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Impact of COVID-19 Infection on Patients with Parkinson's Disease: A Cross-Sectional Study

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic seriously threatened global public health. Patients with Parkinson's disease (PwP) may also have been affected to different degrees in terms of symptoms, medication, medical treatment, and rehabilitation exercise.

Aims and objectives: This study aimed to portray the clinical changes in PwP during the COVID-19 outbreak and after the adjustment of China's epidemic prevention policy.

Design: Cross-sectional study.

Methods: This study enrolled previously diagnosed PwP and their family members or caregivers in China to complete an online survey, which included the following main sections: Sociodemographic information, viral infection status, changes in and prognosis of PD-related symptoms, medical treatment and drug purchases, etc.

Results: Among the 440 valid questionnaires collected from January 3, 2023 to April 10, 2023, 71.59% of those surveyed had COVID-19. The living conditions of PwP changed considerably before and after COVID-19 (P=0.014). 46.35% of patients felt that Parkinson's Disease (PD) symptoms worsened after COVID-19. The main manifestations were bradykinesia (67.81%), rigidity (54.11%), and tremors (47.00%). Additionally, nonmotor symptoms were involved, especially sleep disorders (32.00%), anxiety/depression (31.00%), and urinary and bowel disorders (39.72%). Symptoms usually worsened in the first week after infection. 69.00% PwP showed no relief from aggravated symptoms after COVID-19 recovery. At the same time, COVID-19 had a particular impact on patients' purchase of medicines and medical treatment.

Conclusion: COVID-19 seriously impacted the symptoms, living conditions, medicine purchases, and medical treatment of PwP. This study provides guidance for the treatment and management of PwP infected with COVID-19.

Keywords: Parkinson's disease; COVID-19; Impact; Online survey.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread to China and almost every country worldwide, which has led to considerable and unprecedented challenges for the delivery of healthcare with a clear impact on patients. These impacts occur directly through symptoms and morbidity caused by SARS-CoV-2 or indirectly through the effects of pandemic-related restrictions [1]. COVID-19 has several routes of transmis-

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sion, including direct transmission, contact transmission, aerosol transmission, and even faecal-oral transmission, and due to its robust rate of spread, many infections can occur in a short period and seriously impact the entire country [2,3]. The risk of COVID-19 and its mortality rate are very high in vulnerable populations, such as older adults with chronic diseases, especially those with neurological diseases [4]. Therefore, the focus of research has been shifting from the initial emphasis on symptomatology, morbidity, and mortality caused by SARS-CoV-2 to the interaction of the virus with preexisting diseases, such as movement disorders [1,5].

Parkinson's Disease (PD) is one of the most common neurological diseases in older adults. In addition to motor symptoms, such as bradykinesia, rigidity, tremors, and postural instability, nonmotor symptoms, such as depression, anxiety, sleep disorders, sensory disturbance, and autonomic dysfunction, are expected before motor symptoms appear until the advanced stages of the disease [6]. Thus, the changes and social conditions during the pandemic may have affected motor and nonmotor symptoms in Patients with Parkinson's disease (PwP) and worsened their quality of life [7]. Studies have shown that the COVID-19 pandemic has directly and indirectly affected PD patients worldwide in various ways [8,9]. Although there is no increased risk for PD in the general population, individuals infected with SARS-CoV-2 are more likely to experience worsening symptoms. It is unclear whether PwP may be at greater risk of death from COVID-19 [10]. Some have suggested that infection-induced changes in the role of dopaminergic neurotransmission may even lead to secondary neurodegenerative diseases [11].

Nevertheless, the relationship between COVID-19 and PD is likely to be much more complex than this, and many uncertainties remain. To prevent the spread of COVID-19, PwP have been limited in seeking medical treatment, surgical treatment has been delayed, and regular physical evaluations and medication adjustments in nonemergency situations have also become more complex [12]. At the same time, social, economic, and medical outcomes have led to profound changes in the lifestyles of PwP, including a decrease in overall physical activity, an inability to participate in exercise classes, and increased anxiety and depression [13].

