A 6-month longitudinal study on worsening of Parkinson’s disease during the COVID-19 pandemic

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Further studies are required to investigate the impact of the COVID-19 pandemic on Parkinson’s disease (PD) progression. This study investigated the motor and non-motor progression of people with PD (PWP) at 6 months during the COVID-19 pandemic compared with that during the pre-pandemic period. Patients were recruited from Ain Shams University Hospitals, Cairo, in the period between April 2019 and December 2020. Fifty patients were included, of whom 17 and 33 patients were followed for 6 months before and during the pandemic, respectively. All patients were assessed at baseline and at 6 months using the MDS-UPDRS, Schwab and England scale (S&E), Hoehn and Yahr scale (H&Y), Berg Balance Scale, Timed Up and Go test (TUG), International Physical Activity Questionnaire, New Freezing of Gait Questionnaire, Non-Motor Symptoms Scale, and Beck Depression Inventory (BDI). Both groups were matched in age, gender, and disease characteristics. Patients followed during the pandemic showed more significant worsening of the total, part I and motor part of MDS-UPDRS, and balance scores ($p < 0.001$) than those followed during the pre-COVID-19 period. Gait (TUG), balance, and physical activity worsening were significantly correlated with baseline BDI, gait and balance scores, total and part I MDS-UPDRS scores, H&Y, and S&E OFF scores. Gait deterioration (TUG) was correlated with baseline physical activity ($r = -0.510$, $p = 0.002$). PWP showed worsening of motor and non-motor symptoms during the COVID-19 pandemic at the 6-month follow-up. Worsening of gait, balance, and physical activity was correlated with baseline motor and physical activity OFF scores.

INTRODUCTION

Since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, individuals with Parkinson’s disease (PD) have been considered a vulnerable group to the effects of the COVID-19 pandemic, directly by infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and indirectly by pandemic-related restrictions, chronic stress, anxiety, physical inactivity, and compromised medical care. These effects included worsening of motor symptoms, higher mortality in advanced PD, worse anxiety and depression, impaired physical activity, and disruption of patients’ care1-3. Several recent studies have linked reduced physical activity and exercise to motor worsening during the pandemic, implying the significance of maintaining patients’ activity during restrictions4,5.

Moreover, it has been proposed that the COVID-19 pandemic may be followed by a higher incidence of neurodegenerative diseases; however, the evidence is insufficient to confirm that COVID-19 may trigger or accelerate neurodegeneration6. However, the impact of the COVID-19 pandemic and related measures on disease progression has not been explored. A recent retrospective study has reported a worsening of motor symptoms with a significant increase in motor disease progression during pandemic-related restrictions compared with that during the pre-pandemic period. The assessment was limited to ON-state and motor aspects7. Therefore, longitudinal studies are warranted to investigate the possibility of altered progression of motor and non-motor aspects of PD during the pandemic.

Accordingly, the current longitudinal study investigated the short-term motor and non-motor progression and related determinants of a cohort of people with PD (PWP) during the COVID-19 pandemic compared with the progression during the pre-pandemic period of another matched cohort.

RESULTS

Fifty patients were included, of whom 17 and 33 patients were followed for 6 months before and during the pandemic, respectively. Both groups were matched for demographic and clinical characteristics except for longer disease duration ($p = 0.007$) and lower rigidity ON scores ($p = 0.01$) for patients followed during the pandemic (Table 1). Physical activity (International Physical Activity Questionnaire [IPAQ]) was non-significantly lower in patients during the pandemic. All patients did not report symptoms suggestive of COVID-19 infection. Cronbach’s alpha coefficient of the questionnaires ranged from 0.75 to 0.98, indicating a satisfactory internal consistency.

Disease progression before and during the COVID-19 pandemic

Patients followed before the pandemic showed a moderately significant progression at 6 months of MDS-UPDRS-I (Non-Motor Aspects of Experiences of Daily Living [nM-EDL]) ($p = 0.044$) and OFF-state motor scores ($p = 0.047$). The Schwab and England Activities of Daily Living scale (S&E) OFF- and ON-state scores showed a significant progression ($p = 0.04$ and $0.01$, respectively) although not H&Y. Postural Instability and Gait Disorder (PIGD) ON and OFF-states, axial OFF-state, and New Freezing of Gait Questionnaire (NFOG-Q) OFF-state scores showed a moderately significant progression. The total non-motor symptoms scale (NMSS) and IPAQ showed significant worsening ($p < 0.001$).

