



Risk factors for levodopa-induced dyskinesia in Parkinson's disease patients

Faktori rizika od diskinezija uzrokovanih levodopom kod obolelih od Parkinsonove bolesti

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Abstract

Background/Aim. Levodopa, the precursor of dopamine, is a substitute therapy for Parkinson's disease. Long-term application of levodopa causes fluctuation in motor response and the occurrence of involuntary movements or dyskinesia. The aim of this study was to assess the risk factors for dyskinesia in Parkinson's disease (PD) patients undergoing treatment with levodopa. **Methods.** We included 177 consecutive outpatients with PD, who had been undergoing treatment for at least six months. A semi-structured interview was used to collect demographic and clinical data as well as a number of clinical scales. **Results.** Patients with dyskinesia ($n = 90$) were younger at disease onset and had longer disease duration. They had higher Unified Parkinson's Disease Rating Scale (UPDRS) scores and more frequently had other motor complications, such as wearing-off and freezing of gait, as well as non-motor ones, such as psychosis. They took higher levodopa doses and levodopa equivalent doses and were on levodopa therapy for a longer period of time. Multivariate analysis yielded that independent risk factors for dyskinesia were: disease duration of longer than 10 years [relative risk (RR) = 2.90, 95% confidence interval (CI) 1.19–7.10; $p = 0.019$], dopaminergic treatment duration of longer than 94 months (RR = 3.21, 95% confidence interval (CI) 1.05–9.87; $p = 0.041$) and levodopa dosage of higher than 537 mg (RR = 3.62, 95%IP 1.57–8.35; $p = 0.002$). **Conclusion.** We highlight the importance of known risk factors for dyskinesia and their occurrence in the context of advanced, complicated disease.

Key words:

parkinson disease; disease progression; levodopa; dyskinesia, drug-induced; risk factors; surveys and questionnaires.

Apstrakt

Uvod/Cilj. Levodopa, prekursor dopamine predstavlja supsticionu terapiju Parkinsonove bolesti. Dugotrajna upotreba levodopa uzrokuje fluktacije motornog odgovora i pojavu neželjenih pokreta ili diskineziju. Cilj rada bio je procena značaja faktora rizika od razvoja diskinezija uzrokovanih levodopom kod obolelih od Parkinsonove bolesti (PB). **Metode.** Istraživanje je obuhvatilo 177 bolesnika sa PB, regrutovanih na Neurološkoj klinici Kliničkog centra Srbije (Beograd), čije lečenje je trajalo duže od šest meseci. Za ispitivanje obolelih korišćene su standardizovane skale za kvantifikovanje PB, ali i detaljni posebno konstruisani upitnik za ovu studiju sa demografskim i kliničkim podacima. **Rezultati.** Bolesnici sa diskinezijama ($n = 50$) bili su mlađi na početku bolesti i imali su duže trajanje bolesti. Takođe, oboleli sa diskinezijama imali su veće skorove na Unified Parkinson's Disease Rating Scale (UPDRS), učestalije motorne komplikacije – fluktacije terapijskog odgovora (bilo u formi skraćivanja trajanja pojedinačnih doza ("wearing off") ili motornih blokova hoda ("freezing")) i češće su ispoljavali medikamentoznu psihozu. Oni su bili i na statistički višim dozama levodope, ali i višoj ekvivalentnoj dozi levodope, pri čemu je njihovo lečenje trajalo značajno duže. Multivarijantna analiza pokazala je da su nezavisni prediktori pojave diskinezija u grupi bolesnika sa PB bili: dužina bolesti preko 10 godina [relativni rizik (RR) = 2.90, 95% interval poverenja (IP) 1.19–7.10; $p = 0.019$], dužina terapije više od 94 meseci (RR = 3.21, 95%IP 1.05–9.87; $p = 0.041$), dnevna doza levodope u trenutku ispitivanja veća od 537 mg (RR = 3.62, 95%IP 1.57–8.35; $p = 0.002$). **Zaključak.** Potvrđen je značaj poznatih faktora rizika od razvoja diskinezija u odmakloj fazi Parkinsonove bolesti.

