinical data of PD group. (a) The distribution of onset symptoms in PD; (b) The result of SS-12; (c) Scoring rate of MMSE domain; (d) The result of HAMA scale in PD group; (e) Scoring rate of MoCA domain; (f) The anxiety status of PD group; (g) The distribution of HAMA domain; (h) The distribution of HAMD-24 domain.

dopaminergic therapy of drug-naïve patients with early PD. We revealed that in early PD, the NMS could be diverse and complicated compared to the motor symptoms. We also described the features of variety in UPDRS III scores after the administration of levodopa medication.

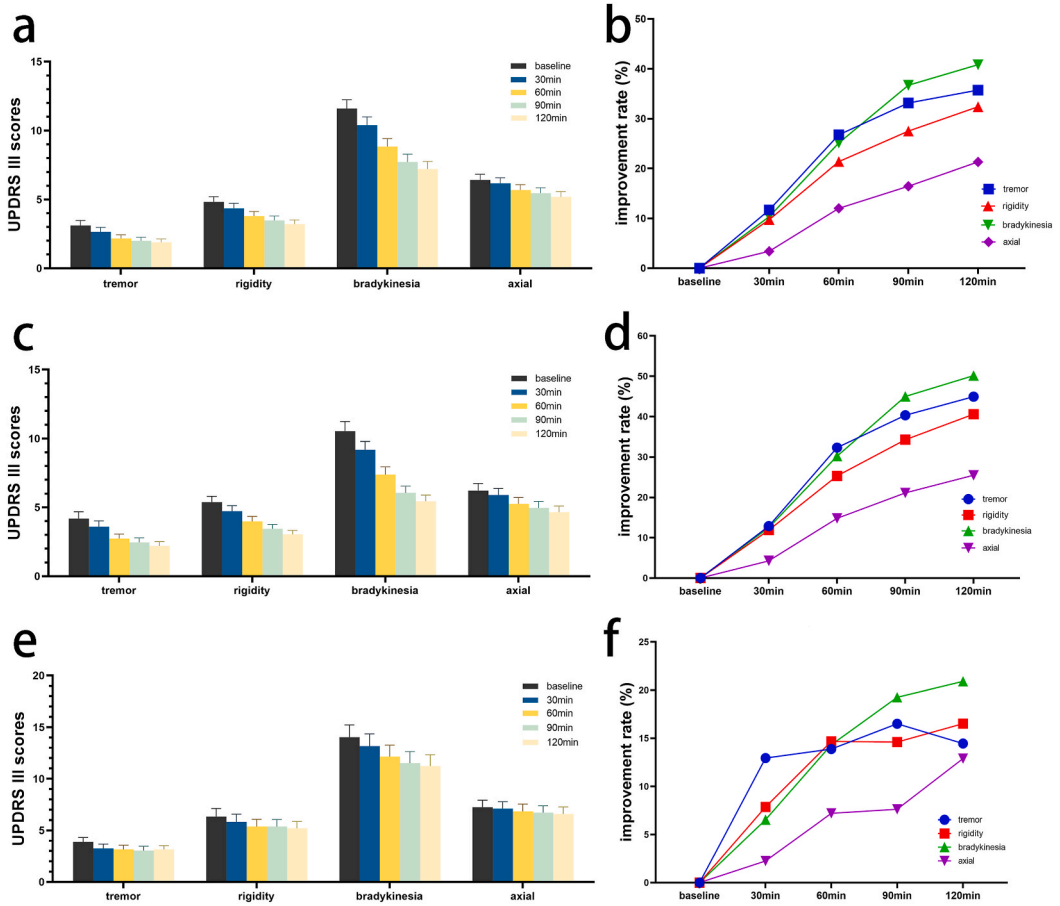

Fig. 3. The improvement of PD-related motor symptoms after acute levodopa challenge test. (a, b) The improvement of UPDRS III score and improvement rate of all patients with PD. (c, d) The improvement of UPDRS III score and improvement rate of patients with PD in levodopa good response group. (e, f) The improvement of UPDRS III score and improvement rate of patients with PD in levodopa poor response group.