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|                                | Patients followed before the COVID-19 period (N = 17) | Patients followed during the COVID-19 period (N = 33) | Mann–Whitney U test |
|--------------------------------|------------------------------------------------------|------------------------------------------------------|---------------------|
|                                | Median/frequency | IQR/% | Median/frequency | IQR/% | z  | p        |
| Agea                          | 55.71 | 6.65  | 56.65 | 10.64 | −0.33a | 0.74     |
| Gender (male)b                | 13    | 76%   | 24    | 73%   | 0.08b | 0.775    |
| Years of education            | 6.53  | 6.29  | 6.39  | 6.05  | 0.07a | 0.941    |
| AOOa                          | 48.38 | 6.08  | 52.77 | 48.38 | −1.54a | 0.130    |
| DOIb                          | 6.38  | 3.33  | 4.10  | 6.38  | 2.79b | 0.007*   |
| Number of vascular risk factors | 0     | 1     | 1    | 1     | −0.49 | 0.619    |
| Number of vascular risk factorsb | 0   | 10    | 17   | 52%   | 2.53b | 0.471    |
| 1                              | 4     | 24%   | 10   | 30%   |        |          |
| 2                              | 3     | 18%   | 3    | 9%    |        |          |
| 3                              | 0     | 0%    | 3    | 9%    |        |          |
| MDS-UPDRS total score OFF      | 79.50 | 75    | 79    | 49    | −0.04 | 0.97     |
| MDS-UPDRS total score ON       | 62.00 | 47    | 60.00 | 38.00 | −0.30 | 0.77     |
| MDS-UPDRS-I                   | 15.50 | 15.50 | 18    | 8     | −0.53 | 0.59     |
| MDS-UPDRS-II                  | 17.00 | 18.25 | 21    | 15    | −0.32 | 0.75     |
| MDS-UPDRS-III OFF             | 47.50 | 40    | 47.00 | 29.00 | −0.51 | 0.61     |
| MDS-UPDRS-III ON              | 30.00 | 24    | 29.00 | 20    | −1.12 | 0.26     |
| Rigidity OFF                  | 9.50  | 9     | 8.00  | 5.00  | −1.34 | 0.18     |
| Rigidity ON                   | 5.50  | 6     | 3.00  | 6     | −2.49 | 0.01*    |
| Bradykinesia OFF              | 16.50 | 19    | 15.00 | 10.00 | −0.03 | 0.98     |
| Bradykinesia ON               | 12.00 | 13    | 9.00  | 8.00  | −0.86 | 0.39     |
| PIGD OFF                      | 7.00  | 12    | 7.00  | 9     | −0.20 | 0.84     |
| PIGD ON                       | 5.00  | 9     | 6.00  | 5.00  | −0.07 | 0.94     |
| Axial OFF                     | 11.00 | 12    | 13.00 | 10.00 | −0.31 | 0.76     |
| Axial ON                      | 7.50  | 10    | 7.00  | 7     | −0.19 | 0.94     |
| Tremors OFF                   | 15.00 | 11    | 11.00 | 13    | −0.49 | 0.62     |
| Tremor ON                     | 9.00  | 8     | 6.00  | 9     | −1.43 | 0.15     |
| H&Y OFF                       | 2.500 | 0.6   | 2.50  | 1.00  | −0.30 | 0.77     |
| H&Y ON                        | 2.000 | 0.8   | 2.00  | 1.00  | −0.14 | 0.89     |
| Schwab and England ADL OFF    | 80.00 | 13    | 70.00 | 20.00 | −0.55 | 0.58     |
| Schwab and England ADL ON     | 85.00 | 10    | 80.00 | 20.00 | −0.75 | 0.45     |
| Motor complication total score | 4.50 | 9     | 5.00  | 4.00  | −0.45 | 0.65     |
| TUG OFF                       | 12.41 | 13.63 | 13    | 9     | −0.57 | 0.57     |
| TUG ON                        | 11.60 | 5.03  | 10    | 5.50  | −0.47 | 0.64     |
| NFOG-Q OFF                    | 12    | 22    | 0     | 21    | −0.51 | 0.61     |
| NFOG-Q ON                     | 8     | 12    | 0     | 13    | −0.84 | 0.40     |
| BBS OFF                       | 48    | 29    | 48    | 11    | −0.06 | 0.95     |
| BBS ON                        | 53.50 | 12    | 53    | 6     | −0.13 | 0.90     |
| IPAQ                          | 2,129.0 | 1,367.3 | 1,950.0 | 1,493.5 | −1.08 | 0.28     |
| LEDD                          | 525   | 662.5 | 625   | 375   | −0.52 | 0.61     |
| MMSE                          | 27.00 | 8     | 28.00 | 4.00  | −0.30 | 0.76     |
| NMSS total score              | 57    | 73    | 47    | 41    | −0.26 | 0.80     |
| BDI                           | 18    | 12    | 19    | 15    | −0.16 | 0.87     |
| PDQ-39                        | 35.41 | 41.59 | 46.35 | 26.85 | −0.85 | 0.40     |

