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ORIGINAL ARTICLE

Effect of onset age on the levodopa threshold dosage for dyskinesia in Parkinson's disease

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Abstract

Introduction With the levodopa threshold effect for dyskinesia observed, threshold dosage of levodopa was identified in the general Parkinson's disease (PD) population. While early-onset PD (EOPD) and late-onset PD (LOPD) differ in the pathogenesis and clinical manifestations, threshold dosage of levodopa for individualized treatment remains unestablished. The objective of this study was to propose threshold dosage of levodopa in EOPD and LOPD patients, respectively.

Methods Data on demographic and clinical and treatment measures were collected in 539 PD patients. Patients were divided into different onset groups using 50 as the cut-off age. We used univariable and multivariable analysis to screen for risk factors for dyskinesia. Receiver operating characteristic curve was used to determine the levodopa threshold dosages for dyskinesia.

Results The prevalence of dyskinesia was 47.7% (53/111) in the EOPD group and 24.1% (103/428) in the LOPD group. Risk factors identified for dyskinesia include high levodopa daily dose and levodopa responsiveness for EOPD patients and high levodopa daily dose, long levodopa treatment duration, low body weight, use of entacapone, and high Hoehn–Yahr stage in off state for LOPD patients. The daily levodopa threshold dosages were 400 mg or 5.9 mg/kg for EOPD and 450 mg or 7.2 mg/kg for LOPD.

Conclusion EOPD patients had lower levodopa threshold dosage comparing with LOPD patients. Treatment of EOPD requires stricter levodopa dose control to delay the onset of dyskinesia.

Keywords Parkinson's disease · Early-onset · Late-onset · Dyskinesia · Levodopa · Threshold dosage

Introduction

Parkinson's disease (PD) is a heterogeneous neurodegenerative disorder, with various subtypes emerged according to clinical, genetic, or pathologic findings [1]. To date, levodopa remains the most effective anti-parkinsonian medication, while chronic levodopa therapy is associated with the development of levodopa-induced dyskinesia (LID), causing impairment on quality of life and disability. At present, most studies on dyskinesia were based on the general PD population. Several risk factors for dyskinesia have been identified, including high levodopa dose, young age at onset, low body weight, female gender, long disease duration, disease severity, non-tremor dominate phenotype, depression, and anxiety [2–5].

In order to establish a better treatment strategy to delay the onset of dyskinesia, levodopa dose was studied as a main and most controllable factor. In the STRIDE-PD study, patients were divided into four groups with different levodopa treatment level, and a levodopa dose of less than 400 mg per day significantly lowered the occurrence of dyskinesia [2]. However, its choice of treatment doses was based on previous assumption instead of statistic calculation. To promote a more objective treatment strategy, we applied receiver operating characteristic (ROC) curve in our previous observational study based on the general Chinese PD population [6, 7]. In the ROC curve, a cut-off value determined by the highest Youden's index (value of

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sensitivity plus specificity minus one) was found eligible to be promoted as the threshold dose of relatively low risk for dyskinesia. Levodopa dose of or less than 400 mg per day was found to be the threshold dose for dyskinesia according to the statistical calculation [7]. Though age at PD onset has been identified as predictor for the occurrence of dyskinesia [8], the underlying mechanism remains unclear. Based on the age at onset, PD can be classified into early-onset PD (EOPD) and late-onset PD (LOPD). EOPD and LOPD were found to differ in terms of clinical manifestations (motor and non-motor symptoms), treatment responsiveness, progression, and prognosis [9–11]. Thus, it is reasonable to believe that the threshold dose of levodopa is distinct for different onset subgroups.

Despite the difference found between EOPD and LOPD, there is limited information regarding individualized levodopa treatment strategy. In this cross-sectional study, we applied 50 as the cut-off age to establish threshold dose of levodopa in EOPD and LOPD patients, respectively. We hypothesized that EOPD patients have lower levodopa threshold dose than LOPD patients. Calculation of the threshold doses were based on ROC curve as it was proved feasible in our previous studies [6, 7]. In ROC analysis, a variable is tested as a predictor for a binary outcome with cut-off or threshold value sought using the Youden's index, while the power of the test is measured by the area under the curve (AUC). It could provide us with objective threshold value based on statistical calculation and avoid the limitation of subjective division.

