

## <研究課題> パーキンソン病とサーカディアンリズムに関する大規模縦断調査

代表研究者 奈良県立医科大学 脳神経内科学講座 准教授 形岡 博史

### 【抄録】

新型コロナウイルス感染症パンデミック中の神経精神症状の変動を、同じ評価尺度を用いた数年以上の追跡調査はない。このような神経精神症状は、特に鬱は概日リズムに深く関連がある。PHASE (Parkinson's disease and the relationships with circadian biological rhythms and sleep)研究の追跡期間内である新型コロナウイルス感染症パンデミックにおいて、鬱を含めた非運動症状の推移を検討した。PHASE 研究に登録された第1(n=161)と第2コホート (n=41)のPD202患者に、自記式調査を実施した。第2コホートを対象とした予備的な1年間、第1波(2020年)と第4波(2021年)の縦断的分析、及び第1と2コホートを対象とした感染症カテゴリーが5に引き下げられた2023年5月を含む縦断的分析においても、鬱が増加する傾向にあった。パンデミック中に疲労がさらに悪化し、パンデミックが終息して通常の生活様式に戻った後も持続していることを示唆した。

### 1. 研究の目的

多くの人が度重なる新型コロナウイルス感染症の波の中、感染への恐怖や外出制限、レジャー活動の制限などにより精神的ストレスを感じました。パーキンソン病 (PD) 患者は、ドーパミン作動系の障害により周囲の突然の変化に適応することが困難になるため、神経精神症状を起こしやすい可能性がある。PD 患者を対象とした世界的な調査で、新型コロナウイルス感染症のパンデミック中に、メンタルヘルス、不安、鬱、身体活動の低下など、運動症状および非運動症状の悪化が報告されている。しかし、新型コロナウイルス感染症パンデミック中の神経精神症状の変動を、同じ評価尺度を用いた数年以上の追跡調査はない。このような神経精神症状は、特に鬱は概日リズムに深く関連がある。PHASE (Parkinson's disease and the relationships with circadian biological rhythms and sleep)研究の追跡期間内である新型コロナウイルス感染症パンデミックにおいて、鬱を含めた非運動症状の推移を検討した。

### 2. 研究方法と経過

前向きコホート研究である PHASE 研究に登録された第1(n=161)と第2コホート (n=41)のPD202患者を対象とした。

#### 2-1 予備的な1年間の縦断的分析

第2コホートを対象とし、新型コロナウイルス感染症パンデミックの第1波(2020年2月~4月)と第4波(2021年3月~4月)に自記式調査を実施した。

#### 2-2 4年間の縦断的分析

新型コロナウイルス感染症パンデミック(感染症カテゴリー2)の期間、及び感染症カテゴリーが5

に引き下げられた2023年5月を含む縦断的分析2021年、2022年、2023年、2024年の1月から2月にかけて、第1と2コホートの自記式調査を実施した。

### 3. 研究の成果

#### 3-1 予備的な1年間の縦断的分析

追跡しえたPD患者は22患者(男性11)であった。新型コロナウイルス感染症第1波と比較して、パンデミックの第4波の鬱スコア Geriatric Depression Scale (GDS)が有意に高かった(中央値: 4.00 vs. 5.50,  $p = 0.022$ )。パンデミックの第1波と第4波における GDS スコア $\geq 6$ (カットオフ値)を満たす患者数は、それぞれ9と11患者であった。第4波での Japanese version of the Movement Disorder Society Revision of the Unified PD Rating Scale (MDS-UPDRS)の副項目である衛生状態( $p=0.033$ )、書字( $p=0.033$ )、趣味やその他の活動( $p=0.035$ )、および寝返り( $p=0.046$ )のスコアが、第1波よりも増加した。ヤール重症度は第1波(中央値2.5, interquartile range IQR [2, 3])に比べ、第4波(中央値2.7, IQR [2, 4])で有意に高かった( $p = 0.025$ )。新型コロナウイルス感染症パンデミック中に GDS スコア $\geq 6$ と定義された鬱病と判断されたPD患者( $n=3$ )と鬱病に至らなかった患者間には、年齢、罹患期間、MDS-UPDRS の副項目等において有意な差はなかった。GDS スコアが悪化したPD患者( $n=13$ )とGDS スコアが悪化を示さなかったPD患者( $n=9$ )間で、MDS-UPDRS の副項目である日中の眠気のスコアが、第1波(中央値2.09, 1.2,  $p=0.052$ )と4波(中央値2.3, 0.67,  $p=0.016$ )で異なっていた