4.1. Motor symptoms of early PD

Traditional motor symptoms of PD included rest tremor, rigidity and bradykinesia. Currently, the diagnostic criteria for the prodromal stage of PD are absent, and the diagnosis of PD mainly depends on the motor symptoms. Improving the recognition rate of motor symptoms in early PD may be helpful to increase the diagnostic rate of early PD.

Among the participants included in the study, the most common first symptoms of PD were motor dysfunctions, especially tremor. A study about early PD patients showed that tremors, stiffness and rigidity, and fatigue were the most common symptoms in early PD [14]. However, the T/AR ratio in our study showed that ankylosis and bradykinesia were more serious than tremors, suggesting that their development was masked and thus not perceived by the patients. Accordingly, clinicians should pay more attention to ankylosis and bradykinesia in early PD.

A few patients with early PD presented subtle motor dysfunction, leading to delayed diagnosis of PD [15]. Here we listed the score of each item of the UPDRS score in supplementary Table 1 with the aim of unravelling the motor symptoms, other than tremors, that are easy to be detected in PD. The mean score of the finger tapping test was the highest, followed by facial expression, body bradykinesia, and hypokinesia. Finger tapping test is an easy way for primary screening PD. Compared with healthy controls, drug-naïve patients with early PD showed worse performance on finger tapping test [16]. But due to the mild motor symptoms of early PD, it is sometimes difficult to detect the subtle motor dysfunction. Recently, wearable devices were applied to evaluate the motor symptoms of PD, which can quantitatively analyze different motor symptoms and improve the detection rate of early PD [17]. A study using wearable devices assessed the motor disorders in patients with early PD and found a strong correlation between some movement features and UPDRS scores [18]. Investigating those characteristic motor symptoms of PD may help physicians in grassroot hospitals who have insufficient clinical experience with movement disorders to improve the diagnosis rate of PD.

Motor symptoms may also affect NMS of PD patients. Patients with postural instability and gait disorder subtype suffered more severe sleep disorders, fatigue, and urinary disturbance compared with patients with the tremor-dominant subtype [19]. This suggested that motor symptoms can predict the NMS.

4.2. NMS in early PD

Recently, the NMS of PD have become more noticeable. The most common NMS include olfactory dysfunction, constipation, sleep disorders, depression, anxiety, and dysfunction of the autonomic neurons. Since the NMS occur in the prodromal period of PD, previous studies predicted the onset of PD through the NMS. However, it is difficult to predict PD through investigating a single NMS due to the absence of specificity and low prevalence of these symptoms [20]. Our study explored the characteristics of olfactory impairment, cognitive impairment, and mood dysfunction in the early phase of PD.

4.2.1. Olfactory dysfunction

Olfactory disorders are among the most common and earliest NMS of PD [21]. The olfactory function of drug-naïve patients with PD which was tested by SS-12 revealed that up to 97% of the patients had hyposmia or anosmia. Remarkably, up to 80% of the participants were not aware of their olfactory disorder, which showed that it was hidden.

The occurrence of olfactory disorder may be related to the susceptibility of the olfactory bulb to Lewy bodies [22]. In the autopsy of patients with PD who had a long course of the disease, it was found that the number of neurons in the anterior olfactory nucleus were significantly decreased and the olfactory nerves were severely atrophied [23]. This susceptibility also explains the development of olfactory disorders in the prodromal stage of PD. The presence of olfactory dysfunctions may be used in the clinical prediction of PD. A prospective study reported that patients with dysosmia had a 3.94-fold higher probability of developing PD [24].

4.2.2. Cognitive dysfunction

We assessed the cognitive function of the PD and HC groups by MMSE and MoCA. The PD group showed a statistically lower performance on both cognitive function scales than that in the HC group. This finding goes in line with previous studies which reported that drug-naïve patients with PD suffered from cognitive impairment [25,26]. However, the cognitive scale score of the participants in this study was lower than that in similar studies. This may be attributed to the smaller number of educational years spent by the included participants compared to a previous study [25].