Ključne reči:

parkinsonova bolest; bolest, progresija; levodopa; diskinezija izazvana lekovima; faktori rizika; ankete i upitnici.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder whose key motor manifestations (e.g., bradykinesia, rigidity, tremor at rest) mainly result from the degeneration and death of dopaminergic neurons in *substantia nigra pars compacta*, with effects of a hypodopaminergic state and disturbed dopaminergic neurotransmission in the striatum¹. Levodopa, the precursor of dopamine, is a substitute therapy, which, following more than half of a century since its introduction, continues to be the basis of PD treatment² because it enables control of the basic motor symptoms which have occurred due to lack of dopamine. In idiopathic PD a good response to levodopa is the rule, which has also become a part of diagnostic criteria for this disease³. However, the long-term application of levodopa has been followed with, amongst others, the occurrence of motor complications which generally involve the fluctuation of motor response and the occurrence of involuntary movements or dyskinesia^{4,5}.

The first description of dyskinesia was given by Cotzias et al.⁶ in affected patients who were initially successfully treated with levodopa. It has been shown that the dyskinesia additionally disables the affected individuals, sometimes even more so than the basic disease, and moreover, it limits the ability for treatment with dopaminomimetic drugs⁷. Even though it is considered that dyskinesias are unavoidable at some point of disease progression, not all affected individuals will develop them at the same time, nor will their intensity be uniform⁸. As a risk factor for the development of dyskinesias, notables are: an earlier onset of PD, a longer duration of disease, longer exposure to levodopa, higher total dose of levodopa, female sex, and likely, different genetic factors^{9,10}. Their recognition is especially important for the planning of individual therapies¹¹.

The aim of our study was to identify demographic and clinical factors of risk which most significantly impact the appearance of dyskinesia during the chronic use of levodopa in our population of affected individuals with PD.

Methods

Our research included 177 patients with PD, who were recruited at the Neurology Clinic of the Clinical Center of Serbia from 2009 to 2011. The PD diagnosis was made according to the afore-published criteria of Ward and Gibb³. Demographic and clinical data were obtained through the use of a detailed, specially designed (for this study) questionnaire which, among other facts, included the age of the patient at onset of PD, the initial dose of levodopa, the latency period between the first PD symptoms and the beginning of levodopa therapy, the time of the occurrence of dyskinesia, and the therapy that the patient underwent at that time, use of other antiparkinsonian drugs and levodopa-equivalent doses (calculated per the method described by Tomlinson et al.¹²).

The PD severity was assessed with reference to the Unified PD Rating Scale (UPDRS)¹³, and in order to determine

the stage of disease, the Hoehn and Yahr¹⁴ (HY) system was applied. The functionality and performance of daily activities were assessed using the modified Activities of Daily Living Scale¹⁵. Dyskinesia was quantified per the modified Abnormal Involuntary Movement Scale (AIMS)¹⁶ and Goetz's scale for the Quantification of Dyskinesia¹⁷. For the assessment of depression and anxiety, the Hamilton Depression Rating Scale (HDRS)¹⁸ and the Hamilton Anxiety Rating Scale (HARS)¹⁹ were used, respectively, and for patient cognitive function, the Mini Mental State Examination (MMSE)²⁰ was applied. Testing was performed during the "on" phase (the phase in which the optimal drug therapy and motor improvement were achieved in the patient).

Statistical analysis of the acquired data involved the following methods: descriptive statistics, parametric and non-parametric tests, univariate and multivariate logistic regression analysis. For the comparison of continuous variables, we used the analysis of variance, and for the categorized variables, the χ^2 test. The criteria for the multivariate model were defined by the statistical significance of 0.05, obtained from the univariate analysis. As a measure of the effects, relative risk (RR) was used with a 95% confidence interval (95% CI).

Results

In our study 177 PD patients were involved, 118 (65.5%) men and 61 (34.5%) women, of an average age of 58.9 ± 10.9 years (mean value \pm standard deviation), with disease onset at the age of 49.0 ± 11.2 years, and a duration of 9.7 ± 6.2 years.

Of the 177 patients in the study group, 90 developed, whereas 87 did not develop dyskinesia (Table 1). Patients in these two groups did not have any differences based on sex, dominant hand, age, education, heredity, and form of PD, or presence of depression symptoms. The statistically significant difference was noted for age at onset of PD, duration of disease and MMSE score (Table 1).

Patients with dyskinesia were at a statistically significant more advanced PD stage, as well as higher scores on the UPDRS, and more problems in daily functioning as measured per the Schwab and England scale (Table 2). This group of affected patients had statistically significant more frequent fluctuations in therapeutic response (either in the form of a shorter duration of individual doses (referred to as wearing off), or the on-off phenomenon. They developed motor blocks while walking (referred to as freezing of gait) more frequently and with a shorter latency from the both disease onset and the moment in which treatment began, in comparison to the patients without dyskinesia (Table 2). Finally, patients with dyskinesia in a statistically significant manner, more often demonstrated medication psychosis.