In 2020, a large online study investigated the impact of the COVID-19 pandemic on PwP. Data were collected from 5429 PD patients with 51 reporting COVID-19 positive diagnoses in the US [14]. The significant effects of COVID-19 positivity on motor symptoms and nonmotor symptoms were revealed [14]. At the end of 2022, in light of the virus mutation, the Chinese government made major adjustments to the epidemic prevention policy. The infection rate of COVID-19 has increased significantly. With this change, the impact of COVID-19 on patients and other diseases has become a research hotspot. There is a lack of relevant research on this period. This study tried to investigate and analyze the status of PwP during the COVID-19 pandemic and after the adjustment of China's epidemic prevention policy. Its goal was to determine the prevalence of COVID-19 in PwP and its impact on the course of PD. So as to guide the formulation and follow-up of further personalized diagnosis and treatment of PwP.

Material and methods

Study design and participants

This was a cross-sectional study approved by the Medical Ethics Committee. Participants read and signed the informed consent form before completing the questionnaire. All procedures performed in this study involving human participants were in accordance with the ethical standards of the hospital, the national research committee, and the 1964 Declaration of Helsinki. The study methods complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

Previously diagnosed patients with idiopathic Parkinson's disease, their family members, and their caregivers in China were included in the survey, regardless of whether they were infected with COVID-19 or had other underlying conditions.

Variables and measurement

The online survey consisted of the following main sections:

(1) Sociodemographic characteristics of the participants (oneself, family member, caregiver), including sex, age, educational level, place of residence, and economic income.

(2) Personal information, including height (cm) and weight (kg).

(3) Disease-related information, including the time of onset of PD symptoms, time of first diagnosis of PD, current use of anti-Parkinson drugs (multiple choice of common anti-Parkinson drugs currently used in China), compliance (whether the participants took medicine regularly, how to adjust medication), combined underlying diseases (including cerebrovascular diseases, hypertension, coronary heart disease, diabetes, respiratory diseases, and others), and living conditions (mainly described according to different stages of the Hoehn and Yahr Scale: Level 1: Fully self-reliant; Level 2: Partially assisted; Level 3: Severely disabled but still able to stand or walk independently; and Level 4: Chronically confined to a wheelchair or bedridden).

(4) COVID-19-related information: COVID-19 vaccination status, reasons for not being vaccinated, changes in PD symptoms after vaccination, COVID-19 infection, severity of COVID-19 illness, time of diagnosis of COVID-19, method of diagnosis, temperature after infection, number of days fever lasted, symptoms after infection (multiple choice; fever, sore throat, dizziness, headache, tears, cough, expectoration, shortness of breath, palpitations, nausea, vomiting, abdominal pain, diarrhoea, hyposmia, dysgeusia, body aches and fatigue), drug use after COVID-19 infection (multiple choice; no medication, traditional Chinese medicine, antipyretic and analgesic drugs, cough and phlegm suppressant drugs, antibiotics, others), use of specific anti-COVID-19 drugs, recovery days after infection, recovery effect, whether anti-Parkinson' drugs were stopped or missed after COVID-19, whether PD symptoms were aggravated after disease and the aggravation symptoms (including motor symptoms and nonmotor symptoms), duration of aggravation, measures taken after disturbance and reasons for not taking measures (worry about side effects of combined medication, adjustment of drugs without doctor's guidance), whether PD symptoms were relieved after recovery from viral infection, living status after infection, influence of epidemic control policy adjustment on medical convenience, change in medical treatment method, impact on drug purchases, difficulty purchasing drugs, modification of drug price, drug purchase expenditure ratio, economic burden, and whether they participated in anti-Parkinson rehabilitation exercise.