Methods

Participants

We recruited 539 patients with the diagnosis of PD at the in-patient department of Beijing Tiantan Hospital, Capital Medical University, from February 2017 to November 2019. Inclusion criteria were (1) diagnosis of idiopathic PD according to the Movement Disorder Society Clinical Diagnostic Criteria for PD [12] by two movement disorders specialists; (2) having regular levodopa intake for at least 6 months; and with historical information of dopaminergic drug use. Exclusion criteria were (1) uncertainly of diagnosis, suspicious secondary parkinsonism (vascular, drug induced, toxic induced, post-infectious, post-traumatic parkinsonism), or parkinsonism-plus syndromes; (2) a history of hydrocephalus, brain tumor, or deep brain stimulation implantation; and (3) a family history of Parkinson's disease, Parkinson-like symptoms, or any other neurodegenerative disorder among the first-, second-, and third-degree relatives.

Age at onset was defined as the age at which a motor symptom that later attributed to PD was first noticed by the patient or a caregiver. Patients were divided into two groups: those with age at onset before 50 years were classified into the EOPD group, and those with onset at age 50 or older were classified into the LOPD group. The cut-off value was determined based on previous studies [10, 13].

Data collection

Demographic information including gender, age, age at PD onset, body mass index (BMI), and exposure to caffeine were collected. Clinical features were measured by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Hoehn–Yahr (H-Y) stage, Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Hamilton Depression Rating Scale (HAMD), Hamilton Anxiety Rating Scale (HAMA), Parkinson's disease Questionnaire (PDQ-39), and Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire (RBDSQ).

We applied the 24-item version of HAMD [14] for the assessment of depression; the presence of depression was defined as HAMD score $\geq$ 8 [15]. Anxiety was assessed using the 14-item HAMA [16] with the presence of anxiety defined as HAMA score $\geq$ 13 [17].

Wearing-off and dyskinesia were determined according to MDS-UPDRS Part IV by two movement disorder specialists blinded to patients' drug use. Patients were further divided into groups with or without dyskinesia.

Levodopa responsiveness was acquired via the acute stepwise levodopa challenge test [18]. Subjective levodopa responsiveness was measured by the reduction of MDS-UPDRS III score comparing with baseline. Examiner rated MDS-UPDRS III at baseline before levodopa intake and then four times at 1-h intervals after levodopa intake. A series of tests were performed until reaching more than 30% reduction of MDS-UPDRS III score or the occurrence of side effects. The highest percentage of MDS-UPDRS III score reduction and the corresponding levodopa dosage were recorded.

Information concerning the use of anti-parkinsonian medications was obtained from medical records including changes of dosage and the schedule of all drugs. Six levodopa dose-related variables were identified in accordance to our pervious study: daily levodopa dose, daily levodopa equivalent dose (LED), weight-adjusted daily levodopa dose, weight-adjusted daily LED, cumulative levodopa dose, and cumulative LED [7].

To be noticed, for the dyskinesia group, weight, BMI, time-relevant factors (age, disease duration, levodopa treatment duration), and all treatment-relevant factors (schedule and dose of drugs) were recorded by the time of dyskinesia first onset, while for the non-dyskinesia group, by the time of recruitment.

Statistical analysis

Statistical analysis was performed using the SPSS 25.0 software. The *t* test or non-parametric Mann–Whitney test was used to compare numeric variables expressed as mean value and standard deviation or median and interquartile range depending on distribution, whereas the Pearson $\chi 2$ test was used to compare proportions of categorical variables. $P < 0.05$ was considered statistically significant.

Multivariate logistic regression analysis was performed to select risk factors for dyskinesia in both groups. After adjusted for disease duration and difference found in demographic features (sex and weight for the LOPD group), variables which remain statistically significant were enrolled in the regression model. Forward stepwise regression based on the likelihood ratio test statistic was used.

The ROC curve was applied for the calculation of levodopa threshold dose. In ROC curve, the cut-off value was identified by Youden's index with equally weighed sensitivity and specificity. We also presented the positive predictive value (PPV) and negative predictive value (NPV) of the proposed doses, as PPV represents the likelihood of developing dyskinesia above the proposed dose and NPV represents the likelihood to be spared of dyskinesia at or below the proposed dose. Accuracy, defined as the ratio of correct prediction of the proposed dose in general, was used to test its clinical practicality. The model's discriminative power was measured by AUC, an AUC between 0.7 and 0.8 was considered acceptable, 0.8 and 0.9 was considered excellent, and ≥ 0.9 was considered outstanding[19].