According to the dimensional analysis, the patients had impairments in abstract ability, visuospatial and executive power, and delayed recall, but the orientation was basically intact, which was similar to previous report [27]. More than 50% of the patients with PD in this study reported subjective cognitive impairment (SCD). Although there is not an effective way to evaluate SCD, it may be one of the risk factors for the development of PD-related cognitive impairment.

According to the guideline of MDS [28], PD cognitive impairment can be classified into PD mild cognitive impairment (PD-MCI) and PD dementia (PDD). If the cognitive impairment affects the daily life activities such as the social role, social function, and self-care ability, it can be classified as PDD. There are some difficulties in the classification of some cases. The participants in this study were not classified. In addition, due to the cross-sectional design of this study, there is a lack of data on the dynamic changes of participants, which can provide evidence regarding the development of cognitive impairment.

There are variations in the clinical manifestations of the PD-related cognitive impairment, which suggests that there may be different underlying pathological processes. Autopsy showed that the deposition of Lewy bodies in the limbic system and cortex was the pathological feature of cognitive impairment. In addition, the deposition of β- Amyloid and tau proteins found in the brain of some patients was associated with PDD. Lewy bodies, β- Amyloid, and tau proteins can collectively cause more serious and faster cognitive impairment and PD progression [29,30].

4.2.3. Mood disorders

Anxiety and depression are often evaluated together and usually exist as comorbid condition [31]. Our study assessed the levels of depression and anxiety in patients with PD by HAMA and HAMD. Although depression or anxiety could not be diagnosed based on two scales, we could evaluate the status of depression and anxiety and the possible sources of emotional disorders from the score distribution of the scales.

Previous studies on anxiety in patients with PD reported that the incidence rate of anxiety was 10.6%–55% [32,33]. Our study revealed that the incidence of psychic anxiety was higher than that of somatic anxiety in most participants; thus, psychic anxiety should be examined more than somatic discomfort in patients with PD. In terms of depression, the positive dimensions of participants with depression were anxiety and somatization, despair, sleep disorders, and retardation. For participants who may have had depression, the positive dimensions were anxiety and somatization, sleep disorders, diurnal variation, and weight loss. When dealing with patients who suffer from emotional disorders, physicians should thoroughly examine these dimensions to alleviate the emotional disorders.

Mood disorders affect the patients' quality of life to a large extent. Previous studies reported that patients with mood disorders have lower quality of life [33,34]. In addition to the quality of life, mood disorders can also affect the patients' social function, deterioration of cognitive functions, increase the disability rate [35], and can even lead to mortality.

4.3. ALCT in drug-naïve patients with PD

ALCT reflected the short-term response of patients to levodopa, which was induced by the increased plasma level of levodopa [36]. After administration of levodopa, the improvement in the movement disorder changes in accordance with the drug plasma concentration. Levodopa has special pharmacokinetic characteristics, and it is mainly absorbed in the upper part of the small intestine. According to the drug specification of doxazide tablets (Medoba) used in this study, the plasma concentration of levodopa reaches its

peak about 60 min after taking the drug, and its half-life is about 90 min. In previous studies, levodopa began to exert its therapeutic effects when the improvement rate of the UPDRS III reached 15% [37]. According to our data, levodopa began exerting its effects within 30–60 min after the intake.

Some studies considered 60–90 min after the intake of levodopa as the final evaluation time point [38]. However, the movement disorders may show further improvement 90 min after the intake of the medication. Accordingly, the end point of observation chosen in this study was 120 min after the intake of levodopa. The extent of improvement in UPDRS III was higher 120 min after the drug intake, although the plasma concentration of levodopa begins to decrease 120 min after the drug intake from the pharmacokinetic perspective. This can be due to a probable delayed effect of levodopa on the nervous system.

A good response to levodopa therapy is one of the criteria that supports the diagnosis of PD. We set the cut-off value for the improvement rate as 30%, as reported in a previous study [39]. For patients with early PD, the cut-off value may be too low to distinguish, resulting in an increased rate of false-positive results. A study which verified the validity of ALCT in the diagnosis of early PD through a 2-year follow-up, concluded that the cut-off value of 33% had 70% sensitivity and 71% specificity rates [38]. This study also demonstrated that the specificity and sensitivity rates can be increased to 91% and 79%, respectively, if combined with patients' other clinical history. A few patients with PD showed negative ALCT results. The possible reasons are: (1) the poor absorption of levodopa by the patients leading to low drug concentration in serum; (2) patients' symptoms were mainly axial symptoms which have a poor response to ALCT; or (3) patients' symptoms were very mild and thus, the UPDRS III score was very low (<5 points), resulting in difficulties identifying an improvement of the symptoms by ALCT.