Data collection and quality control

This was an online survey. We sent the link to the electronic questionnaire primarily through WeChat. Each respondent completed the survey anonymously. We set a restriction in the e-questionnaire link that only one WeChat IP could be used to complete the questionnaire to avoid repeat questionnaires. It took less than 20 minutes to answer the whole questionnaire.

Data analysis

All analyses were conducted using GraphPad Prism 9.5.1. Descriptive statistics are presented as frequencies and constituent ratios or means and standard deviations (*SDs*) according to the data type. T tests, chi-square tests, and Mann-Whitney-Wilcoxon tests were used for statistical analysis. A P value<0.05 was considered statistically significant.

Results

From 440 valid questionnaires collected between January 3, 2023, and April 10, 2023, a total of 171(38.86%) surveys were answered by PwP, 267(60.68%) by family members, and 2(0.45%) by caregivers (supplementary data. 1 A). The respondents came from 16 provinces, and most (70.23%) were from Shaanxi Province. The mean age of PwP was 63.75±10.35 years (ranging from 24 to 92 years), and 43.86% (n=193) were female. Sociodemographic data are shown in Table 1. The average answer time was 11.57 minutes.

The mean disease duration was 6.11±4.61 years (range: 0-23 years). The mean time of diagnosis was 4.56±4.13 years (range: 0-23 years). A total of 84.32% of patients took Parkinson's medication regularly. Among the respondents, 12.05% never performed rehabilitation exercises, 49.55% occasionally, and 38.41% regularly. A total of 49.32% of PwP had a drug expenditure ratio lower than 30%, 34.77% had a ratio between 30-50%, and 15.91% had a ratio greater than 50% (Table 1).

In the survey of the use of anti-Parkinson drugs, Madopar was used most frequently (87.27%), followed by pramipexole (45.45%) and trihexyphenidyl (23.41%). A total of 55.23% of the patients had no other underlying diseases, 24.32% had hypertension, and 12.73% had cardiovascular disease (supplementary data 1B).

Table 2 shows the data related to COVID-19. A total of 71.59% of those surveyed were infected with COVID-19. Most (88.89%) patients experienced symptom relief after taking drugs. 5.4% were asymptomatic, but 4.44% of the patients needed to be hospitalized for oxygen-assisted therapy. Of those infected, 57.14% were diagnosed with clinical symptoms. Others were diagnosed with Antigen tests or nucleic acid tests. Fever (70.16%) was the most common clinical manifestation. Most people (54.92%) had a low fever (37.1-38.5^{O}C), and fever mostly improved 1-3 days after infection (84.94%), followed by cough, expectoration, and shortness of breath, accounting for 60.43%. These symptoms were followed by sore throat (50.00%), fatigue (42.54%), aches and pains (37.00%), headache (26.98%), and dizziness (24.76%). In addition, 18.41% of people had hyposmia/dysgeusia, and 11.00% had palpitations. Nausea and vomiting (6.67%), tears (4.76%) and abdominal pain and diarrhoea (2.86%) were reported in a small number of cases. A total of 55.23% of the patients recovered within one week. A total of 73.02% of patients recovered from COVID-19 symptoms, and 26.03% improved (Table 2).

When PwP who had COVID-19 were compared with patients who did not, there were no significant differences in age, sex, duration of PD 'symptoms, years since PD 'diagnosis, lifestyle, comorbidities, frequency of rehabilitation exercises, or vaccination status (Table 3). A total of 63.86% of PwP completed the 3-dose vaccination. 85.91% of patients who received the vaccine reported no effect on PD symptoms (supplementary data. 2A,B).

We then surveyed changes in living conditions before and after COVID-19 infection according to different stages of the Hoehn and Yahr Scale, as described above. The living conditions of patients after infection were significantly worse than those before infection, with the number of people in level 1 decreasing and that in levels 2-4 increasing significantly (P=0.014 (< 0.05)). The chi-square test indicated that the living conditions of patients with PD were affected considerably after infection (Figure 1).