AOO age of onset, DOI duration of illness, LEDD levodopa equivalent daily dose, MMSE Mini-Mental State Examination, NMSS Non-Motor Symptoms scale, PDQ-39 Parkinson's Disease Questionnaire-39, BDI Beck Depression Inventory, TUG Timed Up and Go Test, NFOG-Q New Freezing of Gait, BBS Berg Balance Scale, MDS-UPDRS Movement Disorder Society–Unified Parkinson's Disease Rating Scale, PIGD Postural Instability and Gait Disorder, ADL activities of daily living, H&Y Hoehn and Yahr, IPAQ International Physical Activity Questionnaire.

*aT-test is used.

bChi-square test is used.

*p-value is significant if <0.05.

**Corrected p-value is significant if ≤0.001 after Bonferroni's adjustment.
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Table 2. Comparison of 6-month disease progression before and during the COVID-19 pandemic.

| Difference between the baseline and 6-month follow-up | Patients followed before the COVID-19 period (N = 17) | Patients followed during the COVID-19 period (N = 33) | Mann–Whitney U test | Percentage of change |
|-------------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|----------------------|----------------------|
|                                                       | Median | IQR | Median | IQR | z | p | Pre-COVID | Post-COVID |
| Δ MDS-UPDRS total score OFF                           | 6      | 9.75 | 18    | 13.5 | −3.29 | <0.001** | 8.94 | 20.97 |
| Δ MDS-UPDRS total score ON                            | 3      | 14.75 | 14    | 13 | −3.88 | <0.001** | 6.06 | 27.59 |
| Δ MDS-UPDRS-I                                        | 0      | 8     | 5     | 4 | −3.87 | <0.001** | 0 | 26.67 |
| Δ MDS-UPDRS-II                                       | 1.5    | 5.75 | 3     | 4 | −0.83 | 0.4 | 22.22 | 14.28 |
| Δ MDS-UPDRS-III OFF                                  | 4.5    | 6.75 | 8     | 7.5 | −2.94 | <0.001** | 6.9 | 21.21 |
| Δ MDS-UPDRS-III ON                                   | −0.5   | 6.5 | 6     | 5.5 | −3.51 | <0.001** | −3.85 | 25 |
| Rigidity OFF                                         | 0      | 4.25 | 2     | 2 | −2.09 | 0.04* | 0 | 18.18 |
| Rigidity ON                                          | −1     | 2.5 | 1     | 1.5 | −3.63 | <0.001** | −30 | 14.29 |
| Bradykinesia OFF                                     | 1.5    | 3.25 | 3     | 4 | −1.93 | 0.05 | 9.38 | 22.22 |
| Bradykinesia ON                                      | 0      | 2.75 | 2     | 3 | −2.83 | <0.001** | 0 | 20 |
| PIGD OFF                                             | 0.5    | 2.5 | 1     | 3 | −0.82 | 0.41 | 5.26 | 21.43 |
| PIGD ON                                              | 0.5    | 2.25 | 1     | 2 | −0.21 | 0.83 | 12.5 | 12.5 |
| Axial OFF                                            | 1      | 2.5 | 4     | 3 | −2.54 | 0.01* | 11.11 | 23.08 |
| Axial ON                                             | 1      | 2.25 | 2     | 2.5 | −1.8 | 0.07 | 22.22 | 32.05 |
| Tremors OFF                                          | 0.5    | 5.5 | 1     | 2 | −0.84 | 0.4 | 0 | 9.09 |
| Tremor ON                                            | −0.5   | 5.5 | 0     | 2 | −1.91 | 0.06 | −17.65 | 0 |
| H&Y OFF                                              | 0      | 0.13 | 0.5 | 0.5 | −1.55 | 0.12 | 0 | 20 |
| H&Y ON                                               | 0      | 0.13 | 0    | 0.5 | −1.51 | 0.13 | 0 | 0 |
| Schwab and England ADL OFF                           | −10    | 10   | −10   | 5 | −1.37 | 0.17 | −12.5 | −12.5 |
| Schwab and England ADL ON                            | −5     | 10   | −10   | 10 | −0.89 | 0.37 | 0 | −11.11 |
| Motor complication total score                        | 0      | 4.5 | 1     | 1 | −0.27 | 0.78 | 0 | 7.14 |
| Δ TUG OFF                                            | 0.32   | 1.52 | 0.79 | 1.33 | −2.62 | 0.01* | 2.5 | 5.26 |
| Δ TUG ON                                             | 0.5    | 1.37 | 0.5 | 0.8 | −0.27 | 0.79 | 5 | 6.67 |
| Δ NFOG-Q OFF                                         | 0      | 7.5 | 0    | 3.5 | −0.29 | 0.77 | 4.2 | 8.04 |
| Δ NFOG-Q ON                                          | 1.5    | 7    | 0    | 2.5 | −0.5 | 0.62 | 12.5 | 15.97 |
| Δ BBS OFF                                            | 0      | 4    | −2   | 4 | −2.94 | <0.001** | 1.82 | −6.45 |
| Δ BBS ON                                             | 0      | 2.25 | −2   | 3 | −2.86 | <0.001** | 0 | −3.85 |
| Δ IPAA                                               | −480.5 | 704.25 | −377 | 392.75 | −1.58 | 0.11 | −30.47 | −26.26 |
| Δ MMSE                                               | −1     | 2    | 0    | 1 | −0.73 | 0.47 | −1.67 | 0 |
| Δ NMSS total score                                    | 8      | 8.5 | 9    | 6.5 | −0.04 | 0.97 | 15.09 | 18.18 |
| Δ PDQ-39                                              | 6.78   | 5.13 | 11.98 | 8.88 | −1.34 | 0.18 | 20.63 | 27.76 |
| Δ LEDD                                               | 0      | 300 | 337.5 | −0.228 | 0.819 |  |