Results

Comparison of demographic and clinical and treatment measures between the EOPD and LOPD groups

Among the 539 PD patients included in our study, 111 patients (20.6%) belonged to the EOPD group, and 428 (79.4%) belonged to the LOPD group. A total of 156 (28.9%) patients were diagnosed with dyskinesia, and distinct difference in prevalence of dyskinesia was found between EOPD and LOPD groups (47.7% vs. 24.1%, $P < 0.001$).

Table 1 gives demographic and clinical and treatment measures of all patients. Compared with the LOPD group, the EOPD group had longer disease duration, higher prevalence of dyskinesia, and better levodopa responsiveness despite lower levodopa dose for acute levodopa challenge test. For the assessment of non-motor symptoms, LOPD group showed more profound cognitive impairment (assessed by MMSE and MoCA) and RBD. EOPD patients also had severer motor dysfunction (assessed by MDS-UPDRS Part III) and depression, but this difference did not reach statistical significance ($P = 0.051$, $P = 0.082$). The evaluation of treatment measures revealed no significant differences between the two groups.

For patients with dyskinesia, those in the EOPD group had higher levodopa responsiveness, lower RBDSQ score, and less weight-adjusted daily levodopa intake than those in the LOPD group. LOPD patients with dyskinesia had higher H-Y stage though not reaching statistical significance ($P = 0.071$). Further comparison in the non-dyskinesia group found no significant difference in levodopa responsiveness between EOPD and LOPD patients (41.3 ± 18.6 vs. 40.8 ± 16.3, $P = 0.881$); a lower levodopa dose for acute levodopa challenge test was observed, but there was no statistically significant difference (150 (150,200) vs. 175 (150,200), $P = 0.500$), indicating a significantly better levodopa response only in EOPD patients with dyskinesia.

Risk factors for dyskinesia in the EOPD and LOPD groups

The results of univariable analysis are listed in Table 1. In both groups, patients with dyskinesia had longer duration of PD and were more likely to experience depression. For treatment measures, significantly longer duration of levodopa treatment and higher dosage of all six measures were observed in the dyskinesia group.

Better response to levodopa therapy was only found in dyskinesia patients in the EOPD group, whereas in the LOPD group, treatment responsiveness did not differ with the onset dyskinesia. For LOPD patients, the dyskinesia group was also found with significantly lower weight and BMI, higher percentage of female, wearing-off phenomenon, and use of entacapone, higher H-Y stage, and higher scores of MDS-UPDRS Part III, RBDSQ, and PDQ-39.

Multivariable analysis was performed in the EOPD and LOPD groups, respectively, to screen for risk factors for dyskinesia. In the EOPD group, variables found significant in univariable analysis were adjusted for disease duration. Depression, disease/treatment duration, levodopa responsiveness, and levodopa daily dose were entered into the multivariate logistic regression model. High levodopa daily dose and levodopa responsiveness were identified as risk factors, and the overall accuracy of the model was 84% according to the ROC curve. In the LOPD group, after adjusted for sex, weight, and disease duration, six variables were included in the final model: sex, weight, H-Y stage in off state, use of entacapone, disease/treatment duration, and levodopa daily dose. High levodopa daily dose, long treatment duration, low body weight, use of entacapone, and high H-Y stage in off state were considered risk factors for dyskinesia with a correct classification of 86.2% according to the ROC curve. To avoid collinearity between the dose-related measures,

