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The relationship between the phenotype of Parkinson's disease and levodopa-induced dyskinesia

Yu-han Zhang [a], Bei-sha Tang [a,b], Chen-yuan Song [a], Qian Xu [a], Ming-xin Lou [a], Zhen-hua Liu [a], Ren-he Yu [c], Xin-xiang Yan [a,b], Ji-feng Guo [a,b,*]

[a] Department of Neurology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, PR China
[b] Neurodegenerative Disorders Research Center, Central South University, Changsha, Hunan 410008, PR China
[c] School of Public Health, Central South University, Changsha, Hunan 410008, PR China

HIGHLIGHTS

- Phenotype of Parkinson's disease associated with dyskinesia was analyzed.
- Dyskinesia was less likely in tremor-dominant patients.
- Tremor-dominant manifestation was a predictor of dyskinesia.

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ABSTRACT

Levodopa has been demonstrated to be an effective medication for Parkinson's disease (PD), but its long-term use is complicated by the subsequent development of dyskinesias. Few studies have distinguished distinct PD subtypes associated with the occurrence of Levodopa-Induced Dyskinesia (LID). Therefore, we performed a retrospective analysis to determine if the specific phenotype of PD and other epidemiological factors are associated with the development of LID. Of 367 PD patients taking levodopa, 101 of them developed LID. Multivariate logistic regression analysis demonstrated that initial tremor-dominant manifestation was associated with a reduced risk of LID, independent of other risk factors, such as age at the onset of PD, the duration and dose of levodopa.

1. Introduction

Parkinson's disease (PD) is characterized by the cardinal symptoms of tremor, stiffness, slowness and poverty of movement. Central physical features include resting tremor, bradykinesia, rigidity and postural instability. It has been demonstrated that distinct subtypes of PD have different clinical courses [1]. In patients with the tremor-dominant subtype, slower disease progress is observed [2].

The dopamine precursor levodopa is an effective antiparkinsonian medication; however, long-term levodopa therapy is complicated by the subsequent development of motor complications, including motor fluctuations and dyskinesias. These motor complications limit the long-term usability of levodopa. A study by Rascol et al. [3] showed that the incidence of levodopa-induced dyskinesia (LID) in patients with early PD was 45%. The risk factors associated with the development of dyskinesias are gender, age at the onset of disease, rate of disease progression, and dose and duration of levodopa treatment [4].

However, few studies have focused on the association between PD subtype and the occurrence of LID. Therefore, the present study was designed to investigate a possible association between the specific phenotype of PD and development of LID during levodopa therapy. Contribution of other risk factors to development of dyskinesia was also analyzed.

2. Methods

2.1. Participants

In this cross-sectional study, 367 participants were recruited from the outpatients of Department of Neurology in Xiangya Hospital and the Neurodegenerative Disorders Research Center between October and December 2012. Inclusion criteria were: (1) native Chinese, with no family history of PD; (2) clinical diagnosis of PD according to the United Kingdom PD Society Brain Bank

* Corresponding author at: Department of Neurology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, PR China. Tel.: +86 731 84327398; fax: +86 731 84327332.
E-mail addresses: guojifeng2003@163.com, guojifeng2003@aliyun.com (J.-f. Guo).

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criteria [5]; (3) treatment with levodopa for at least 2 months; and (4) no history of stroke, moderate to severe head trauma, or deep brain stimulation surgery. Patients who had an uncertain diagnosis or who had features consistent with multiple-system atrophy, vascular Parkinsonism, or atypical Parkinsonism were excluded. All patients were examined by two or more experienced neurologists from the Neurodegenerative Disorders Research Center. The patients' Hoehn–Yahr stage and their score on the motor component (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS) [6] were recorded while they were 'on' their antiparkinsonian medication. Clinical data, including gender, age at disease onset, initial clinical manifestation, time when levodopa therapy was started, and current treatment were collected for each patient. Onset of PD was defined as the year in which a cardinal sign of PD was first noted by the patient or family members. Duration of PD was defined as the period between the onset of PD and the time of evaluation. The main initial clinical manifestations of PD were based on the standard classification for subtypes of PD patients in the study of Rajput et al. [7], and included tremor-dominant, mixed (tremor combined with bradykinesia or rigidity), and akinetic/rigid type. Levodopa Equivalent Dose (LED) was calculated using the following conversions to 100 mg of levodopa: pramipexole, 1 mg; piribedil, 100 mg; entacapone, 120 mg; selegiline, 10 mg; amantadine, 100 mg [8,9]. LID was considered to be present if the patient had a score of 1 or more on item 32 of the UPDRS Part IV [6].

