Original Article

Predictors of Levo-dopa induced Dyskinesias in Parkinson's Disease

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Abstract

Background: Levodopa has a superior antiparkinsonian effect than dopamine agonists making it the standard of care for patients with Parkinson's disease (PD). During the initial stages, PD patients show a steady response to levodopa. Response fluctuations and levodopa-induced dyskinesias (LID) develop subsequently. The timing and onset of dyskinesias vary among individuals, and there are very few studies identifying the predictors of dyskinesia in India. **Aims:** We aimed to study the clinical profile, disability, and predictors of LID in a patient with PD. **Materials and Methods:** This was a cross-sectional observational study of consecutive patients with PD attending our movement disorder clinic. Patients on levodopa treatment with a minimum follow-up of 6 months were included in the study. All patients were observed before and after administration of levodopa to assess onset, duration of action, and timing of dyskinesias. Dyskinesias were video recorded and classified. Bivariate analysis was performed using Chi-square test or Fisher's exact test and multivariate analysis using binary logistic regression. **Results:** This study recruited 110 patients with PD on levodopa therapy. Thirty-one (28.1%) out of 110 had LID. Of these, 25 patients (80.6%) had on-time dyskinesia, 19 patients (61.3%) had off-time dystonia, and 13 patients (41.9%) had diphasic dyskinesia. Majority had only mild-to-moderate dyskinesia. Incapacitating dyskinesias were during off time, primarily affecting the foot. Age, disease duration, disease severity, duration of treatment, and total dose of levodopa were found to be predictors of LID. Multivariate regression analysis showed younger age and longer duration of levodopa treatment to be independent predictors for LID. **Conclusions:** LID is fairly common in PD though not severely disabling. Patients with younger age of onset, longer disease duration, and severe disease were more likely to get early LID. We observed the lower prevalence of LID when initiating at lower doses and slow titration of levodopa.

Keywords: Levodopa, levodopa-induced dyskinesias, Parkinson's disease

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases encountered in clinical practice. Increased awareness and access to quality health care have seen a greater number of patients on Levodopa treatment in India. The initial solace patients and treating doctors' experience due to the exquisite response to levodopa gives way to despair with the onset of disabling dyskinesias. Invariably, most PD patients go on to develop levodopa-induced dyskinesias (LID).[1] However, some patients develop early or severe disabling dyskinesias. The factors deciding which subset of PD patients go on to develop early or severe disabling dyskinesias are less clear. Dyskinesias can vary in type and severity. The management of LID also depends on the same. We undertook this study to analyze the clinical profile, disability, and predictors of LID.

Materials and Methods

This was a cross-sectional observational study conducted in the Department of Neurology, Government Medical College, Thiruvananthapuram. Consecutive patients with PD (The UK PD Brain Bank Clinical Criteria), attending our movement disorder clinic, were included in the study after obtaining the Institutional Ethics Committee approval. Patients on levodopa treatment with a minimum follow-up of 6 months were included in the study. Patients on antipsychotics, those with alternative causes for dyskinesia, and who had premorbid dyskinesia were excluded from the study. The predictors of LID in patients with PD were studied and analyzed. We also examined the clinical profile and effect of LID on activities of daily living (ADL).

After obtaining written informed consent, the patient's demographic details and clinical information including disease duration, duration of treatment with levodopa, the total dose of levodopa per day, and drugs currently used were noted. Video recordings of dyskinesias were analyzed for classification.[2] The modified Hoehn and Yahr stage,[3] Unified PD Rating Scale Part III, Unified Dyskinesia Rating Scale,[4] and PDY-26 item questionnaire were recorded. All patients were observed before and after administration of levodopa to assess onset,

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duration of action, and timing of dyskinesia. Statistical analysis was done using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Quantitative variables, not normally distributed, were expressed as median and interquartile intervals and qualitative variables were expressed as percentage. Bivariate analysis was done using Chi-square test or Fisher's exact test and Mann–Whitney U-test and multivariate analysis was done using binary logistic regression.

Results

This study recruited 110 patients with Parkinson's disease (PD) on levodopa therapy. Thirty-one (28.1%) out of 110 patients had LID. Of these, 25 patients (80.6%) had on-time dyskinesia, 19 patients (61.3%) had off-time dystonia, and 13 patients (41.9%) had diphasic dyskinesia. The percentage of patients with young-onset PD (≤40 years) in our study was 2.7% (3 patients). Table 1 shows the baseline characteristics of PD patients.