Table 2. Comparison of 6-month disease progression before and during the COVID-19 pandemic.

| Δ MDS-UPDRS total score OFF | Δ MDS-UPDRS total score ON | Δ MDS-UPDRS-I | Δ MDS-UPDRS-II | Δ MDS-UPDRS-III OFF | Δ MDS-UPDRS-III ON | Rigidity OFF | Rigidity ON | Bradykinesia OFF | Bradykinesia ON | PIGD OFF | PIGD ON | Axial OFF | Axial ON | Tremors OFF | Tremor ON | H&Y OFF | H&Y ON | Schwab and England ADL OFF | Schwab and England ADL ON | Motor complication total score | Δ TUG OFF | Δ TUG ON | Δ NFOG-Q OFF | Δ NFOG-Q ON | Δ BBS OFF | Δ BBS ON | Δ IPAA | Δ MMSE | Δ NMSS total score | Δ PDQ-39 | Δ LEDD | Δ 6 m FU-baseline, MMSE Mini-Mental State Examination, NMSS Non-Motor Symptoms Scale, PDQ-39 Parkinson's Disease Questionnaire-39, TUG Timed Up and Go test, NFOG-Q New Freezing of Gait, BBS Berg Balance Scale, MDS-UPDRS Movement Disorder Society–Unified Parkinson's Disease Rating Scale, PIGD Postural Instability and Gait Disorder, ADL activities of daily living, H&Y Hoehn and Yahr, IPAA International Physical Activity Questionnaire, LEDD Levodopa equivalent daily dose. *p-value is significant if <0.05. **Corrected p-value is significant if p ≤ 0.001 after Bonferroni's adjustment.

Patients followed during the COVID-19 pandemic showed a significant marked worsening at 6 months of MDS-UPDRS total and all subscores, S&E and Hoehn and Yahr (H&Y) (p < 0.001), PIGD, NFOG-Q, Timed Up and Go test (TUG), Berg Balance Scale (BBS) in OFF and ON states, total NMSS, IPAQ, and Mini-Mental State Examination (MMSE) (p < 0.001) (Supplementary Table 2).