Next, we analysed the impact of COVID-19 infection on PD symptoms. A total of 87.62% of PwP still regularly took anti-Parkinson drugs after infection. In comparison, 12.38% of patients stopped taking or missed taking anti-Parkinson drugs after infection (Figure 2A). Madopar (77.50%) was stopped or missed the most, followed by pramipexole (25.00%). A total of 46.35% of patients experienced aggravated Parkinson-like symptoms after COVID-19 infection, including motor symptoms and nonmotor symptoms (Figure 2B). Motor symptoms included bradykinesia (67.81%), rigidity (54.11%), tremors (47.00%), freezing (34.00%), balance disturbance (25.00%), and dyskinesia (8.22%). Nonmotor symptoms included sleep disorder (32.00%), anxiety/depression (31.00%), frequent/urgent urination, incontinence (28.08%), aches (21.00%), anosmia (19.18%), memory impairment/dementia (16.44%), speech/pitch change (15.75%), constipation/faecal incontinence (11.64%), dyspnoea (12.00%), dysphagia (10.00%), and mental disorders (6.16%) (Figure 2C). The period of aggravation of Parkinson-like symptoms was mainly 1-7 days after infection (38.36%), 27.40% were aggravated for 7-14 days, and 19.18% worsened after recovering from COVID-19 (Figure 2D). Among the patients with aggravated Parkinson-like symptoms, 62.33% did not receive appropriate treatment. A total of 19.86% received proper therapy for COVID-19, and 18.00% adjusted their anti-Parkinson drugs (Figure 2E). After COVID-19 recovery, only 31.00% of patients experienced remission of PD symptoms, while 69.00% did not improve (Figure 2F).

We also investigated drug purchases and medical treatment among PwP during the COVID-19 pandemic. 61.82% of the patients believed that there was no difficulty buying drugs during the COVID-19 pandemic (Figure 3A). In the survey on the price of anti-Parkinson drugs, 42.73% thought that the price did not change during the COVID-19 pandemic, 40.23% did not pay attention to whether the price changed, and 15.00% thought that the price increased (Figure 3B). The majority of patients (76.36%) still chose to buy drugs in the hospital (Figure 3C), and 69.09% believed that the COVID-19 pandemic did not influence their drug-buying habits (Figure 3D). According to the intention survey, 89.55% of patients received outpatient treatment, and 32.05% received online medical treatment. A total of 63.18% hoped to buy medicine in the hospital, and 24.32% wished to purchase medicine in the pharmacy (Figure 3E,F).

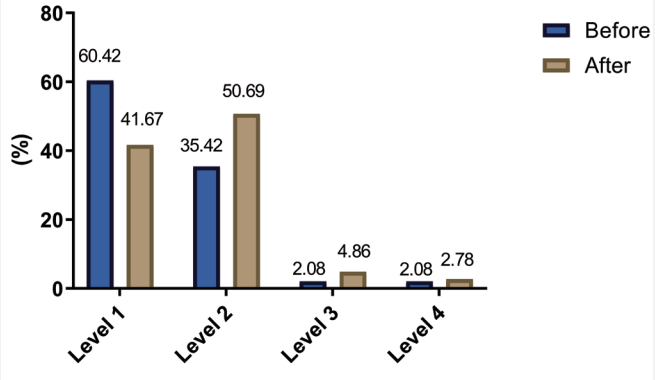

Figure 1: Influence on the living conditions of PwP before and after COVID-19 infection. Level 1: fully self-reliant; Level 2: partially assisted; Level 3: severely disabled but still able to stand or walk independently; Level 4: chronically confined to a wheelchair or bedridden.

