



Parkinson's Disease and the COVID-19 Pandemic: Do Quarantine Affect the Motor and Non-Motor Symptoms of Patients with and without Deep Brain Stimulation?

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Abstract

Aim: Patients with chronic diseases were forced into lockdown due to the coronavirus disease-2019 pandemic. Extended quarantine could lead to physical inactivity and psychiatric problems. We investigated the effects of quarantine and social isolation during the pandemic on the motor and non-motor symptoms (NMS) of Parkinson's disease (PD) patients with and without deep brain stimulation (DBS).

Methods: This study included 168 patients with PD who were in quarantine for 2 months (between April 1, 2020 and May 31, 2020). Eighty-three patients had undergone bilateral subthalamic DBS surgery. A questionnaire with three parts was administered via phone: 1) motor symptoms, 2) NMS, and 3) the reasons for impairment.

Results: Of the patients, 54.7% reported impairment in at least one motor symptom and 58.9% reported impairment in at least one NMS. Increased tremors, difficulty with turning in bed, and insomnia were significantly more pronounced in patients without DBS. Patients with DBS complained less of being bored due to staying at home and had less deterioration due to lack of exercise and slower disease progression.

Conclusion: Half of the symptoms of patients with PD worsened during quarantine, but patients with DBS tolerated the lockdown better. Telemedicine and online physiotherapy programs should be recommended to prevent rapid disease progression.

Keywords: COVID-19, deep brain stimulation, Parkinson's disease, quarantine

Introduction

Coronavirus disease-2019 (COVID-19) can be fatal, particularly in the elderly and in patients with chronic diseases (1). The best way to avoid contracting the virus is to be to quarantine these individuals at home or in nursing homes. While quarantine prevents the spread of the disease, it also increases the likelihood of the emergence of physical and psychological problems. Physical inactivity due to staying home causes disability (2). Psychological

problems such as depression, anxiety, and the feeling of loneliness are also frequent (3).

Parkinson's disease (PD) is a progressive, chronic disease characterized by motor and non-motor symptoms (NMS) (4,5). Regular neurologist follow-up has a significant positive effect on the disease symptoms and reduces the mortality rate (6,7). Dose titration of PD drugs under physician control and medication adherence is essential for controlling the motor symptoms, while

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Received: 15.02.2022 **Accepted:** 23.05.2022

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Istanbul Haseki Training and Research Hospital
The Medical Bulletin of Haseki published by Galenos Yayinevi.

physiotherapy and exercise are important for treating both motor symptoms and NMS (8-10). However, the need to stay at home, physical inactivity, the lack of visits by family members, and stress may lead to symptom deterioration (11). Prasad et al. (12) showed that 3 weeks of quarantine led to 10% impairment in motor symptoms and NMS in a group of 100 patients with PD. Falla et al. (13) found that the UPDRS-NMS scores worsened after 3 months of quarantine but not the motor scores.

Deep brain stimulation (DBS) is an effective treatment for controlling the symptoms of PD (14). Patients who have undergone DBS surgery are likely to experience both drug and battery problems during the pandemic, such as battery depletion, infection, and programming (15).

COVID-19 will continue to have an enormous effect worldwide, so being aware of how to remain in quarantine and face prolonged social isolation is necessary when making treatment plans for patients with PD. In this study, we investigated the effects of quarantine during the pandemic on PD symptoms in patients who had undergone DBS surgery and those who had not.

Materials and Methods

Compliance with Ethical Standards and Study Design

The study enrolled 168 patients (92 males and 76 females) with PD who were in quarantine and social isolation due to COVID-19 between April 1, 2020 and May 31, 2020 in two movement disorder centers. Patient records and phone numbers were obtained from the hospital database. Of these, 83 patients had undergone bilateral subthalamic nucleus (STN) DBS surgery (46 males and 37 females). The DBS batteries of the four patients were rechargeable. Two patients had a patient programmer. Patients who had been diagnosed with PD at least 1 year ago and who had undergone the DBS surgery at least 6 months previously were included. Patients who were at Hoehn and Yahr stage 5, had dementia, or had been diagnosed with COVID-19 were excluded.

