

Longitudinal analysis of circadian rhythm and Parkinson's disease; findings from longitudinal analysis of the PHASE study during the recurrent COVID-19 pandemics

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Abstract

No longitudinal study over several years has assessed the fluctuation of neuropsychiatric symptoms during the COVID-19 pandemic using the same scale. These non-motor symptoms are closely related with circadian rhythm, especially in mood or depression. The purpose of this study was to assess changes per year of these non-motor symptoms across a longer four-year period, spanning the COVID-19 pandemic in enrolled patients with Parkinson's disease (PD) of the PHASE study (Parkinson's disease and the relationships with circadian biological rhythms and sleep). We launched a questionnaire survey in 202 PD patients who were enrolled in the PHASE study. Both the preliminary 1-year of second cohort (n = 41) and longitudinal 4-year survey of first and second cohort (n = 202) including the duration after the category of infection was lowered to category 5 showed a trends in increasing depression. The specific fatigue scale for PD worsened during the COVID-19 pandemics and persisted even when category of infection was lowered to category 5, meaning that individuals are going back to living their lives as they did before the COVID-19 epidemic.

1. Aim of Research

During the repeated COVID-19 waves, many people experienced mental stress due to the fear of infection, and restrictions of leaving the house and leisure activities. Patients with Parkinson's disease (PD) may be at a higher risk of developing neuropsychiatric symptoms because they have difficulties adapting to a drastic change in the environment due to impaired functioning of the dopaminergic system. Global surveys of people with PD population revealed deterioration of motor and non-motor symptoms during the COVID-19 pandemic, including mental health, anxiety, depression, and decreased physical activity. To our knowledge, no longitudinal study over several years has assessed the fluctuation of neuropsychiatric symptoms during the COVID-19 pandemic using the same scale. These non-motor symptoms are closely related with circadian rhythm, especially in mood or depression. The purpose of this study was to assess changes per year of these non-motor symptoms across a longer four-year period, spanning the COVID-19 pandemic.

2. Method of Research & Progression

We launched a prospective cohort study among 202 PD patients who were enrolled in the PHASE study (Parkinson's disease and the relationships with circadian biological rhythms and sleep). Depending on when the baseline survey was completed, the study participants were split into two cohorts: a first cohort (n = 161) and a second cohort (n = 41).

2-1 preliminary investigation

The present study includes 22 patients of the second cohort who completed a questionnaire survey about psychiatric symptoms both in the first and the fourth wave of the COVID-19 pandemic. We conducted a questionnaire survey during the first wave (from February to April 2020) and the fourth wave of the COVID-19 pandemic (from March to April 2021).

2-2 longitudinal 4-year investigation

According to Japanese law, the SARS-CoV-2 infection during the COVID-19 pandemic falls under category 2, meaning that it necessitates hospitalization, isolation, and significant government participation. The category of infection was lowered to category 5 in May 2023, meaning that individuals are going back to living their lives as they did before the COVID-19 epidemic. These durations were included. We conducted a questionnaire survey as the timing between January and February in the following years: 2021, 2022, 2023, and 2024.

3. Results of Research

3-1 preliminary findings

22 patients with PD (men 11) completed the survey. Compared with the first wave, the depression score was significantly higher in the fourth wave of the pandemic (median score of GDS: 4.00 vs. 5.50, $p = 0.022$). The number of GDS scores ≥ 6 in the first and fourth waves of the pandemic were 9 and 11,

respectively. The scores of symptoms on MDS-UPDRS part 1 in the fourth wave were significantly higher in hygiene ($p=0.033$), handwriting ($p=0.033$), performing hobbies and other activities ($p=0.035$), and turning in bed ($p=0.046$) than in the first wave. The Hoehn-Yahr stage was significantly higher in the fourth COVID-19 wave (2.7 IQR[2, 4]) than in the first wave (2.5 [2, 3]) ($p=0.025$). There was no significantly different factor including MDS-UPDRS part 1 between PD patients who became depressed defined ≥ 6 on GDS scores ($n=3$) and those who did not become depressed during the COVID-19 pandemic. Between PD patients with worsened GDS scores ($n=13$) and those whose GDS score was not deteriorated ($n=9$), the score of daytime sleepiness on the MDS-UPDRS part 1 Patient Questionnaire differed in the first (median 2.09 and 1.2, respectively, $p=0.052$) and fourth (median 2.3 and 0.67, respectively, $p=0.016$) waves.