PD patients with dyskinesia, as compared to those without dyskinesia, in a statistically significant manner, differed with respect to the duration of treatment, application of therapy (more often were on levodopa, amantadine and clozapine, and less often on monoamine oxidase (MAO) B inhibitors) (Table 3). In addition, these patients were on larger

Table 1
Demographic and clinical characteristics of Parkinson's disease (PD) patients (n = 177), with and without dyskinesia

Parameters	PD-Dys+	PD-Dys-	<i>p</i>
Patients, n (%)	90 (50.8)	87 (49.2)	0.214
Male, n (%)	57 (63)	59 (68)	0.530
Right-hand dominant, n (%)	88 (98)	84 (97)	0.623
Age (years), $\bar{x} \pm SD$ (range)	60.3 \pm 8.9 (38–79)	57.3 \pm 12.7 (28–82)	0.067
Education (years), $\bar{x} \pm SD$ (range)	11.4 \pm 3.7 (3–17)	12.4 \pm 3.3 (4–17)	0.136
Positive family history, n (%)	20 (22)	13 (15)	0.214
Age at PD onset (years), $\bar{x} \pm SD$ (range)	47.3 \pm 9.6 (20–66)	50.7 \pm 12.4 (27–72)	0.045
Duration of disease (years), $\bar{x} \pm SD$ (range)	12.5 \pm 6.7 (3–37)	6.7 \pm 5.1 (0–25)	0.001
Form of disease, n (%)			0.241
tremor dominant	44 (49)	43 (49)	
akinetic-rigid	24 (27)	20 (23)	
postural instability	12 (13)	11 (13)	
MMSE score, n (%)	27.6 \pm 3.1 (14–30)	28.5 \pm 2.2 (16–30)	0.033
HDRS score, n (%)	11.7 \pm 8.6 (0–39)	10.3 \pm 7.2 (0–26)	0.220
HARS score, n (%)	7.7 \pm 6.1 (0–21)	6.9 \pm 5.8 (0–22)	0.506

PD-Dys+ – PD patients with dyskinesia; PD-Dys- – PD patients without dyskinesia; MMSE – Mini Mental State Examination; HARS – HDRS – Hamilton's Depression Rating Scale; Hamilton's Anxiety Rating Scale; \bar{x} – mean; SD – standard deviation.

Table 2
Severity of motor and non-motor symptoms in Parkinson's disease (PD) patients with and without dyskinesia

Parameters	PD-Dys+	PD-Dys-	<i>p</i>
H-Y state, $\bar{x} \pm SD$ (range)	2.5 \pm 0.7 (1.5–4)	2.1 \pm 0.5 (1–3)	0.001
UPDRS total score, $\bar{x} \pm SD$ (range)	68.9 \pm 22.3 (15–125)	48.8 \pm 22.2 (7–101)	0.001
SE score, $\bar{x} \pm SD$ (range)	72.6 \pm 16.1 (3–100)	80.6 \pm 13.2 (50–100)	0.001
Fluctuations, n (%)	72 (80)	26 (30)	0.001
latency from PD onset (months), $\bar{x} \pm SD$ (range)	77.2 \pm 47.3 (0–252)	61.8 \pm 50.9 (0–180)	0.179
latency from introduction of therapy (months), $\bar{x} \pm SD$ (range)	73.7 \pm 46.7 (12–294)	55.2 \pm 30.5 (5–144)	0.073
Wearing off, n (%)	60 (67)	21 (24)	0.001
On-off, n (%)	25 (28)	7 (8)	0.001
Motor blockade (freezing), n (%)	50 (56)	22 (25)	0.001
Latency from PD onset (months), $\bar{x} \pm SD$ (range)	97.2 \pm 59.6 (6–240)	62.8 \pm 67.3 (0–288)	0.037
Latency from introduction of therapy (months), $\bar{x} \pm SD$ (range)	102.5 \pm 53.6 (20–294)	62.7 \pm 39.6 (0–168)	0.004
Medication psychosis, n (%)	31 (34)	10 (12)	0.001

PD-Dys+ – PD patients with dyskinesias; PD-Dys- – PD patients without dyskinesia; H-Y – Hoehn-Yahr; UPDRS – Unified Parkinson's Disease Rating Scale; SE – Schwab and England. \bar{x} – mean; SD – standard deviation.