Table 1 Demographic, clinical and treatment measures of the study population

Variable	EOPD			LOPD			P-value			
	Total	Dyskinesia(-)	Dyskinesia(+)	Total	Dyskinesia(-)	Dyskinesia(+)	EOPD Total	EOPD Dyskinesia(-)	LOPD Dyskinesia(-)	EOPD Dyskinesia(+)
	n=111	n=58	n=53	n=428	n=325	n=103	versus LOPD Total	versus Dyskinesia(+)	versus Dyskinesia(+)	versus LOPD Dyskinesia(+)
Gender, male/female	62/49	35/23	27/26	240/188	193/132	47/56	0.967	0.319	0.014*	0.529
Age, year	51(46,54)	50(46,54)	52(46.5,55)	67(62,71)	66(62,71)	68(63,72)	<0.001*	0.345	0.093	<0.001*
Weight, kg	67(60,75)	70(60,75)	65(60,71)	66(59,75)	68(60,75)	63(52,70)	0.55	0.311	<0.001*	0.063
BMI, kg/m^2	24.2(21.2,26.6)	24.2(21.1,26.6)	24.2(21.1,26.8)	24.2(22.0,26.5)	24.4(22.5,26.7)	23.7(20.0,25.6)	0.663	0.898	0.001*	0.172
Caffeine exposure, %	5.8	5.7	5.9	7.3	7.3	7.2	0.581	0.961	0.965	0.759
Age at onset, year	44(40,47)	44(40,46)	45(40,47.5)	59(55,64.75)	60(55,65)	59(54,63)	<0.001*	0.998	0.077	<0.001*
Disease duration, year	7(5,10)	5.5(4,9)	7(6,11)	6(4,9)	5(3,8)	8(6,11)	0.014*	0.014*	<0.001*	0.636
MDS-UPDRS										
Part I	10(5,14)	9(5,14)	13(5.5,17.5)	12(7,16)	12(6,16)	10.5(7,17)	0.137	0.164	0.638	0.669
Part II	15(11,21)	15(11,23)	15(10.5,20.5)	16(11,23)	16(11,22)	17(12,24.8)	0.384	0.79	0.411	0.241
Part III (Off)	41(31,53.5)	41(32,56)	40.5(29.3,53.3)	39(28,50)	37.5(27,49)	40.5(32,55.8)	0.051	0.388	0.032*	0.695
Hoehn-Yahr stage (Off)	3(2,4)	3(2,3)	3(2.5,4)	3(2,4)	3(2,3)	3(3,4)	0.811	0.155	<0.001*	0.071
Wearing-off, %	77.3	70.7	84.6	67.8	61	89.2	0.143	0.082	<0.001*	0.412
Dyskinesia, %	47.7			24.1			<0.001*			
MMSE	28(24.8,29)	28(25,29)	27(23,29)	27(23,29)	27(24,29)	26(22,28)	0.035*	0.259	0.319	0.256
MoCA	24(19,26.3)	24.5(20.3,27)	23.5(17,26)	22(17,25)	22(17,25)	21(16,25)	0.001*	0.264	0.291	0.068
HAMA	13(8,19)	10.5(5,14.25)	14(9,19)	12(7,18)	12(7,17)	12.5(7,19)	0.65	0.074	0.455	0.414
HAMA≥13, %	50.5	41.3	60	44.6	45.6	50	0.51	0.075	0.505	0.289
HAMD	12(7,18)	11(4.8,15.8)	14.5(9.3,19.8)	11(5,17)	11(5,17)	13(7,21)	0.36	0.05	0.041*	0.559
HAMD≥8, %	73.3	63	84.1	63.4	60.3	73.3	0.082	0.024*	0.041*	0.176
RBDSQ	2(1,5)	2(1,5)	2(1,5)	4(1,7)	3(1,6)	5(3,8)	0.009*	0.8	0.006*	0.003*
PDQ-39	49(34,72)	51(27.5,70.5)	49(34,73.3)	50.5(28,76)	49(24,75)	61(42,80.5)	0.897	0.768	0.027*	0.164
Levodopa dose for acute levodopa challenge test, mg	150(150,200)	150(150,200)	150(125,200)	175(150,200)	175(150,200)	175(150,200)	0.151	0.45	0.924	0.215

Table 1 (continued)