Bivariate analysis showed the age of the patient, modified Hoehn and Yahr stage, disease duration, duration of treatment with levodopa, the total dose of levodopa per day, and total levodopa equivalent dose to be determinants of LID [Table 1]. On multivariate regression analysis, younger age and longer duration of levodopa treatment were found to be independent predictors for LID.

Time spent with dyskinesia and the effect of dyskinesia on ADL was assessed using the Unified Dyskinesia Rating Scale. One patient (4%) spent <25%, 8 patients (32%) spent 26%–50%, 9 patients (36%) spent 51%–75%, and 7 (28%) patients spent >75% of on time with dyskinesia. On-time dyskinesia affected ADL to a variable extent. On-time dyskinesia showed a mild effect on ADL such as chewing, eating habits, dressing, hygiene, and walking balance in >50% of the patients. On-time dyskinesia caused a moderate effect in doing hobbies, in public places, and exciting situations in more than a third of the patients. On-time dyskinesia caused a severe effect on ADL such as in handwriting and exciting situations in 22.6% of the patients. Off dystonia was also studied with regard to time spent and effect on ADL. One patient (5.3%) spent <30 min a day, 6 patients (31.6%) spent <60 min a day, 2 patients (10.5%) spent <2 h a day, and 10 patients (52.6%) had >2 h a day with off dystonia. The effect of spasms and cramps due to off dystonia on ADL was also varied. We found a slight effect in 1 person (5.3%), mild in 1 person (5.3%), moderate in 6 persons (31.6%), and severe in 11 persons (57.9%). Pain due to off dystonia affected ADL slightly in 1 patient (5.3%), mildly in 2 persons (10.5%), moderately in 4 persons (21.1%), and severely in 12 persons (63.2%). We found that dystonia pain caused a slight effect in 1 person (5.3%), mild in 1 person (5.3%), moderate in 4 persons (21.1%), and severe in 13 persons (68.4%). Overall, off dystonia had a severe effect on ADL compared to on-time dyskinesias.

Greater than 60% of patients with LID had only mild-to-moderate dyskinesia (Unified Dyskinesia Rating Scale Part III). Around 16% had severe or incapacitating dyskinesia. The disability caused by dyskinesia in communication, drinking, dressing, and ambulation were video recorded and graded. Dyskinesia did not impair communication in 32.2% of the patients, impaired communication but still understandable in 19.3% of the patients, parts of communication not understood (the overall content understandable) in 38.7% of the patients, and interfered with overall communication in 9.6% of the patients. Dyskinesia did not affect drinking in 45.1% of the patients, affected the smooth performance but caused no splashing or spilling in 16.1% of the patients, and resulted in coughing or choking in 6.4% of the patients. Dyskinesia did not interfere with or caused slow dressing in 41.9% of the patients, affected the smooth performance of the dressing minimally in 22.5% of the patients, and precluded completion of the dressing within 60 s in 16.1% of the patients. Dyskinesia did not alter gait in 25.8% of the patients; changed the cadence of rising, sitting,

Table 1: Baseline characteristics of idiopathic Parkinson's disease patients

	Total PD patients	Patients with LID	Patients without LID	*P*
n (%)	110	31 (28.1)	79 (71.9)	
Median age (IQI)	61 (54-66)	60 (49-63)	63 (54-66)	0.010
Male gender, *n* (%)	57 (51.8)	15 (48.4)	42 (53.2)	0.652
Years of median formal education (IQI)	9.5 (6-10)	10 years (6-10)	9 (6-10)	0.832
Unmarried, *n* (%)	23 (21.45)	7 (22.6)	16 (20.3)	0.787
APL, *n* (%)	28 (25.5)	6 (19.4)	22 (27.8)	0.358
Vegetarian, *n* (%)	0.9	3.2	0	0.282
UPDRS motor median score (IQI)	12 (9-16.25)	16 (12-23)	12 (8-14)	0.085
Median-modified Hoehn and Yahr stage (IQI)	2.5 (2.5-3)	2.5 (2.5-3)	2.5 (2.5-2.5)	0.031
Median disease duration, years (IQI)	4 (2-6)	6 (4-10)	4 (2-5)	0.001
Median duration of treatment with levodopa, years (IQI)	3 (1-5)	5 (2-7)	2 (1-4)	0.001
Median total dose of levodopa per day, mg (IQI)	300 (300-500)	400 (300-600)	300 (200-400)	0.024
Median total levodopa equivalent dose, mg (IQI)	350 (300-550)	500 (300-850)	300 (300-500)	0.014
Median on-time, h (IQI)	13.5 (11.75-15)	12 (10-14.5)	14 (12-15)	0.231
Median off-time, h (IQI)	3 (2-4)	4 (2.5-6)	3 (2-4)	0.114