Table 3
Therapy applied in Parkinson's disease (PD) patients with and without dyskinesia

Parameters	PD-Dys+	PD-Dys-	<i>p</i>
Latency (symptoms onset until therapy introduction) (months), $\bar{x} \pm SD$	22.5 \pm 25.6	19.2 \pm 17.9	0.320
Duration of therapy (months), $\bar{x} \pm SD$	129.5 \pm 62.7	58.1 \pm 52.8	0.001
Levodopa, n (%)	90 (100)	70 (81)	0.001
Pramipexole, n (%)	36 (40)	28 (32)	0.279
Ropinirole, n (%)	23 (26)	16 (18)	0.250
Bromocriptine, n (%)	15 (17)	5 (6)	0.022
Amantadine, n (%)	64 (71)	25 (29)	0.001
MAO B inhibitors, n (%)	2 (2)	9 (11)	0.024
COMT inhibitors, n (%)	4 (4)	5 (6)	0.693
Clozapine, n (%)	27 (31)	10 (12)	0.003
Anticholinergics, n (%)	13 (14)	6 (7)	0.117

PD-Dys+ – PD patients with dyskinesia; PD-Dys- – PD patients without dyskinesia; MAO-B – monoamine oxidase B; COMT – catechol-O-methyltransferase. \bar{x} – mean; SD – standard deviation.

doses of levodopa (605 \pm 212 mg vs 450.7 \pm 200.8 mg), and also on higher levodopa equivalent doses (808.3 \pm 256.9 mg vs 497.3 \pm 286.5; *p* = 0.000).

Multivariate analysis demonstrated that independent predictors of the onset of dyskinesia in the group of patients with PD were: duration of disease of more than 10 years (RR = 2.90,

95% CI 1.19–7.10; *p* = 0.019), duration of levodopa therapy of more than 94 months (RR = 3.21, 95% CI 1.05–9.87; *p* = 0.041), daily dose of levodopa at the date of testing of more than 537 mg (RR = 3.62, 95% CI 1.57–8.35; *p* = 0.002), and amantadine therapy (RR = 2.99, 95% CI 1.29–6.89; *p* = 0.010). The results of univariate analysis are not shown.

In regard to certain types of involuntary movements (dyskinesias) that were noted, the most frequent among them were choreatic ones (82.2%), followed by dystonic movements (77.8%), whereas ballistic dyskinesias (8.9%) were least frequent. Dyskinesias were most often presented at the moment when the highest concentration of levodopa was attained after each individual dose ("peak of dose" dyskinesia, 77.8%), in approximately one-half of patients they appeared at the end of the effectiveness of the individual dose of levodopa ("end of dose" dyskinesia, 45.6%), whereas diphasic dyskinesia (at the beginning and at the end of the effectiveness of the individual dose of levodopa) were identified in only 4.4% of the test subjects. Dyskinesias in 73% of the patients worsened their functional abilities, and such disability was heavy in 15.4%, moderate in 46.2% and light in 38.5% of the PD patients. Dyskinesia appeared with a latency of 74.6 ± 48.8 months from the initiation of dopaminergic therapy.

Discussion

The main findings of our research indicate that PD patients who developed dyskinesia, differed from those who did not, according to the following: age at the onset of disease, length of disease, results on the MMSE scale, and had a more difficult form of Parkinson's disease, higher scores on the UPDRS, greater difficulty in daily functioning, more frequent motor fluctuations and medication-induced psychosis, in the duration of treatment and in larger daily doses of levodopa, or of dopaminomimetics. As the strongest predictors of dyskinesia induced by levodopa, the following were identified: the length of disease of more than 10 years, length of treatment of more than 94 months and an actual daily dose of levodopa of more than 537 mg.

Dyskinesias developed in approximately 50% of patients involved in our study, which is in accordance with the average findings of other researches (30%–80%). This range is explained by the variety of methodological approaches used in identifying dyskinesia, by the different age groups that were analyzed, and by the difference in the length of monitoring of affected patients. In individuals who have had PD for 4 to 7 years, the presence of dyskinesia has been 20%–40%^{21–23}. Schrag and Quinn²⁴ found dyskinesia in 32% of patients treated with levodopa for 6 to 9 years, and in 89% of patients treated for more than 10 years. In the DATATOP study²³ after 20.5 months of being treated with Levodopa, dyskinesias presented in a third of the PD patients. In short, it is assumed that after a sufficiently long treatment period with levodopa, all patients will, in the end, develop dyskinesia²⁵.