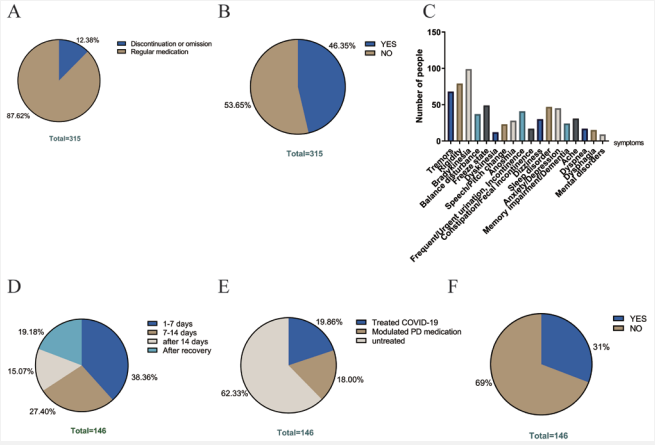

Figure 2: The impact of COVID-19 infection on PD. A Use of PD medication after contracting COVID-19. **B** Worsening of PD symptoms after COVID-19 infection. **C** Aggravation of PD symptoms after COVID-19 infection. **D** Time when symptoms worsened after infection with COVID-19. **E** Measures taken after the exacerbation of PD symptoms. **F** Alleviation of PD symptoms after COVID-19 recovery.

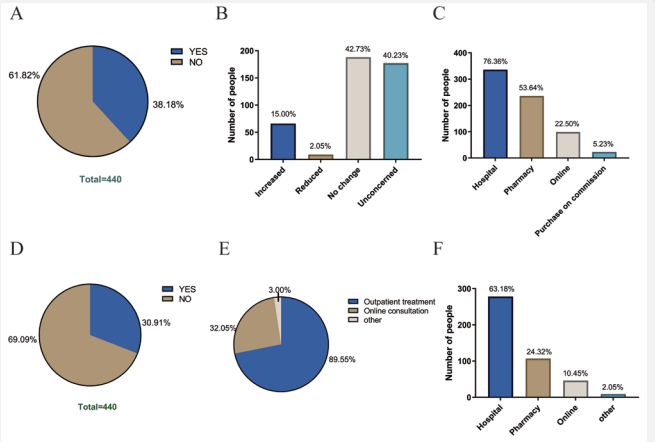

Figure 3: The impact of COVID-19 on drug purchases and medical treatment. A Difficulty in buying medicine for PD due to COVID-19. **B** Changes in drug prices for PD during COVID-19. **C** Current drug purchasing habits. **D** Changes in drug purchasing habits due to COVID-19. **E** Expected way of medical treatment. **F** Expected way of Drug purchase.

Table 1: Characteristics of the sample.

Demographic variables	Response options	Patients with PD (*n*=440)
Sex	Male Female	247(56.14%) 193(43.86%)
Age (yr)	-	63.75±10.35 years (range: 24–92 years)
Height	-	166.44±7.84 cm (range: 145-193 cm)
Weight	-	71.79±22.93 kg (range: 40-185 kg)
Educational level	Primary school and below Junior high school Senior high school Junior college Bachelor's degree or above	99(22.50%) 129(29.32%) 110(25.00%) 56(12.73%) 46(10.45%)
Duration of PD (yr)	-	6.11±4.61 years (range: 0-23 years)
Years since PD diagnosis (yr)	-	4.56±4.13 years (range: 0-23 years)
Regular medication	Yes No	371(84.32%) 69(15.68%)
Rehabilitation exercise	Never Occasionally Often	53(12.05%) 218(49.55%) 169(38.41%)
Drug expenditure ratio	<30% 30-50% >50%	217(49.32%) 153(34.77%) 70(15.91%)

Note. Mean ± SD.
Abbreviations: PD: Parkinson's disease.