The protocol for the research project has been approved by the Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee (date: 03-07-2020 and approval number: 10840098-604.01.01-E.15486). The questionnaires designed to evaluate the motor symptoms and NMS of PD were administered to 91 patients (54.2% of the participants) and 77 caregivers (45.8% of the participants) who agreed to participate in the study. Questions were asked via phone calls by three neurologists (N.H.Y., B.B., and A.S.A.).

Patient Assessment

The information about the status of the 77 patients was obtained from the caregiver because these patients with PD did not want to talk on the phone for such a long time. Forty-three patients with PD with DBS and 48 patients with PD without DBS answered the questionnaire by themselves, while 40 with DBS and 37 without DBS let the caregiver answer.

The questionnaire consisted of three parts [tremors, slowness of movements, gait impairment, falls, imbalance, freezing of gait (FOG), difficulty with turning in bed, receiving help from the caregiver for standing up, and dyskinesia]. The second part evaluated the NMS [nervousness, anxiety, insomnia, daytime sleepiness, visual hallucinations, forgetfulness, pain, REM sleep behavior disorder (RBD), and constipation]. The response "better" was scored as 2 points, "already absent" was scored 0 points, "the same" was scored 1 point, and "worse" was scored 2 points. Total motor symptoms and NMS scores were calculated.

The third part included 10 questions investigating the causes of patient deterioration during this process. The 10 items were as follows:

1. I am under stress because of COVID-19.
2. I am bored because I am always at home.
3. My relatives/friends cannot visit me.
4. I cannot take my medications regularly/I sometimes take more drugs.
5. I finished my prescription and could not refill it.
6. I reduced my medication dose as I was afraid it would run out.
7. I cannot walk/exercise/do physiotherapy.
8. I can not visit my doctor for follow-up.
9. I think that my disease progressed during this period.
10. I cannot take care of myself/My caregiver cannot take care of me.

A "no" answer was scored at 0 points, and "yes" at 1 point. The total impairment score was calculated.

The patients with DBS were asked about the charge status of their battery, infection, problems with extension wires, and the need for programming.

Statistical Analysis

The data was evaluated using IBM SPSS ver. 24. Frequencies, percentages, means, standard deviations, and ranges were used to analyze the descriptive data. Chi-square and advanced chi-square tests were used to assess categorical variables. The Mann-Whitney U test was used to compare the mean values between groups when the data did not meet the parametric assumptions. A p-value of <0.05 was set as statistically significant.

	PD without DBS (n=85)	PD with DBS (n=83)	Z;p
	Mean ± SD	Mean ± SD	
Age (years)	67.49±8.61	65.76±7.19	3,131; 0.207
Duration of education (years)	7.52±4.82	8.02±5.15	3,775; 0.420
Duration of PD (years)	7.32±3.96	16.45±6.62	6,367; <0.001

Chi-square test (statistical analysis) DBS: Deep brain stimulation, n: number, SD: Standard deviation, PD: Parkinson's disease

Results

Table 1 summarizes the distributions of age, education status, and disease duration in the two groups. The disease duration was longer in the DBS group.

Table 2 shows the distribution of the motor scores in the patients with and without DBS.

Figure 1 shows the percentage of the patients whose motor symptoms worsened.

Ninety-two patients (46 without DBS, 46 with DBS) (54.7%) reported deterioration in at least one motor sign. When the two groups were compared, patients without DBS showed significant deterioration in the tremor (26 DBS- vs. 9 DBS+ patients; $\chi^2=9,239$, $p=0.002$) and turning in bed (30 DBS- vs. 17 DBS+ patients; $p=0.039$).

The distributions of the NMS scores in the two groups are presented in Table 3.

Figure 2 shows the percentage of the patients whose NMS worsened.

In total, 99 patients (58.9%) (44 DBS- and 55 DBS+) reported impairment in at least one NMS sign. When the

groups were compared, insomnia got significantly worse to a greater extent in the patients without DBS (24 without DBS vs. 11 with DBS; $p=0.023$).