4.4. Limitations

There are some limitations to this study. First, the NMS scale was not adopted because it was not advantageous with respect to the dimensional analysis in cognitive dysfunction and mood disorders. Second, this was a single-center study, which may have neglected some patients. Third, the misdiagnosis rate of early PD is high. Although we excluded the non-PD participants to a large extent, a few non-PD participants might have affected the results of the study due to the lack of longitudinal data.

4.5. Conclusion and prospects

In conclusion, the mean age of onset of PD was similar to that reported in the previous studies. However, the time from the development of symptoms to the clinic visit was longer, which may explain the more serious motor symptoms of the patients in our study. The motor symptoms of patients with early PD were mild but virous. They also suffered from different non-motor symptoms. The proportion of emotional disorders and cognitive impairment such as the delayed recall, visuospatial and executive ability, and abstract ability was high in the included patients. In ALCT, most patients with early PD showed good response to levodopa. Among four aspects of motor symptoms, bradykinesia reacted best to ALCT while axial symptoms were the worst.

In future, we will recruit more patients with drug naïve PD and continue the follow-up study of the cohort. We are looking forward to finding biomarkers that can predict disease onset and progression of PD.

Ethics statement

The study was approved by the Medical Ethics Committee of Tongji Medical College, Huazhong University of science and technology ([2020]S253). All the participants provided informed consent prior to participating in the study.

Author contribution statement

Weiqi Zeng: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Yukai Wang: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

Ling Liu: Performed the experiments; Wrote the paper.

Yi Wu, Yu Xu, Heng Zhai, Xiaoman Yang: Performed the experiments.

Xuebing Cao, Yan Xu: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

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.

.

Acknowledgments

including sources of support

This study was supported by Guangdong Basic and Applied Basic Research Foundation (2022A1515111015), and The National Natural Science Foundation of China (81974200, 81873734, 81701673, 81701258). Funding acquisition was supported by W.Z., L.L., X.C., and Yan X.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e18081.