Variable	EOPD			LOPD			P-value			
	Total	Dyskinesia(-)	Dyskinesia(+)	Total	Dyskinesia(-)	Dyskinesia(+)	EOPD Total	EOPD Dyskinesia(-)	LOPD Dyskinesia(-)	EOPD Dyskinesia(+)
	n=111	n=58	n=53	n=428	n=325	n=103	versus LOPD Total	versus Dyskinesia(+)	versus Dyskinesia(+)	versus LOPD Dyskinesia(+)
Levodopa responsiveness, %	49.1±20.1	40.4±18.6	58.1±17.7	40.8±16.6	40.7±17.0	41.2±16.0	0.003*	<0.001*	0.911	<0.001*
Duration of levodopa therapy, month	48(30,96)	36(23.5,77)	65(38,108.5)	48(28,84)	44(24,67)	84(52,108)	0.56	0.002*	<0.001*	0.119
Use of amantadine, %	28.8	27.6	30.2	23	23.4	21.6	0.197	0.762	0.704	0.237
Use of entacapone, %	16.4	10.5	22.6	15.5	11.4	28.4	0.823	0.086	<0.001*	0.438
Daily levodopa dose, mg/d	300(400,600)	300(200,400)	550(425,713)	400(300,550)	300(225,450)	600(450,750)	0.512	<0.001*	<0.001*	0.244
Daily LED, mg/d	550(350,800)	400(294,563)	750(550,940)	500(332,700)	450(300,600)	775(600,932)	0.142	<0.001*	<0.001*	0.567
Daily levodopa dose (weight-adjusted), mg/kg/d	5.8(3.9,8.6)	4.3(3.0,5.7)	8.2(6.1,11.2)	6.0(4.1,8.5)	5.0(3.5,7.1)	9.6(7.3,12.5)	0.84	<0.001*	<0.001*	0.04*
Daily LED (weight-adjusted), mg/kg/d	8.1(5.3,11.9)	5.6(4.2,8.5)	11.7(8.0,14.9)	7.4(5.0,10.9)	6.5(4.4,8.9)	13.0(9.0,16.8)	0.274	<0.001*	<0.001*	0.099
Cumulative levodopa dose, g	536(216,927)	324(102,635)	684(486,1239)	468(200,860)	333(144,632)	918(576,1422)	0.524	<0.001*	<0.001*	0.107
Cumulative LED, g	648(322,1260)	379(197,729)	996(675,1843)	576(243,1050)	414(167,756)	1262(774,1751)	0.15	<0.001*	<0.001*	0.248

EOPD, early-onset Parkinson's disease; *LOPD*, late-onset Parkinson's disease; *BMI*, body mass index; *MDS-UPDRS*, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; *MMSE*, Mini-mental state examination; *MoCA*, Montreal Cognitive Assessment; *HAMA*, Hamilton anxiety rating scale; *HAMD*, Hamilton depression rating scale; *RBDSQ*, Rapid eye movement sleep behavior disorder screening questionnaire; *PDQ-39*, Parkinson's disease Questionnaire; *LED*, levodopa equivalent dose; * *P*-value < 0.05

Table 2 Multivariable analysis of risk factors for dyskinesia in EOPD and LOPD patients

	Variable	P-value	OR	95% CI
EOPD	Levodopa daily dose, mg/d	<0.001	1.005	1.002-1.008
	Levodopa responsiveness, %	0.001	1.05	1.019-1.082
LOPD	Levodopa daily dose, mg/d	<0.001	1.006	1.004-1.008
	Duration of levodopa therapy, month	0.003	1.011	1.004-1.018
	Weight, kg	0.001	0.962	0.939-0.985
	Use of entacapone	0.012	2.35	1.210-4.565
	Hoehn-Yahr stage (Off)	0.019	1.505	1.070-2.118

EOPD, early-onset Parkinson's disease; *LOPD*, late-onset Parkinson's disease; *OR*, odds ratio; *CI*, confidence interval

only levodopa daily dose was included in the multivariate logistic regression model. Disease duration and treatment duration were entered separately in both groups. However, only treatment duration was found as risk factor in LOPD patients. Detailed information of odds ratios (OR) and 95% confidence intervals (CI) were presented in Table 2.

Threshold dosages of levodopa treatment for EOPD and LOPD patients

The threshold dosages of all six variables determined by the ROC models (Fig. 1) are presented in Table 3. The daily levodopa threshold dosages were 400 mg (AUC = 0.80) for EOPD patients and 450 mg (AUC = 0.82) for LOPD patients. Seventy-eight percent EOPD patients (or 89% LOPD patients) would not develop dyskinesia at or under the threshold dosage of 400 mg (or 450 mg) per day, and 75% EOPD patients (or 50% LOPD patients) patients would develop dyskinesia above the threshold dosage. The EOPD group had lower risk thresholds of levodopa than the LOPD group in all dosage measures.