Ten questions pertained to the subjective reasons for the symptom deterioration. Of the 168 patients, 48 (28.6%) stated that they were under stress because of COVID-19, 68 (40.5%) were bored staying at home, 44 (26.2%) felt badly because their relatives or friends could not come to visit them, 5 (3%) could not take their medications regularly, 8 (4.8%) had finished their medications, 2 (1.2%) had reduced the dose of the drugs as they feared their prescriptions would run out, 54 (32.1%) could not go walking, perform exercise, or receive physiotherapy. Fifty-seven (33.9%) could not visit their doctors for follow-up. Seventy-three (43.5%) believed that their illness had progressed during this process, and 24 (14.3%) stated that they could not take care of themselves or that their caregivers could not take care of them. Ninety-nine patients (79.0%) (58 without DBS and 41 with DBS patients) answered "yes" to at least one question.

When the two groups were compared, being bored due to staying at home, deterioration due to not being able to go for a walk, perform exercise, or receive physiotherapy,

	PD without DBS (n=85)	PD with DBS (n=83)	Z;p
	Mean ± SD	Mean ± SD	
Tremor	0.90±0.92	0.33±0.72	2,160; <0.001
Slowness of movements	1.27±0.94	1.17±0.73	3,076; 0.118
Gait impairment	1.15±0.95	1.32±0.64	3,718; 0.507
Falls	0.36±0.85	0.51±0.80	4,066; 0.046
Imbalance	0.81±0.94	1.01±0.80	4,024; 0.096
FOG	0.62±0.83	0.87±0.86	4,099; 0.047
Difficulty with turning in bed	0.95±0.95	0.82±0.75	3,155; 0.210
Receiving help from the caregiver for standing up	0.68±0.94	0.43±0.78	2,896; 0.020
Dyskinesia	0.37±0.72	0.71±0.86	4,351; 0.003
Total motor score	7.12±5.36	7.19±3.96	3,550; 0.945

Chi-square test (statistical analysis) DBS: Deep brain stimulation, n: number, SD: Standard deviation, FOG: Freezing of gait, PD: Parkinson's disease

	PD without DBS (n=85)	PD with DBS (n=83)	Z;p
	Mean ± SD	Mean ± SD	
Nervousness	0.78±1.06	0.57±0.95	3,094; 0.126
Anxiety	0.64±0.95	0.50±0.96	3,252; 0.294
Insomnia	0.59±1.12	0,63±0.70	3,527; 0.997
Daytime sleepiness	0.63±0.89	0.90±0.83	4,170; 0.030
Visual hallucination	0.34±0.78	0.27±0.62	3,441; 0.596
Forgetfulness	0.69±0.86	0.82±0.74	3,861; 0.257
Pain	0.73±0.97	0.77±0.87	3,582; 0.855
RBD	0.48±0.75	0.64±0.91	4,227; 0.016
Constipation	0.68±0.89	0.91±0.79	4,047; 0.078
Total NMS score	5.57±4.95	6.03±3.80	3,956; 0.173

Chi-square test (statistical analysis) NMS: Non-motor symptoms, DBS: Deep brain stimulation, n: number, SD: Standard deviation, RBD: REM sleep behaviour disorder, PD: Parkinson's disease

and believing that their disease had progressed during this period were significantly higher in the group without DBS ($p=0.000$, $p=0.008$, and $p=0.020$, respectively). The mean total impairment score was 2.65 ± 2.46 in the patients without DBS versus 1.90 ± 2.31 in the patients with DBS. The difference was significant ($p=0.028$).

Of the 83 patients with DBS, 33 (39.8%) required programming. Additionally, the batteries had depleted in six patients (7.2%). The patients with DBS did not report any problems with the DBS extension wire or infection.

Discussion

After a certain period of lockdown, patients with PD developed impaired motor symptoms, or NMS, or new symptoms. Schirinzi et al. (16) evaluated 162 patients with PD from Italy during 2 weeks of quarantine and found impaired motor signs in 50%, anxiety in 25%, hallucinations, and agitation in 18%, and other NMS in 16% of patients with PD. Baschi et al. (17) reported that motor, cognitive, and behavioral symptoms were impaired and new behavioral symptoms appeared during lockdown, leading to caregiver burden in 26% of patients. Luis-Martínez et al. (18) declared that there was an increased risk of falls in patients with PD after 2 months of quarantine. In our study, both motor and NMS symptoms deteriorated after 2 months of quarantine. At least 40% of the patients showed impairment of gait and motion. Nervousness, anxiety and pain were the most affected NMS in both groups.