Discussion

The adjustment of China's COVID-19 prevention and control policy at the end of 2022 has significantly impacted all aspects of society. In the face of the significant increase in the infection rate of COVID-19, the impact of the novel coronavirus on PwP has aroused our great attention. This study investigated the effect of epidemic prevention policies on PD 'patients during the COVID-19 outbreak and after adjusting China's epidemic prevention policies through a questionnaire. As China has a large population, this research is worthwhile and significant. Our study was carried out immediately after the policy adjustment and was advanced and innovative. The survey found that the quality of life of PwP significantly decreased after COVID-19 infection, and most patients had aggravation of motor and nonmotor symptoms after COVID-19 infection. In contrast, some patients showed no improvement in their aggravation of Parkinson-like symptoms with COVID-19 recovery. The COVID-19 pandemic has raised extensive concerns among neurologists, as influenza has long been considered a potential driver in PD pathogenesis [15,16]. Studies have linked influenza to an increased risk of Parkinson's disease. The COVID-19 mortality rate among PD patients is higher than that in the general elderly population. In addition, in the case of SARS-CoV-2 infection, PD patients are more likely to experience increased motor and nonmotor symptoms [17-19]. COVID-19 significantly worsened motor performance, motor-related disability, and daily living experiences. Worsening of levodopa-responsive motor symptoms and increased daily off time are caused either by acute systemic inflammatory response or changes in pharmacokinetics [20]. Among the changes in nonmotor symptoms, the increase

Table 2: COVID-19 infection.

	Response options	Patients with PD
Infected with COVID-19?	Yes No	315(71.59%) 125(28.41%)
Severity	Asymptomatic Spontaneous remission by taking drugs Hospitalization, no oxygen therapy Hospitalization, oxygen therapy Hospitalization, ventilation Death	17(5.40%) 280(88.89%) 4(1.27%) 14(4.44%) 0(0%) 0(0%)
COVID-19 confirmation methods	Nucleic acid test positive Antigen test positive Symptom diagnosis	62(19.68%) 73(23.17%) 180(57.14%)
Body temperature	Normal ≤36.5 °C 37.1-38.5 °C >38.5 °C	76(24.13%) 11(3.00%) 173(54.92%) 55(17.46%)
Duration of fever	1-3 days 3-6 days >6 days	203(84.94%) 26(10.88%) 10(4.18%)
Main symptom	Fever Cough, expectoration, shortness of breath Sore throat Fatigue Aches and pains Headache Dizziness Hyposmia, dysgeusia Palpitations Nausea, vomit Tears Abdominal pain, diarrhoea	70.16% 60.43% 50.00% 42.54% 37.00% 26.98% 24.76% 18.41% 11.00% 6.67% 4.76% 2.86%
Recovery days	1-3 days 4-7 days 8-14 days >14 days	46(14.60%) 128(40.63%) 90(28.57%) 51(16.19%)
Recovery condition	Recovered well Improved Exacerbated Death from illness	230(73.02%) 82(26.03%) 3(0.95%) 0(0%)

Note. Mean ± SD.

Table 3: Symptoms related to PD and other comorbidities.

	Patients with COVID-19 (n = 315)	Non-COVID-19 patients (n = 25)	P (patients with COVID-19 vs. non-COVID-19 patients)
Age (yr)	63.46±10.19	64.50±10.71	0.344
Sex (%) Male Female	 56.51 43.49	 55.20 44.80	0.832
Duration of PD (yr)	6.09±4.53	6.16±4.81	0.884
Years since PD diagnosis (yr)	4.50±3.97	4.71±4.49	0.621
Hoehn and Yahr Scale (%) Level 1 Level 2 Level 3 Level 4	 63.81 31.75 3.17 1.27	 54.40 40.00 3.20 2.40	0.071
Comorbidities (%) None Cerebrovascular disease Hypertension Coronary heart disease	 51.75 13.97 26.67 6.98	 61.60 8.80 16.80 10.40	0.055

Diabetes	11.75	5.60	
Respiratory diseases	4.44	5.60	
Other	8.25	6.40	
Rehabilitation exercise (%)			
Never	11.11	15.20	0.101
Sometimes	47.94	54.40	
Often	40.95	30.40	
COVID-19 vaccination (%)			
Unvaccinated	15.56	20.00	
1 dose	5.71	2.40	0.677
2 doses	14.92	11.20	
3 doses	63.49	64.00	
4 doses	0.32	2.40	