Discussion

In the present study, we reviewed the clinical data of 539 Chinese PD patients and promoted individualized levodopa treatment strategy for EOPD and LOPD. Six levodopa

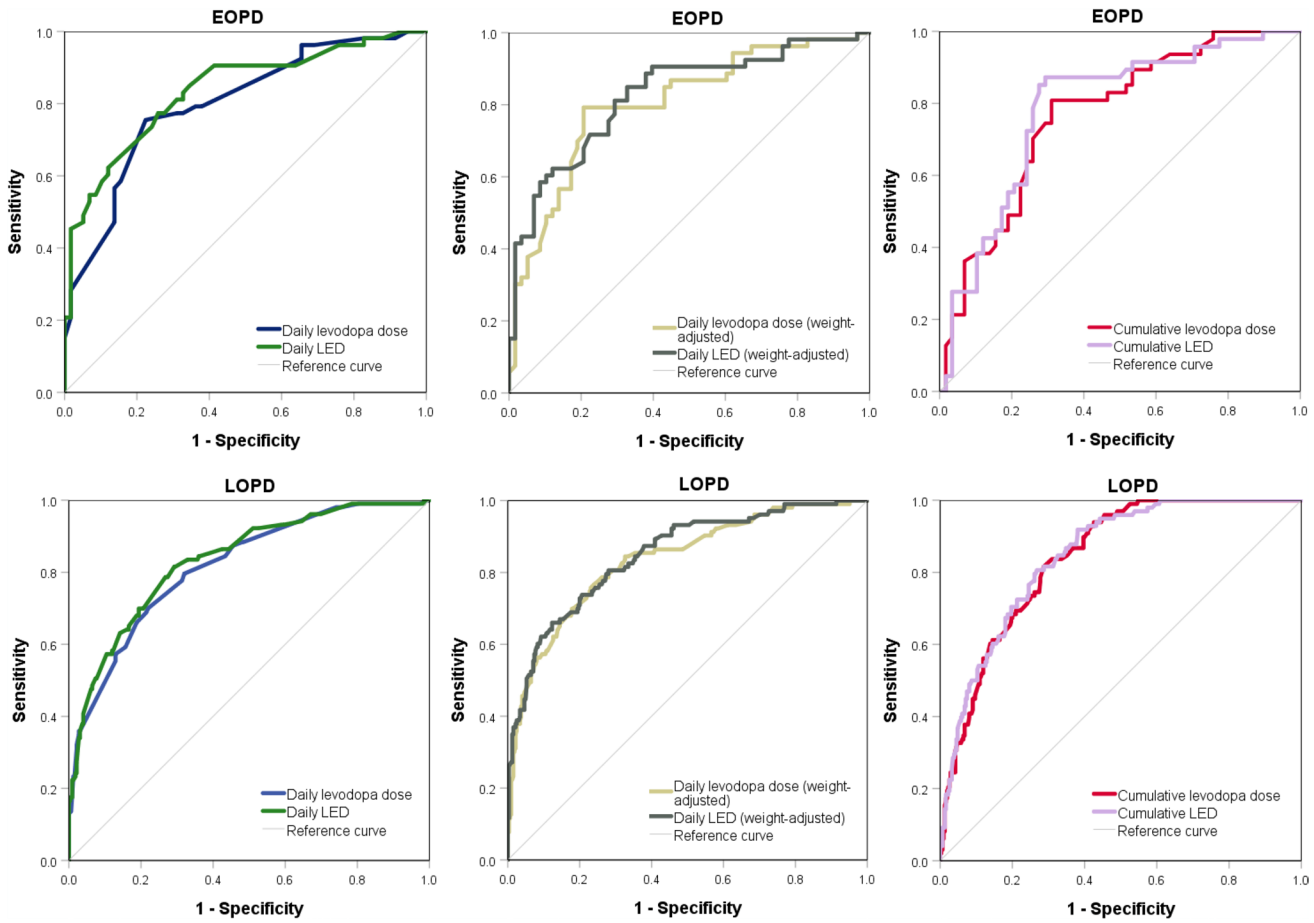

Fig. 1 Levodopa threshold dosage determined by ROC model for the EOPD and LOPD groups. ROC, receiver operating characteristic; EOPD, early-onset Parkinson's disease; LOPD, late-onset Parkinson's disease; LED, levodopa equivalent dose

Table 3 Threshold dosage of levodopa treatment for EOPD and LOPD patients

Variable	EOPD					LOPD				
	Threshold dosage	PPV(%)	NPV(%)	ACC(%)	AUC	Threshold dosage	PPV(%)	NPV(%)	ACC(%)	AUC
Daily levodopa dose, mg/d	400	75	78	77	0.8	450	50	89	76	0.82
Daily LED, mg/d	535	73	78	76	0.84	569	47	92	73	0.83
Daily levodopa dose (weight-adjusted), mg/kg/d	5.9	78	81	79	0.8	7.2	50	91	76	0.84
Daily LED (weight-adjusted), mg/kg/d	7.2	70	83	76	0.83	10.8	62	89	82	0.85
Cumulative levodopa dose, g	426	68	82	74	0.77	549	47	92	74	0.84
Cumulative LED, g	603	71	87	78	0.78	730	49	92	75	0.85