PD=Parkinson's disease, LID=Levodopa-induced dyskinesias, UPDRS=Unified Parkinson's Disease Rating Scale, APL=Above poverty line, IQI= Interquartile interval

or walking but did not slow overall performance in 29% of the patients; disrupted arising, sitting, or walking with slowed performance in 38.7% of the patients; and prohibited walking safely without assistance in 6.4% of the patients.

Dyskinesia resulted in mild affection (PDY 0–26) of ADL in 3 patients (12%), moderate affection (PDY 27–53) in 14 patients (56%), and severe affection (PDY >53) in 8 patients (32%). The subset of patients with diphasic dyskinesias were compared with other dyskinesias and the younger age was found to be significantly associated with diphasic dyskinesias (P = 0.048). Analysis revealed that gender was not associated with diphasic dyskinesias. Bivariate analysis was done in patients with LID to determine the predictors of those with severe dyskinesias affecting ADL. Greater disease duration, duration of treatment with Levodopa, higher Levodopa equivalent dose, and greater off duration were found to be significant predictors for severe dyskinesia affecting ADL [Table 2]. Female gender had an increased proportion of severe dyskinesias although this finding did not approach significance. Six out of the 16 female patients with LID had severe dyskinesias whereas only 2 out of the 15 male patients had severe dyskinesia. The median time to initiation of Levodopa in our cohort was 1 year (0–2). Six out of 31 (10.1%) patients who had LID were initiated on dopamine agonists (pramipexole) in contrast to 8 out of 79 (19.4%) among the patients without LID. This difference in proportions was not statistically significant (P = 0.212).

Discussion

This cross-sectional observational study reaffirms the role of age, disease duration, severity of disease, duration of treatment with levodopa, and total dose of levodopa as critical factors determining LID. The prevalence of LID in this study was 28.18%. Majority of previous studies showed a higher prevalence of LID. Hospital-based studies usually show a higher prevalence of LID compared to community-based studies. A lower prevalence was observed in this study similar to a community-based study by Schrag *et al*.[5] We propose the higher prevalence in previous studies to a higher initial dose of levodopa.[6] In a previous study with optimal use of Levodopa, the prevalence of LID could be restricted to 12%.[7] Our study found that LID is related to the duration of levodopa therapy, dose of Levodopa, and disease duration. Researchers have questioned the role of length of Levodopa therapy as the cause of LID due to the presence of confounders. The disease duration, Levodopa dose, and severity of disease all tend to be higher in patients with a more extended period of Levodopa therapy. Literature supports disease duration and the severity rather than the length of exposure to Levodopa to be related to LID.[8] This argues for early initiation of Levodopa at a lower dose as first-line agents, except for young-onset PD. Our patients with LID had a long median disease duration of 7.35 years compared to 4 years among those without LID. The observations by Cilia*et al*. in populations that remain drug naive for long periods separate the effect of duration of therapy with Levodopa from disease duration.[8] They concluded that motor dyskinesias are not associated with the duration of exposure to levodopa therapy, but rather to disease progression itself. However, most studies still show Levodopa therapy duration as a determinant of LID. In a study by Van Gerpen *et al*., the rate of LID increased from 30% at 5 years to 59% at 10 years of levodopa therapy.[7] The prevalence of 28.18% LID at 4 years compares well with this study. In another study, LID was developed at 10% for every year of levodopa therapy.[6] We initiated levodopa in patients with significant disability at a low dose with slow titration to maintain the ADL. The duration of levodopa treatment was found to be an independent risk factor for LID in our study. Our patients with LID had a higher median total dose of levodopa than those without LID.[5,9-13]

Table 2: Predictors of severe dyskinesias (PDY >53)