3-2 longitudinal 4-year investigation

62 patients with PD (men 30) completed the survey. Between 2021 to 2024, Hoehn-Yahr stage (P for trend < 0.001) and the score for Parkinson's Fatigue scale (P for trend < 0.001) were significantly increased, and the score for GDS ($P=0.014$) and Starkstein's Apathy scale ($P=0.022$) trend to be worsened. In the years 2021, 2022, 2023, and 2024, the corresponding numbers of Parkinson's Fatigue scale ≥ 3.3 were 7, 30, 31, and 32, respectively. The corresponding proportion of GDS scores ≥ 6 and Starkstein's Apathy scale ≥ 16 were 38 and 38 in 2021, 39 and 43 in 2022, 44 and 46 in 2023 and 44 and 46 in 2024, respectively. Parkinson's Fatigue Scale scores in 2022 ($P<0.001$) and 2024 ($P<0.001$) was significantly higher than that of 2021. In comparison to 2021, the GDS ($P=0.001$) and Starkstein's Apathy scale ($P=0.002$) scores in 2024 were both significantly higher. The MDS-UPDRS part 1 symptom scores consistently showed significant increases in walking and balance ($p=0.004$), handwriting ($P=0.009$), hygiene ($p=0.007$), and freezing ($P=0.002$). The following scores show a trend toward increase: turning in bed ($P=0.015$), walking and balance ($p=0.004$), freezing ($P=0.002$), chewing and swallowing ($P=0.030$), dressing ($P=0.022$), constipation problem ($P=0.048$), fatigue ($p=0.011$), dressing ($P=0.040$) and engaging in hobbies and other activities ($P=0.045$). After adjustment for potential confounders, the score for Parkinson's Fatigue scale

was significantly increased by 14.2 (95% confidence interval [CI], 7.8–20.5; $P<0.001$) at 2022, by 12.9 (95% CI, 6.4–19.4; $P<0.001$) at 2023 and by 16.5 (95% CI, 9.6–22.5; $P<0.001$) at 2024 compared with that of 2021.

Patients with Parkinson's disease without coronavirus-2 (SARS-CoV-2) infection.

Eight patients infected SARS-CoV-2 (coronavirus-2) between 2021 and 2024.

In the years 2021–2024, there were worsenings in the Hoehn-Yahr stage (P for trend < 0.001), Parkinson's fatigue scale score (P for trend < 0.001), GDS ($P=0.015$), and Starkstein's Apathy scale ($P=0.019$). According to the MDS-UPDRS part 1 subitem scores, there was a significant increase in fatigue ($p=0.008$) and freezing ($P=0.004$), as well as a trend toward worsening activities such as turning in bed ($P=0.012$), chewing and swallowing ($P=0.019$), dressing ($P=0.030$), hygiene ($p=0.019$), handwriting ($P=0.030$), engaging in hobbies and other activities ($P=0.045$), and walking and balance ($p=0.014$). The Parkinson's Fatigue scale score declined by 14.2 (95% CI, 7.3–21.1; $P<0.001$) in 2022, 13.1 (95% CI, 6.0–20.1; $P<0.001$) in 2023, and 17.0 (95% CI, 9.6–24.4; $P<0.001$) in 2024 after potential confounders were taken into account.

4. Future Area to Take Note of, and Going Forward

Although this study found that depression and fatigue in PD worsened during the COVID-19 pandemic, these exacerbating factors need to be explored from the PHASE study, which was investigated before the COVID-19 pandemic.

5. Means of Official Announcement of Research Results preliminary investigation

Kataoka H, Obayashi K, Tai Y, Sugie K, Saeki K. Increased depressive symptoms in Parkinson's disease during the COVID-19 pandemic: Preliminary findings from longitudinal analysis of the PHASE study. Clin Park Relat Disord. 2023;8:100194. doi: 10.1016/j.prdoa.2023.100194.

longitudinal 4-year investigation

preparation of submission to abroad journal.