Compared with the patients followed before the pandemic, those followed during the pandemic had greater significant worsening of the total and motor MDS-UPDRS OFF- and ON-state scores, MDS-UPDRS part I (p < 0.001), rigidity OFF (p = 0.04) and ON-state scores (p < 0.001), bradykinesia ON-state scores (p < 0.001), BBS OFF- and ON-state scores (p < 0.001) (significant after Bonferroni correction), axial OFF-state scores, and TUG (p = 0.01, non-significant after Bonferroni correction). Levodopa equivalent daily dosage (LEDD), MMSE, NMSS, IPAQ, and PDQ showed similar changes in both groups (Table 2).

Correlations of disease progression during the pandemic

During the pandemic, the worsening of motor severity (H&Y) was correlated with disease duration (r = 0.500, p = 0.003), whereas motor complications (part IV) were directly correlated with baseline cognition (p = 0.02) and S&E (p = 0.03) and inversely correlated with depression and total and motor MDS-UPDRS scores (p = 0.04) (non-significant after Bonferroni correction);
Conversely, total and other MDS-UPDRS progression did not show significant correlations (Table 3).

Cognitive worsening was correlated with years of education, baseline MDS-UPDRS part II \( (r = -0.430, p = 0.01) \), PIGD \( (r = -0.370, p = 0.03) \), and axial scores \( (r = -0.370, p = 0.03) \). Total NMSS worsening was correlated with baseline NFQG-Q \( (r = 0.450, p = 0.001) \) and PIGD scores \( (r = 0.360, p = 0.04) \) (non-significant after Bonferroni correction). TUG (OFF), BBS (OFF), and IPAQ worsening were significantly correlated with baseline Beck Depression Inventory (BDI), gait (TUG) and balance (BBS) OFF scores, total and part I MDS-UPDRS scores, and H&Y and S&E scores. After Bonferroni correction, a significant correlation was noted between TUG and baseline OFF-state TUG, PIGD, axial, H&Y, S&E, and IPAQ scores; BBS and baseline OFF PIGD and NFQG-Q; and IPAQ and baseline MMSE, MDS-UPDRS-total and part II-OFF, BDI, TUG-OFF, and IPAQ scores \( (p \leq 0.002) \) (Table 3).

On comparison between the two groups regarding the assessment scale scores after 6 months, significant worsening was noted in MDS-UPDRS-I in the patients followed during the COVID-19 period \( (p = 0.003) \) (Supplementary Table 3).

**DISCUSSION**

Several cross-sectional studies have constantly described the worsening of motor and non-motor symptoms during the COVID-19 pandemic. However, its impact on disease progression was not adequately investigated. Distinctively, this longitudinal study explored disease progression during the pandemic and showed worsening of motor and non-motor symptoms over a 6-month follow-up during the pandemic compared with that during the pre-pandemic period. Gait, balance, and physical activity worsening were correlated with baseline motor and physical activity scores. The current study showed the possibility of deleterious effects of pandemic lockdown on disease progression in PWP.

The current findings are consistent with those of previous cross-sectional studies. An Indian study showed worsening of motor symptoms, especially bradykinesia in 69.2% of cases during the COVID-19 pandemic, followed by tremor, rigidity, and gait freezing. Additionally, PWP reported worsening in mental health, quality of life, and physical inactivity during this pandemic. These indirect effects of COVID-19 are more confirmed and may be more common and more harmful than the direct effects of viral infections. The worsening of motor and non-motor symptoms has been attributed to stress, physical inactivity, pharmacodynamic effects, dramatic changes in routine, and social isolation. The impact of stress on PD progression has been previously investigated and proven to negatively affect the course of the disease.

Conversely, the impact on disease progression is not well investigated. However, a recent study by Ineichen et al. has reported increased motor disease progression during pandemic-related restrictions compared with that before the COVID-19 pandemic, which is consistent with the current study. Similar to symptom worsening, more deterioration during the pandemic could be explained by stress, physical inactivity, and social isolation.