EOPD, early-onset Parkinson's disease; *LOPD*, late-onset Parkinson's disease; *PPV*, positive predictive value; *NPV*, negative predictive value; *ACC*, accuracy; *AUC*, area under the curve; *LED*, levodopa equivalent dose

dose-related variables were identified, and threshold dosages were generated according to the ROC curves. In accordance with our hypothesis, the EOPD group had lower thresholds than the LOPD group in all six measures. The application of the ROC curve proved feasible in our study as ten out of the twelve ROC models showed excellent discriminative power with their AUC between 0.8 and 0.9, while the remaining two models (cumulative dosages in the EOPD group) were also considered acceptable with their AUC above 0.7. To our knowledge, this is the first study to establish the threshold dosage of levodopa treatment in different subgroups based on age at disease onset. The result of our study may provide insights into clinical practice and research design.

In our previous study [7], levodopa 400 mg or 6.3 mg/kg per day was considered threshold dosage for PD patients in general. In the current study, EOPD patients had the same absolute daily dose but a lower weight-adjusted dose, which may reflect a higher accuracy of weight-adjusted dose. Both PPV and NPV were presented for each threshold dosage. PPV represents the patient's chance of developing dyskinesia above the threshold dose, whereas NPV represents the patient's chance to be spared of dyskinesia below the threshold dose. As our goal is to avoid the occurrence of dyskinesia, a higher NPV is more important than a higher PPV. We noticed a relatively higher PPV and lower NPV of the risk thresholds in the EOPD group comparing with the LOPD group despite similar predictive value in terms of AUC. Thus, the levodopa dose control should be stricter for EOPD patients, and lower threshold doses may be proposed based on larger patient sample.

The lower levodopa threshold dosage for EOPD patients is related to the different pathophysiological changes in EOPD and LOPD. The mechanism of levodopa-induced dyskinesia consists of complex interaction of neurotransmitters, receptors, and their pathways, involving dopaminergic and non-dopaminergic systems. The onset of dyskinesia is the result of both nigrostriatal denervation and the discontinuous intake of levodopa [20]. Sossi et al. found age dependence of disease-induced changes in dopamine (DA) turnover, as younger-onset PD patients tend to have greater alteration in DA turnover, causing larger swings in synaptic DA levels which result in motor complications [21]. A previous dopamine transporter (DAT) imaging study showed higher caudate/anterior putamen DAT binding ratio with rather preserved function of the caudate in EOPD patients, suggesting the existence of a more efficient compensatory mechanism in the early-onset subgroup [22]. Analysis of the PPMI cohort recognized high baseline striatal asymmetric index as an independent predictor of better levodopa response and susceptibility to dyskinesia [23]. As for the non-dopaminergic system, unlike the dopaminergic neurons, the serotonin neurons lack the feedback-controlled release of DA. In serotonin terminals, exogenous levodopa is converted to DA

and then released as "false neurotransmitter," which could also cause excessive swings in extracellular DA levels and thus trigger the onset of LID [20]. Park et al. revealed better preserved serotonergic activity in early-onset PD, indicating an enhanced compensation for the dopaminergic deficit [24]. These findings suggest a higher levodopa sensitivity in EOPD that requires lower threshold value to induce dyskinesia, which we believe is a possible explanation to the lower levodopa threshold dosage in EOPD.

In the multivariable analysis, high levodopa responsiveness was identified as an independent risk factor of dyskinesia for EOPD. It should be emphasized that better response to levodopa was only found in EOPD patients with dyskinesia; EOPD patients without dyskinesia and all LOPD patients showed relatively low responsiveness in our study. The presence of high levodopa responsiveness is related to many factors. Aside from the perseverance of striatal dopaminergic and serotonergic function mentioned above [22–24], the presence of dyskinesia itself may also lead to improvement of motor scores, with dyskinesia described as "wiggling, jerking, twitching, and irregular movements" in MDS-UPDRS [25]. Moreover, gene mutations should also be considered. For instance, Parkin was found related to the early onset of PD with excellent treatment response and commonly developed dyskinesia, and LRRK2 is manifested by late-onset PD as well as good levodopa response. While all patients had negative family history in our study, the presence of gene mutations in sporadic PD has been widely reported, especially in early-onset PD [26].