	Total dyskinesia patients	Severe dyskinesia (PDY >53)	Mild-to-moderate dyskinesia	*P*
n	31	8	23	
Median age (IQI)	60 (49-63)	53 (42.25-61)	60 (57-63)	0.093
Female gender (%)	16 (51.61)	6 (37.5)	10 (62.5)	0.220
Years of median formal education (IQI)	10 (6-10)	9 (6.25-10)	10 (4-10)	0.481
Unmarried, *n* (%)	7 (22.58)	3 (42.85)	4 (57.14)	0.335
APL, *n* (%)	6 (19.35)	0 (0)	6 (100)	0.298
Vegetarian, *n* (%)	1 (3.22)	0 (0)	1 (100)	1.000
UPDRS motor median score (IQI)	16 (12-23)	17.50 (12-27)	15 (11-20)	0.248
Median-modified Hoehn and Yahr stage (IQI)	2.5 (2.5-3.0)	3.0 (2.5-3.0)	2.5 (2.5-3.0)	0.163
Median disease duration, years (IQI)	6 (4-10)	10.50 (6.25-12.75)	5 (3-7)	0.011
Median duration of treatment with levodopa, years (IQI)	5 (2-7)	7.5 (6-11.75)	4 (1-6)	0.002
Median total dose of levodopa per day, mg (IQI)	400 (300-600)	600 (375-825)	300 (300-600)	0.081
Median total levodopa equivalent dose, mg (IQI)	500 (350-850)	850 (575-1150)	450 (300-600)	0.025
Median on-time, h (IQI)	12 (10-14.5)	12 (9.25-15.12)	12 (10-14.50)	0.662
Median off time, h (IQI)	7.5 (3.5-10.5)	10.25 (6.37-12.87)	6 (0-9)	0.046

UPDRS=Unified Parkinson's Disease Rating Scale, APL=Above poverty line, PDY=Parkinson's disease Dyskinesia rating scale (26 item), IQI= Interquartile interval

An earlier study using a higher dose of levodopa (>600 mg per day) in the initial 6 months had a higher prevalence of LID.[6] Cheshire *et al*. found that a higher levodopa equivalent dose was a risk factor for LID.[14] The lower median dose of 400 mg and a total Levodopa equivalent dose 500 mg/day could explain the lower prevalence of LID in our study. We kept our median off time for PD patients at 3 h/day by adjusting the frequency of administration of levodopa based on the duration of action of levodopa. We did not find off-time duration, a risk factor for LID. We found that chorea and dystonia, the most frequent involuntary movements, were associated with LID, in line with previous literature.[15] We observed an earlier onset of Parkinson's disease, which is an independent risk factor for LID, similar to previous publications.[7,10,11,14,16-18] Young-onset Parkinson's disease patients are known to develop more chorea and dystonia than late-onset patients.[19] In addition, patients started on levodopa therapy as the initial medication developed LID 2.5 years earlier than those initiated on dopamine agonist.[20] Therefore we prefer to start dopamine agonist in those with earlier onset of Parkinson's disease.[21] On- time dyskineisas were the most common dyskinesias followed by off-time dystonia and the least common diphasic dysknesia. Subgroup analysis revealed that younger age was found to be associated with the presence of diphasic dyskinesias. This was similar to the study by Shrag *et al*.[5] Unified Dyskinesia Rating Scale measured the effect of on-time dyskinesia on ADL. We found off-time dystonia more disabling than on-time dyskinesia. Off-time dystonia caused moderate-to-severe affection of ADL in >80% of patients. LID caused severe disability in >20% of patients in communication, drinking, dressing, and ambulation, similar to that reported earlier.[7,9,22] On-time dyskinesia (PDY 26-item questionnaire) severely affected ADL only in a third of the patients. LID adversely affects the quality of life only in the late stages of PD with severe dyskinesia, primarily severe painful dystonia. The choice between DA and levodopa depends on a trade-off between lower incidence of dyskinesia and the antiparkinsonian effects. We prefer DA over levodopa in young-onset parkinsonism due to the lower incidence of dyskinesia.[23] Therefore, we prefer to keep the dose of levodopa minimum to reduce LID, which will determine the quality of life. The need for uptitration increases with the duration of the treatment.

Conclusions

Our study showed that LID is more common in PD patients with younger age of onset, longer disease duration, and patients on longer duration of levodopa therapy. We observed the lower prevalence of LID due to starting low doses of levodopa and slow titration. In addition, we found off-time dystonia more disabling.

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Conflicts of interest

There are no conflicts of interest.

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