PWP are more vulnerable to recent stressors, which is attributed to more dopamine depletion and consequently reduced coping mechanisms for stress. Moreover, chronic stress may induce oxidative damage to the cell membrane, as well as inflammatory and regulatory T-cell dysfunction, leading to a possible increase in midbrain dopaminergic neuron loss and motor symptom worsening. Additionally, chronic stress accelerates dopaminergic cell loss in animal PD models and exacerbates the neuropathological changes. The accompanying microglial activation and oxidative stress may mechanistically justify the stress-induced neurodegeneration in PD.
|                          | Δ MMSE | Δ NMSS | Δ TUG-OFF | Δ NFQG-Q OFF | Δ BBS OFF | Δ IIPAQ | Δ MDS UPDRS
|--------------------------|--------|--------|-----------|--------------|-----------|---------|--------------------------|
| **Age**                  |        |        |           |              |           |         |                           |
| Spearman                 | 0.08   | -0.15 | 0.27      | -0.16        | 0.02      | 0.19    | -0.11                     |
| Sig                      | 0.65   | 0.41  | 0.13      | 0.36         | 0.91      | 0.29    | 0.56                      |
| **Years of education**   |        |        |           |              |           |         |                           |
| Spearman                 | 0.41   | -0.35 | -0.07     | 0.27         | -0.48     | -0.04   | -0.29                     |
| Sig                      | 0.02   | 0.96  | 0.05      | 0.69         | 0.13      | 0.005* | 0.81                      |
| **AOO**                  |        |        |           |              |           |         |                           |
| Spearman                 | 0.06   | -0.21 | 0.27      | -0.17        | 0.05      | 0.14    | -0.14                     |
| Sig                      | 0.72   | 0.25  | 0.13      | 0.34         | 0.78      | 0.43    | 0.43                      |
| **DOI**                  |        |        |           |              |           |         |                           |
| Spearman                 | 0.16   | 0.19  | 0.19      | 0.07         | -0.12     | 0.19    | 0.23                      |
| Sig                      | 0.37   | 0.29  | 0.28      | 0.72         | 0.49      | 0.29    | 0.24                      |
| **MMSE**                 |        |        |           |              |           |         |                           |
| Spearman                 | 0.12   | -0.33 | -0.01     | 0.24         | -0.52     | -0.03   | -0.02                     |
| Sig                      | 0.5    | 0.69  | 0.06      | 0.94         | 0.17      | 0.002**| 0.85                      |
| **NMSS total score**     |        |        |           |              |           |         |                           |
| Spearman                 | -0.12  | -0.11 | 0.38      | 0.15         | -0.35     | 0.3     | 0.04                      |
| Sig                      | 0.49   | 0.54  | 0.03*     | 0.4          | 0.05      | 0.09    | 0.8                       |
| **BDI**                  |        |        |           |              |           |         |                           |
| Spearman                 | -0.16  | 0.05  | 0.5       | 0.17         | -0.46     | 0.51    | 0.09                      |
| Sig                      | 0.38   | 0.78  | 0.003*    | 0.35         | 0.007     | 0.002**| 0.63                      |
| **TUG OFF**              |        |        |           |              |           |         |                           |
| Spearman                 | -0.29  | 0.13  | 0.52      | 0.17         | -0.45     | 0.51    | 0.26                      |
| Sig                      | 0.1    | 0.46  | 0.002**   | 0.34         | 0.009*    | 0.002**| 0.14                      |
| **NFQG-Q OFF**           |        |        |           |              |           |         |                           |
| Spearman                 | 0.06   | 0.008*| 0.003*    | 0.18         | 0.002**   | 0.57    | 0.1                        |
| Sig                      | 0.14   | 0.06  | 0.003*    | 0.16         | 0.04*     | 0.05    | 0.36                      |
| **BBS OFF**              |        |        |           |              |           |         |                           |
| Spearman                 | 0.15   | 0.41  | 0.02*     | 0.56         | 0.04*     | 0.002**| 0.71                      |
| Sig                      | 0.59   | 0.87  | 0.007*    | 0.79         | 0.03*     | 0.02*  | 0.92                      |
| **H&Y OFF**              |        |        |           |              |           |         |                           |
| Spearman                 | -0.43  | 0.24  | 0.51      | 0.11         | -0.36     | 0.51    | 0.09                      |
| Sig                      | 0.01   | 0.19  | 0.003*    | 0.56         | 0.04      | 0.002**| 0.63                      |
| **PFQD OFF**             |        |        |           |              |           |         |                           |
| Spearman                 | 0.26   | 0.18  | 0.35      | 0.15         | -0.31     | 0.43    | 0.09                      |
| Sig                      | 0.14   | 0.32  | 0.05      | 0.41         | 0.08      | 0.01*  | 0.62                      |
| **Axial OFF**            |        |        |           |              |           |         |                           |
| Spearman                 | -0.37  | 0.36  | 0.61      | 0.24         | -0.51     | 0.24    | 0.26                      |
| Sig                      | 0.03*  | 0.04* | <0.001**  | 0.18         | 0.42      | 0.39    | 0.24                      |
| **H&Y OFF**              |        |        |           |              |           |         |                           |
| Spearman                 | 0.04*  | 0.06  | <0.001**  | 0.15         | 0.01*     | 0.02*  | 0.19                      |
| Sig                      | 0.38   | 0.06  | 0.001**   | 0.31         | 0.04*     | 0.004* | 0.24                      |
| **Schwab and England ADL OFF** | 0.34   | -0.24 | -0.54    | -0.2         | 0.36      | -0.49 | -0.14                     |
| Sig                      | 0.06   | 0.18  | 0.001**   | 0.28         | 0.04*     | 0.004* | 0.24                      |
| **Motor complication total score** | -0.12 | 0.16  | 0.37      | 0.35         | -0.32     | 0.33    | 0.02                      |
| SIG                      | 0.51   | 0.37  | 0.04*     | 0.04*        | 0.07      | 0.06   | 0.27                      |
| **IPQ**                  |        |        |           |              |           |         |                           |
| Spearman                 | 0.37   | 1      | 0.002**   | 0.6          | 0.05      | <0.001**| 0.29                      |
| Sig                      | 0.16   | -0.51 | -0.1      | 0.34         | -0.63     | -0.19  | 0.0                     |