Similarly to the other authors²⁶, we identified chorea and dystonia as the most frequent types of dyskinesia that arise from levodopa use. They presented most frequently as the peak of dose dyskinesias, but in almost half of the patients, they manifested at the end of the levodopa dose effectiveness ("end of dose" dyskinesia). Dyskinesia heavily disabled only 15% of our patients. This result is similar to the finding that dyskinesia whose intensity requires therapeutic in-

tervention, or otherwise the adjustment of levodopa therapy after a treatment period of 10 years, is found in 12% of patients⁸. This finding is identical to the Sidney study²⁵ that revealed that only 12% of patients developed a difficult (or heavy) form of dyskinesia.

The development of dyskinesia is associated with different risk factors such as an earlier onset of disease, a longer duration and difficulty of PD, a longer duration of treatment with levodopa, a larger cumulative dose of levodopa, a higher daily dose of levodopa at the time of testing, and also its initial daily dose, female sex and possible genetic factors^{9,10,27}. Our study confirmed the significance of these factors in the development of dyskinesia arising from levodopa.

Of particular significance in the planning of individual therapy is the finding that in individuals who had an earlier onset of PD, fluctuations and dyskinesia more frequently presented, and thus such affected patients had a more difficult disease progression. After five years of treatment with levodopa, more than 50% of patients in which PD was presented during the ages of 40 through 59, had dyskinesia, while such frequency decreased in the group with PD was arising during the ages of from 60 to 69, to 26% or even 16% in so far as the PD was presented after the age of 70^{9,28}. Kostic et al.²⁸ indicate that after five years of levodopa treatment, they identified dyskinesia in 90% of patients in which PD had been presented before the age of 40. Hence, the same authors suggest initial therapy with dopamine agonists instead of levodopa for patients with PD for whom disease onset is presented at earlier age¹¹. Dyskinesia was more prevalent in patients treated with higher daily doses of levodopa. This is in agreement with the findings of the ELLDOPA study²⁹ which demonstrated that the prevalence of dyskinesia increased with the increase in a daily dose of levodopa.

In our research, the length of the duration and difficulty of PD were significant factors. Van Gerpen et al.⁸ showed that in a group of 126 PD patients, the likelihood that dyskinesia will develop during the first five years of illness was 30%, whereas it was 59% during the first ten years of illness. Advanced forms of PD with greater pathological findings upon the introduction of levodopa were followed by the faster onset of heavier forms of dyskinesia in comparison to the lighter forms of the illness³⁰, which also was confirmed in the animal model of PD³¹.

As a key factor in the development of dyskinesia, intermittent ("pulse"), non-physiologic stimulation of dopamine receptors in the basal ganglia utilizing standard oral forms of dopamine mimetics was noted, as in all of our patients^{32,33}. Hence a large segment of pharmacotherapeutic interventions is focused on establishing forms of treatment by which continuous dopaminergic stimulation is achieved³⁴. The finding that dyskinesia is more rarely presents in patients being treated with dopamine agonists in relation to levodopa³⁵ is explained by their longer half-life in blood plasma. The finding of our study that PD patients with dyskinesias, in comparison to those without them, were significantly more frequently treated with amantadine, can be explained by the fact that at this moment, it is the only drug that specifically lessens their intensity³⁶. This can in part be an explanation for the more frequent use of clozapine in this

group of patients because it possesses anti-dyskinetic effects too³⁶, however, it is much more likely that a more frequent presentation of medication psychosis occurred in this group. It is interesting to note that affected patients who did not develop dyskinesia, in a statistically relevant manner more frequently received selegiline therapy (MAO B inhibitor), however the scope and methodology of our study are inadequate so as to be able to present the assumption that this drug has a protective effect involved in the onset of dyskinesia. The application of MAO B inhibitors in the early phase of PD was connected with the statistically relevant, less frequent fluctuations in motor response, whereas such a difference was not noted with respect to dyskinesias³⁷.

Conclusion

In our research, on average, slightly more than half of our PD patients developed dyskinesia. In comparison to the patients without dyskinesia, they were significantly younger at the onset of disease, the PD had a longer duration, and PD patients were on levodopa therapy for a longer period, and on the statistically significant higher daily dose.

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