References

[1] C. Raza, R. Anjum, N.U.A. Shakeel, Parkinson's disease: mechanisms, translational models and management strategies, Life Sci. 226 (2019) 77–90, https://doi.org/10.1016/j.lfs.2019.03.057.
[2] S. Sveinbjornsdottir, The clinical symptoms of Parkinson's disease, J. Neurochem. 139 (Suppl 1) (2016) 318–324, https://doi.org/10.1111/jnc.13691.
[3] P.A. LeWitt, Levodopa therapy for Parkinson's disease: pharmacokinetics and pharmacodynamics, Mov. Disord. Off. J. Mov. Disord. Soc. 30 (2015) 64–72, https://doi.org/10.1002/mds.26082.
[4] T. Pringsheim, N. Jette, A. Frolkis, T.D.L. Steeves, The prevalence of Parkinson's disease: a systematic review and meta-analysis, Mov. Disord. Off. J. Mov. Disord. Soc. 29 (2014) 1583–1590, https://doi.org/10.1002/mds.25945.
[5] Z.-X. Zhang, G.C. Roman, Z. Hong, C.-B. Wu, Q.-M. Qu, J.-B. Huang, B. Zhou, Z.-P. Geng, J.-X. Wu, H.-B. Wen, H. Zhao, G.E.P. Zahner, Parkinson's disease in China: prevalence in beijing, xian, and shanghai, Lancet Lond. Engl. 365 (2005) 595–597, https://doi.org/10.1016/S0140-6736(05)17909-4.
[6] E. Tolosa, A. Garrido, S.W. Scholz, W. Poewe, Challenges in the diagnosis of Parkinson's disease, Lancet Neurol. 20 (2021) 385–397, https://doi.org/10.1016/S1474-4422(21)00030-2.
[7] R.B. Postuma, D. Berg, M. Stern, W. Poewe, C.W. Olanow, W. Oertel, J. Obeso, K. Marek, I. Litvan, A.E. Lang, G. Halliday, C.G. Goetz, T. Gasser, B. Dubois, P. Chan, B.R. Bloem, C.H. Adler, G. Deuschl, MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. Off. J. Mov. Disord. Soc. 30 (2015) 1591–1601, https://doi.org/10.1002/mds.26424.
[8] E.H. Pinkhardt, H. Liu, D. Ma, J. Chen, A. Pachollek, M.S. Kunz, J. Kassubek, A.C. Ludolph, Y. Huang, H. Chen, G.B. Landwehrmeyer, Z. Wang, W. Su, Olfactory screening of Parkinson's Disease patients and healthy subjects in China and Germany: a study of cross-cultural adaptation of the Sniffin' Sticks 12-identification test, PLoS One 14 (2019), e0224331, https://doi.org/10.1371/journal.pone.0224331.
[9] S.J.G. Lewis, T. Foltynie, A.D. Blackwell, T.W. Robbins, A.M. Owen, R.A. Barker, Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach, J. Neurol. Neurosurg. Psychiatry 76 (2005) 343–348, https://doi.org/10.1136/jnnp.2003.033530.
[10] J. Li, L.D. Oakley, R.L. Brown, Y. Li, Y. Luo, Properties of the early symptom measurement of post-stroke depression: concurrent criterion validity and cutoff scores, J. Nurs. Res. JNR. 28 (2020) e107, https://doi.org/10.1097/jnr.0000000000000380.
[11] S. Pan, Z.-W. Liu, S. Shi, X. Ma, W.-Q. Song, G.-C. Guan, Y. Zhang, S.-M. Zhu, F.-Q. Liu, B. Liu, Z.-G. Tang, J.-K. Wang, Y. Lv, Hamilton rating scale for depression-24 (HAM-D24) as a novel predictor for diabetic microvascular complications in type 2 diabetes mellitus patients, Psychiatr. Res. 258 (2017) 177–183, https://doi.org/10.1016/j.psychres.2017.07.050.
[12] L.K. Sahoo, V.V. Holla, D. Batra, S. Prasad, A. Bhattacharya, N. Kamble, R. Yadav, P.K. Pal, Comparison of effectiveness of trihexyphenidyl and levodopa on motor symptoms in Parkinson's disease, J. Neural Transm. Vienna Austria 127 (2020) (1996) 1599–1606, https://doi.org/10.1007/s00702-020-02257-0.
[13] J.-H. Kang, D.J. Irwin, A.S. Chen-Plotkin, A. Siderowf, C. Caspell, C.S. Coffey, T. Waligórska, P. Taylor, S. Pan, M. Frasier, K. Marek, K. Kieburtz, D. Jennings, T. Simuni, C.M. Tanner, A. Singleton, A.W. Toga, S. Chowdhury, B. Mollenhauer, J.Q. Trojanowski, L.M. Shaw, Parkinson's Progression Markers Initiative, Association of cerebrospinal fluid β-amyloid 1-42, T-tau, P-tau 181, and α-synuclein levels with clinical features of drug-naive patients with early Parkinson disease, JAMA Neurol. 70 (2013) 1277–1287, https://doi.org/10.1001/jamaneurol.2013.3861.