#### 3-2 4年間の縦断的分析

追跡しえたPD患者は62患者(男性30)であった。

2021年から2024年にかけて、ヤール重症度(P for trend< 0.001)と Parkinson's Fatigue scale (P for trend< 0.001) が大幅に増加した。GDS (P for trend=0.014) と Starkstein's Apathy scale(P for trend=0.022)は悪化傾向を示した。2021年、2022年、2023年および2024年での Parkinson's Fatigue scale  $\geq 3.3$ (カットオフ値)に対応する患者数は、それぞれ7、30、31 および 32 患者であり、GDSスコア $\geq 6$ と Starkstein's Apathy scale $\geq 16$ は、2021年が38と38、2022年が39と43、2023年が44と46、2024年が44と46患者であった。2021年と比較し、2022年(P<0.001)と2024年(P<0.001)の Parkinson's Fatigue scale、2024年の GDS(P=0.001) と Starkstein's Apathy scale(P=0.002)のスコアが有意に高かった。MDS-UPDRS の副項目である歩行とバランス(p=0.004)、書字(P=0.009)、衛生状態(p=0.007)、すくみ(P=0.002)で有意な悪化を示し、寝返り(P=0.015)、歩行とバランス(p=0.004)、咀嚼と嚥下(P=0.030)、着衣(P=0.022)、便秘(P=0.048)、疲労(p=0.011)、着替え(P=0.040)、趣味やその他の活動への参加(P=0.045)は悪化傾向を示した。潜在的な交絡因子を調整後の Parkinson's Fatigue scale のスコアは、2021年と比較して2022年に14.2(P<0.001)、2023年は12.9(P<0.001)増加し、2024年には16.5(P<0.001)悪化した。

新型コロナウイルスに感染の罹患がなかった PD 患者。

2021年から2024年の間に新型コロナウイルスに感染した8患者を除いた PD 患者においても、2021年から2024年にかけてヤール重症度(P for trend< 0.001)と Parkinson's Fatigue scale (P for trend< 0.001)、GDS (P for trend =0.015)、Starkstein's Apathy scale(P for trend=0.022)が悪化していた。MDS-UPDRS の副項目である疲労

(p=0.008) およびすくみ足(P=0.004)が大幅に悪化し、寝返り(P=0.012)、咀嚼と嚥下(P=0.019)、服装(P=0.030)、衛生状態(p=0.019)、書字(P=0.030)、趣味やその他の活動への参加(P=0.045)、歩行とバランス(p=0.014)に悪化傾向が見られた。2021年に比べ、潜在的な交絡因子を調整後の Parkinson's Fatigue scale のスコアが2022年には14.2(95% CI, 7.3-21.1; P<0.001)、2023年は13.1(95% CI, 6.0-20.1; P<0.001)、2024年では17.0(95% CI, 9.6-24.4; P<0.001)有意に増加していた。

#### 4. 今後の課題

今回の調査で、COVID-19 パンデミック中に PD の鬱と疲労が悪化することが判明したが、これらの増悪因子等を、COVID-19 パンデミック前に調査した PHASE 研究から探索する必要がある。

#### 5. 研究成果の公表方法

予備的な1年間の縦断的分析

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.

2021年から2024年の縦断的分析

海外誌へ論文発表準備中である。

以上

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

**Primary Researcher:** Hiroshi Kataoka

Associate Professor, Department of Neurology, Nara Medical University

## 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  $\geq 6$  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  $\geq 6$  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  $\geq 3.3$  were 7, 30, 31, and 32, respectively. The corresponding proportion of GDS scores  $\geq 6$  and Starkstein's Apathy scale  $\geq 16$  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.