Note. The results represent the means ± standard deviations or percentages (%). Chi-square and Mann–Whitney-Wilcoxon tests were applied.
Abbreviations: PD: Parkinson's disease; COVID-19: coronavirus disease 2019.

in fatigue in our study was entirely explained by COVID-19, confirming that it is a common symptom of COVID-19 as described in PD after systemic inflammation [21,22]. The increase in other nonmotor symptoms may have been related to infection, fluctuation of motor symptoms, and pharmacokinetics. α-synuclein aggregation is the most critical driver in PD development. Recent studies have reported that the SARS-CoV-2 protein can directly interact with α-syn to accelerate the formation of α-syn aggregates [23]. The short- and long-term impact of COVID-19 on PD was demonstrated in rodent models, in which neuronal loss and microglial activation were more severe in PD mice infected and recovered from SARS-CoV-2 infection [24]. Angiotensin-converting enzyme 2(ACE2) receptors are highly expressed in dopamine neurons and are decreased in PD due to a degenerative process. Thus, brain penetration associated with SARS-CoV-2 may cause additional harm, worsen symptoms, and increase the requirement for dopamine replacement therapy [25]. Interestingly, the ability of SARS-CoV-2 to enter the brain through the nasal cavity determined anosmia/hyposmia in many infected subjects, a symptom very similar to one of the most prominent preexercise symptoms of PD [26]. In addition, we investigated the situation and willingness of patients to adjust drugs, seek medical treatment, and purchase medications after COVID-19 infection, which further suggested the necessity of whole-process management and personalized diagnosis and treatment for PD 'patients.

Limitations

Our study has several limitations. First, the main limitation of this study was that it was a single-centre study with a small cohort of COVID-19 patients. Second, consecutive PwP and their caregivers who agreed to participate in the survey at our outpatient clinic were included, but the possibility of selection bias cannot be ruled out. Third, as a quantitative survey, our questionnaire was unable to fully explore how patients had been affected. Moreover, changes in motor symptoms after the outbreak of COVID-19 were assessed with a questionnaire and not a clinical examination by neurologists, which may have resulted in underestimation or overestimation.

Conclusion

This study demonstrated that COVID-19 brought about changes in clinical symptoms, prognoses, and medical treatments for PwP in China. These results showed that, as a special population, it is important for PD patients to strengthen the prevention of viral infection, undergo vaccination, complete management, and receive personalized treatment.

Strengths and limitations of this study

At the end of 2022, China made significant prevention and control policy adjustments for COVID-19, resulting in a dramatic increase in COVID-19 cases. The number of infections in well-protected PwP had surged, and the impacts of COVID-19 on special populations had attracted our attention. The timely initiation of our investigation has positive implications for the management of PD.

Our study has several limitations. First, the main limitation of this study was that it was a single-centre study with a small cohort of COVID-19 patients. Second, consecutive PwP and their caregivers who agreed to participate in the survey at our outpatient clinic were included, but the possibility of selection bias cannot be ruled out. Third, as a quantitative survey, our questionnaire was unable to fully explore how patients had been affected. Moreover, changes in motor symptoms after the outbreak of COVID-19 were assessed with a questionnaire and not a clinical examination by neurologists, which may have resulted in underestimation or overestimation.

Relevance for clinical practice

This study highlighted the changes in clinical symptoms, living conditions, and drug use of PD patients before and after infection with COVID-19. This study investigated the situation of COVID-19 infection, vaccination, medical treatment, and drug purchases to improve clinicians' awareness of post-COVID-19 PD and to make recommendations on diagnosis, treatment, and management strategies.

Declarations

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Conflicts of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Dataset/data availability statement: The data supporting the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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