In the LOPD group, low body weight and use of entacapone were considered risk factors for dyskinesia. Consist results were found in the general PD population [2]. The disease duration is a widely accepted factor predicting dyskinesia according to previous study [27], and similar result was found in our univariable analysis. Further multivariable analysis identified levodopa treatment duration as an independent risk factor for dyskinesia. However, both should be considered as important contributors, as treatment duration was measured more precisely due to different order of magnitude in our study. After adjustment of demographic features and disease duration, H-Y stage in off state remained statistically significant and was identified as an independent risk factor in further analysis, indicating a faster disease progression in LOPD patients with dyskinesia. Gender difference was found in univariable analysis but not in multivariable analysis. To date, it remains unclear whether female gender could be considered as an independent risk factor for dyskinesia, for this gender discrepancy could result from lower female body weight and genetic polymorphisms [28].

Several non-motor symptoms (NMS), though not identified as independent risk factors, should also be considered. Motor complications were found associated with higher NMS burden even at an early stage of the disease [29]. EOPD patients showed less cognitive impairment consistent in previous studies [30]. The relationship between dementia and dyskinesia was not observed as difference between patients with and without dyskinesia in both onset subgroups was not significant. RBD was more frequent in LOPD patients with dyskinesia, while all EOPD patients had lower RBDSQ scores. In line with a previous cross-sectional study of 994 PD patients, RBD was found related to older age and dyskinesia [31]. This finding implies a shared pathway by RBD and dyskinesia in LOPD. However, the overlap of their pathogenesis is still unclear. As depression and anxiety were identified as risk factors for motor complications in previous studies [3], we assessed both symptoms in the EOPD and LOPD groups. Depression was common in all patients with dyskinesia and remained a significant factor for dyskinesia after adjustment of disease duration in the EOPD group. Regarding anxiety, while it was more frequent in EOPD patients with dyskinesia, the difference did not reach statistical significance in our study. And no difference in the occurrence of anxiety was found in the LOPD group. Based on our findings, depression seems to be a more specific factor for dyskinetic EOPD patients, while RBD may be more relevant to dyskinesia in LOPD. Multiple non-dopaminergic dysfunctions in the cholinergic, serotonergic, opioid, and noradrenergic systems are involved in the pathophysiology of LID and non-motor symptoms like anxiety, depression, pain, dementia, and sleep disturbances [32–34]. Further studies are warranted to investigate the relationship between non-motor systems, age at onset, and LID.

Our study has certain limitations. Firstly, genetic variations related to the age at onset and clinical manifestations of PD should be considered, and the best way is to perform genome sequencing, which is also our next step. Secondly, as a cross-sectional study, all patients were assessed at the time of recruitment. To have more accurate calculation of levodopa risk thresholds, only patients receiving levodopa for more than 6 months were enrolled. Thus, we failed to acquire the baseline data at an early stage of disease to better reveal the predictive value of motor and non-motor symptoms. Finally, our study had higher ratio of EOPD compared to previous community-based study [35]. As our cases were recruited at the in-patient department, this selection bias requires further correction in larger patient population. Further study should be conducted in larger prospective cohort and propose levodopa risk thresholds of PD subtypes based on clinical, pathological, and genetic features.

In conclusion, we investigated the levodopa risk threshold for dyskinesia in different PD onset subgroups. The daily levodopa threshold dosages were 400 mg or 5.9 mg/kg for EOPD and 450 mg or 7.2 mg/kg for LOPD. EOPD patients had lower levodopa threshold dosage than LOPD

patients. Individualized treatment strategy should be considered according to the patient's age at PD onset and presence of certain risk factors. Stricter levodopa dose control is necessary in the treatment of EOPD to delay the onset of dyskinesia.

Author contribution All authors participated in the study design and data collection.

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Declarations

Ethical approval and consent to participate This study was approved and supervised by the ethics committee of the Beijing Tiantan Hospital and was performed in accordance with the Declaration of Helsinki. Informed consents were obtained either from the participants or their closest relatives.

Conflict of interest The authors declare no competing interests.

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