[14] H. Staunton, K. Kelly, L. Newton, M. Leddin, R. Rodriguez-Esteban, K.R. Chaudhuri, D. Weintraub, R.B. Postuma, P. Martinez-Martin, A patient-centered conceptual model of symptoms and their impact in early Parkinson's disease: a qualitative study, J. Park. Dis. 12 (2022) 137–151, https://doi.org/10.3233/JPD-202457.
[15] C.W. Hess, M.S. Okun, Diagnosing Parkinson disease, Contin. Minneap. Minn. 22 (2016) 1047–1063, https://doi.org/10.1212/CON.0000000000000345.
[16] C.A. Haaxma, B.R. Bloem, S. Overeem, G.F. Borm, M.W.I.M. Horstink, Timed motor tests can detect subtle motor dysfunction in early Parkinson's disease, Mov. Disord. Off. J. Mov. Disord. Soc. 25 (2010) 1150–1156, https://doi.org/10.1002/mds.23100.
[17] R. Lu, Y. Xu, X. Li, Y. Fan, W. Zeng, Y. Tan, K. Ren, W. Chen, X. Cao, Evaluation of wearable sensor devices in Parkinson's disease: a review of current status and future prospects, Park. Dis. 2020 (2020), 4693019, https://doi.org/10.1155/2020/4693019.
[18] M. Ricci, G. Di Lazzaro, A. Pisani, N.B. Mercuri, F. Giannini, G. Saggio, Assessment of motor impairments in early untreated Parkinson's disease patients: the wearable electronics impact, IEEE J. Biomed. Health Inform. 24 (2020) 120–130, https://doi.org/10.1109/JBHI.2019.2903627.
[19] X. Huang, S.Y.-E. Ng, N.S.-Y. Chia, F. Setiawan, K.-Y. Tay, W.-L. Au, E.-K. Tan, L.C.-S. Tan, Non-motor symptoms in early Parkinson's disease with different motor subtypes and their associations with quality of life, Eur. J. Neurol. 26 (2019) 400–406, https://doi.org/10.1111/ene.13803.
[20] N. Visanji, C. Marras, The relevance of pre-motor symptoms in Parkinson's disease, Expert Rev. Neurother. 15 (2015) 1205–1217, https://doi.org/10.1586/14737175.2015.1083423.
[21] R.L. Doty, D.A. Deems, S. Stellar, Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration, Neurology 38 (1988) 1237–1244, https://doi.org/10.1212/wnl.38.8.1237.
[22] T.G. Beach, C.H. Adler, L. Lue, L.I. Sue, J. Bachalakuri, J. Henry-Watson, J. Sasse, S. Boyer, S. Shirohi, R. Brooks, J. Eschbacher, C.L. White, H. Akiyama, J. Caviness, H.A. Shill, D.J. Connor, M.N. Sabbagh, D.G. Walker, Arizona Parkinson's Disease Consortium, Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction, Acta Neuropathol. 117 (2009) 613–634, https://doi.org/10.1007/s00401-009-0538-8.
[23] R.K. Pearce, C.H. Hawkes, S.E. Daniel, The anterior olfactory nucleus in Parkinson's disease, Mov. Disord. Off. J. Mov. Disord. Soc. 10 (1995) 283–287, https://doi.org/10.1002/mds.870100309.
[24] D. Berg, K. Marek, G.W. Ross, W. Poewe, Defining at-risk populations for Parkinson's disease: lessons from ongoing studies, Mov. Disord. Off. J. Mov. Disord. Soc. 27 (2012) 656–665, https://doi.org/10.1002/mds.24985.
[25] D. Muslimovic, B. Post, J.D. Speelman, B. Schmand, Cognitive profile of patients with newly diagnosed Parkinson disease, Neurology 65 (2005) 1239–1245, https://doi.org/10.1212/01.wnl.0000180516.69442.95.
[26] D. Muslimović, B. Post, J.D. Speelman, R.J. De Haan, B. Schmand, Cognitive decline in Parkinson's disease: a prospective longitudinal study, J. Int. Neuropsychol. Soc. JINS. 15 (2009) 426–437, https://doi.org/10.1017/S1355617709090614.
[27] M. Broeders, D.C. Velseboer, R. de Bie, J.D. Speelman, D. Muslimovic, B. Post, R. de Haan, B. Schmand, Cognitive change in newly-diagnosed patients with Parkinson's disease: a 5-year follow-up study, J. Int. Neuropsychol. Soc. JINS. 19 (2013) 695–708, https://doi.org/10.1017/S1355617713000295.