DBS leads to significant improvement in motor signs (tremor, bradykinesia, and rigidity), while FOG and frequent falls develop in approximately 50% of patients during subsequent years (19,20). In our study, patients with PD with and without DBS were asked about how their motor signs of PD changed during quarantine. Falls and

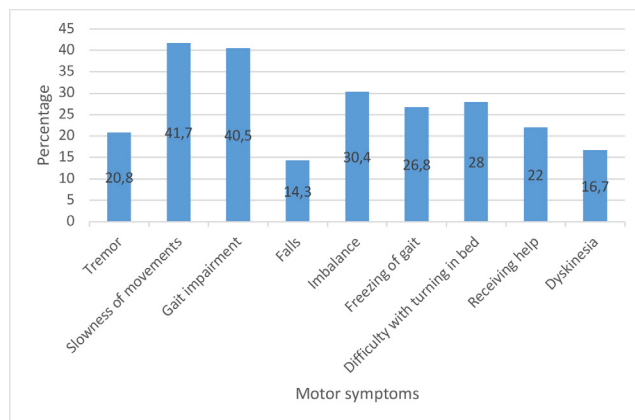


Figure 1. The percentage of motor symptoms: 20.8% tremor; 41.7% slowness of movements; 40.5% gait impairment; 14.3% falls; 30.4% imbalance; 26.8% freezing of gait; 28.0% difficulty with turning in bed; 22.0% receiving help; 16.7% dyskinesia

FOG were more common in patients with DBS, consistent with the literature. Tremors were less common in patients with DBS, and the proportion of those receiving help from a caregiver was lower. The long-term use of levodopa leads to dyskinesia, and patients with DBS frequently have a more advanced disease stage and motor fluctuations (21-23). DBS has positive effects on dyskinesia (19,23). The rate of dyskinesia was higher in the patients with DBS, which may be related to the higher rate of on-off fluctuations and longer disease duration in the patients with DBS. The slowness of movement and gait impairment (40% impairment) were the symptoms that worsened most frequently in both patient groups within 60 days of quarantine. The severity of tremor and difficulty in turning in bed were higher in the group without DBS than in the group with DBS.

Anxiety and depression, which are frequent in PD, reduce the quality of life, independent of the motor signs of PD (24). They also have adverse effects on motor signs and complications (25). While DBS improves some NMS, the severity of other NMS remains the same or deteriorates (26). Although bilateral STN DBS leads to increased sleep quality, it also leads to greater daytime sleepiness (27). Patients with RBD have a longer disease duration and a more advanced disease (28). In our cohort, the rates of daytime sleepiness and RBD were higher in patients with DBS. Overall, nervousness and anxiety were the NMS impaired most frequently (~30%). When the two groups were compared, insomnia was more common in the group without DBS.

Exercise and physiotherapy can positively affect the limitations of PD, reduce the severity of motor symptoms and improve daily activities (29). In a previous study, after a one month quarantine, the physiotherapy of 88.6% of the patients with PD was interrupted, and this led to a

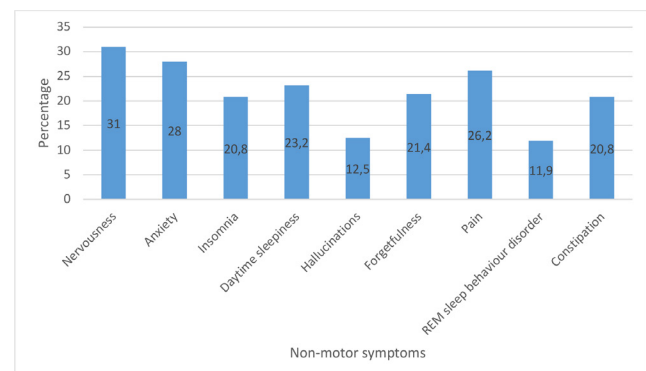


Figure 2. The percentage of non-motor symptoms: 31.0% nervousness; 28.0% anxiety; 20.8% insomnia; 23.2% daytime sleepiness; 12.5% hallucinations; 21.4% forgetfulness; 26.2% pain; 11.9% REM sleep behaviour disorder; 20.8% constipation REM: Rapid eye movement