**Correlation coefficient**: Spearman

**Spearman correlation coefficient**: p-value is significant if <0.05.

**Corrected p-value**: p-value is significant if ≤0.002 after Bonferroni’s adjustment.
(6-month follow-up) periods, and those who underwent functional brain surgery (before or during the follow-up period).

**Sampling and sample size**

The sample size was calculated using an online calculator (https://www.calculator.net/sample-size-calculator.html), where for a 95% confidence level and a margin of error 5, the minimal sample size was estimated to be 16 patients for each group.

**Ethical considerations**

All participants provided written informed consent. The study was approved by the ethical committee of the Faculty of Medicine of Ain Shams University according to the Declaration of Helsinki.

**Data collection**

All patients were evaluated at baseline and at 6-month follow-up using the total and different parts of the MDS-UPDRS (parts include part I [inM-EDL], part II [motor aspects of daily living], part III [motor examination], and part IV [motor complications]), H&Y for disease severity, S&E for activities of daily living24, 25, NFQG-O27 for gait freezing, BBS28 for balance assessment, and TUG29 for gait and mobility assessment during the OFF and ON states. Other scales included the IPAQ-SF30 for physical activities, NMSS 31 for non-motor symptoms assessment during the OFF and ON states. All patients have been evaluated in person by a trained physician. LEDD was calculated at baseline and follow-up as the sum of the daily dose of all dopaminergic agents.

**Statistical analysis**

Data analysis was performed using IBM SPSS software package version 25.0 (IBM Corp., Armonk, NY). Qualitative data were described as frequencies and percentages and compared using the chi-square test, whereas quantitative data were presented as medians and interquartile ranges or means ± standard deviations and compared using either the Mann–Whitney U test or Student’s t test according to the distribution of the data, respectively. The Wilcoxon signed-rank test was used to compare baseline and follow-up data within each group. The Spearman correlation coefficient was used to evaluate the correlation between different variables. The significance was set at p < 0.05. Bonferroni correction was performed for the multiple comparisons and correlations, and an adjusted p-value was used. Cronbach’s coefficient was used as a measure of the internal consistency of used questionnaires.

**DATA AVAILABILITY**

The datasets generated during the current study will be made available from the corresponding author upon request.

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AUTHOR CONTRIBUTIONS
Research project: conception: A.S. and M.E., organization: A.S. and E.H., and execution: A.H., E.H., A.G., and A.S.; statistical analysis: design and execution: E.H. and A.S., and review and critique: A.G., M.E., and M.S.; thematic analysis: design and execution: A.H., E.H., and A.S., and review and critique: A.S., A.G., M.E., and M.S.; and manuscript: writing of the first draft: A.S., E.H.; and review and critique: A.S., E.H., A.G., M.E., and M.S.

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COMPETING INTERESTS
The authors declare no competing interests.

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