[28] M. Emre, D. Aarsland, R. Brown, D.J. Burn, C. Duyckaerts, Y. Mizuno, G.A. Broe, J. Cummings, D.W. Dickson, S. Gauthier, J. Goldman, C. Goetz, A. Korczyn, A. Lees, R. Levy, I. Litvan, I. McKeith, W. Olanow, W. Poewe, N. Quinn, C. Sampaio, E. Tolosa, B. Dubois, Clinical diagnostic criteria for dementia associated with Parkinson's disease, Mov. Disord. Off. J. Mov. Disord. Soc. 22 (2007) 1689–1707, https://doi.org/10.1002/mds.21507. ; quiz 1837.
[29] Y. Compta, L. Parkkinen, S.S. O'Sullivan, J. Vandrovcova, J.L. Holton, C. Collins, T. Lashley, C. Kallis, D.R. Williams, R. de Silva, A.J. Lees, T. Revesz, Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain J. Neurol. 134 (2011) 1493–1505, https://doi.org/10.1093/brain/awr031.
[30] D.R. Howlett, D. Whitfield, M. Johnson, J. Attems, J.T. O'Brien, D. Aarsland, M.K.P. Lai, J.H. Lee, C. Chen, C. Ballard, T. Hortobágyi, P.T. Francis, Regional multiple pathology scores are associated with cognitive decline in lewy body dementias, Brain Pathol. Zurich Switz. 25 (2015) 401–408, https://doi.org/10.1111/bpa.12182.
[31] M.A. Menza, L.I. Golbe, R.A. Cody, N.E. Forman, Dopamine-related personality traits in Parkinson's disease, Neurology 43 (1993) 505–508, https://doi.org/10.1212/wnl.43.3_part_1.505.
[32] Y.-H. Wu, Y.-C. Liao, Y.-H. Chen, M.-H. Chang, C.-H. Lin, Risk of premotor symptoms in patients with newly diagnosed PD: a nationwide, population-based, case-control study in Taiwan, PLoS One 10 (2015), e0130282, https://doi.org/10.1371/journal.pone.0130282.
[33] T. Yamanishi, H. Tachibana, M. Oguru, K. Matsui, K. Toda, B. Okuda, N. Oka, Anxiety and depression in patients with Parkinson's disease, Intern. Med. Tokyo Jpn. 52 (2013) 539–545, https://doi.org/10.2169/internalmedicine.52.8617.
[34] B. Müller, J. Assmus, K. Herlofson, J.P. Larsen, O.-B. Tysnes, Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease, Park. Relat. Disord. 19 (2013) 1027–1032, https://doi.org/10.1016/j.parkreldis.2013.07.010.
[35] D. Weintraub, P.J. Moberg, J.E. Duda, I.R. Katz, M.B. Stern, Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease, J. Am. Geriatr. Soc. 52 (2004) 784–788, https://doi.org/10.1111/j.1532-5415.2004.52219.x.
[36] E. Anderson, J. Nutt, The long-duration response to levodopa: phenomenology, potential mechanisms and clinical implications, Park. Relat. Disord. 17 (2011) 587–592, https://doi.org/10.1016/j.parkreldis.2011.03.014.
[37] C. Lucetti, C. Logi, P. Del Dotto, C. Berti, R. Ceravolo, F. Baldacci, C. Dolciotti, G. Gambaccini, G. Rossi, U. Bonuccelli, Levodopa response in dementia with lewy bodies: a 1-year follow-up study, Park. Relat. Disord. 16 (2010) 522–526, https://doi.org/10.1016/j.parkreldis.2010.06.004.
[38] S. Schade, F. Sixel-Döring, J. Ebentheuer, X. Schulz, C. Trenkwalder, B. Mollenhauer, Acute Levodopa Challenge Test in Patients with de novo Parkinson's Disease: data from the DeNoPa Cohort, Mov. Disord. Clin. Pract. 4 (2017) 755–762, https://doi.org/10.1002/mdc3.12511.
[39] M. Merello, M.I. Nouzeilles, G.P. Arce, R. Leiguarda, Accuracy of acute levodopa challenge for clinical prediction of sustained long-term levodopa response as a major criterion for idiopathic Parkinson's disease diagnosis, Mov. Disord. Off. J. Mov. Disord. Soc. 17 (2002) 795–798, https://doi.org/10.1002/mds.10123.