worsening of the motor symptoms (30). van der Heide et al. (31) reported that half of their patients became less inactive during quarantine, and the presence of anxiety, depression, and cognitive dysfunction before quarantine led to increased psychological distress during the pandemic. Zipprich et al. (32) found that while 58% of the patients had anxiety and worries, remaining immobile by staying at home and not being able to receive physiotherapy led to impaired PD signs in 31%. We also inquired about the reasons for subjective impairment in motor symptoms and NMS. While almost half of the patients suggested that the disease had progressed, one-third complained of not being able to go to their doctor, and one-third complained of not being able to go walking, exercising, or receiving physiotherapy.

In a previous study, the authors found that living alone during quarantine caused more deterioration of both motor and NMS (33). According to our results, most of the patients did not complain about being not visited (only 3%). In Turkey, there is traditionally a situation of helping parents and not leaving them alone.

In community-based studies, COVID-19-related stress is more common in the younger population and among females (34). The rate of stress reaches 80% in healthy individuals (35). In our study, this rate was 28%, half of that reported in a previous study of patients with PD (16). The stress due to COVID-19 was low in our patients, which might be because they already had a chronic disease (i.e. PD), were older, and were predominantly male.

Only 1-5% of the patients experienced difficulties with medications (1-5%), possibly because the government arranged a way for chronic disease patients to obtain their medications during the COVID-19 pandemic.

The numbers of patients who were bored because they stayed at home and who showed deterioration in their clinical condition because they could not go for walks, exercise, or undergo physiotherapy suggest that the disease had progressed more in the group without DBS. The disease duration and proportion of patients experiencing disability due to PD were higher in the patients with DBS. Learning how to cope with this disease, the significant improvement in motor signs after DBS surgery, and hoping for a future battery programming after the quarantine might have helped the patients feel safer. Approximately 40% of the patients with DBS thought that they needed battery reprogramming. The batteries had depleted in six patients, although this number will likely increase if the duration of quarantine is prolonged.

Study Limitations

There are several limitations of this study: First MDS-unified PD rating scale and NMS questionnaire

are structured and frequently used scales for motor and NMS symptoms of PD. We did not apply these questionnaires because we wanted to ask the patients the change of symptoms, especially after quarantine, so we prepared a new questionnaire for lockdown. Second, we evaluated the patients by phone. It would be better to see the patients via a video call. Third, the gait impairment and FOG are motor problems that are difficult to evaluate by phone call. Finally, the current drug therapy was not administered to the patients. The equivalent dose of levodopa was not calculated. So we could not estimate the effect of drug therapy on these results.

Despite these limitations, the study has strengths: 1- This is the first study that questioned a high number of patients with PD with DBS under quarantine. 2- Both motor and NMS got worse according to our results. We also investigated the reasons for this clinical outcome with a specifically structured questionnaire.

Conclusion

While approximately half of the patients with PD had impaired motor symptoms and NMS, only 43% believed that their disease had progressed. Fewer patients with DBS indicated that their clinical condition had deteriorated, although they had longer disease durations. Considering these findings, providing psychological support using technology, making patients feel that they are not alone, and communicating with patients' and their relatives via video meetings could prevent deterioration of PD symptoms during the quarantine. It is necessary to allow the patients to walk outside during the hours when the rest of the population is inside and to schedule online exercise programs. Although patients with DBS seem to experience fewer problems than the group without DBS, adopting patient programmers and rechargeable batteries may be helpful.

Ethics

Ethics Committee Approval: The protocol for the research project has been approved by the Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee (date: 03-07-2020 and approval number: 10840098-604.01.01-E.15486).

Informed Consent: We got consent from the patients and caregivers for this study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: N.H.Y., L.H., Design: N.H.Y., L.H., Data Collection, or Processing: N.H.Y., B.B.K., T.A.Z., A.S.A., Analysis, or Interpretation: N.H.Y., B.B.K., Literature Search: N.H.Y., L.H., Writing: N.H.Y., B.B.K., L.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this research did not receive any specific grant from the funding agencies.

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