The Expert Committee of Xiangya Hospital of the Central South University in China approved the study. Informed consent was obtained from all individuals.

2.2. Statistics

Patients were divided into 2 groups depending on the presence or absence of LID. The data were analyzed using SPSS for Windows version 18.0 (SPSS, Inc., Changsha, China). The means and standard deviations of quantitative variables were compared between the groups using independent sample *t*-tests with normal distribution and the Mann–Whitney test for non-normally distributed (Kolmogorov–Smirnov test) variables. The Chi-square test was used to assess frequencies (i.e., percentage of occurrence) of categorical variables. Scores of 0 or 1 were assigned to the binary variables (name these variables here), and a series of univariate logistic regression analyses were performed to examine their contribution to LID. A stepwise multivariate logistic regression analysis was used to identify independent predictors of LID. Associations were considered statistically significant when the *P*-values were ≤ 0.05.

3. Results

The clinical details of participants are summarized in Table 1. Of the 367 cases included, 101 patients developed LID by the end of the study. From these 101 patients, 56 (55.4%) were female. There was no statistically significant differences in gender between the two groups ($P > 0.05$). Of the 367 PD patients, 43 experienced onset of PD between the ages of 25 and 40, and 25 of these 43 patients (58.1%) exhibited LID, among the 324 patients who were above the ages of 40 at the onset of PD, 76 (23.5%) developed LID. Patients in the LID group had a significantly earlier onset of PD ($P < 0.001$). In the LID group, 21 patients were tremor-dominant, 53 patients showed an akinetic-rigid clinical subtype, and 27 patients were classified as mixed. For all three phenotypes the majority of patients did not develop LID. The number of patients with and without LID was 21 vs. 85 for tremor-dominant phenotype, 53 vs. 120 for akinetic-rigid phenotype, and 27 vs. 61 for mixed phenotype. However, only for the tremor-dominant phenotype the difference was significant ($P = 0.035$). The Hoehn–Yahr stage revealed that most patients had mild to moderate disease severity: 264 of the 367 PD patients (71.9%) were categorized into stages 1–2, 67 of these 264 (25.4%) exhibited LID, while 103 (28.1%) were above stage 2, 34 of these 103 (33.0%) developed LID. Of the 367 PD patients, 127 (34.6%) had UPDRS III scores more than 35, 46 of these 127 patients (36.2%) developed LID, among the 240 patients (65.4%) who had UPDRS III scores less than 35, 55 (22.9%) occurred LID. In addition, compared to patients without LID, those in the LID group had a longer duration of PD (8 ± 4 years vs. 5 ± 3 years, $P < 0.001$), a longer duration of levodopa use (65 ± 41 months vs. 33 ± 27 months, $P < 0.001$), a higher daily dose of levodopa (603 ± 279 mg vs. 284 ± 212 mg, $P < 0.001$), and a higher Hoehn–Yahr stage (4 ± 2 vs. 3 ± 2, $P = 0.011$) and UPDRS III score (37 ± 15 vs. 32 ± 15, $P = 0.001$). Taking the presence of LID as the dependent variable, univariate logistic regression analysis identified 6 out of the 10 variables to be significantly associated with LID (Table 2). Multivariate logistic regression analysis showed that the presence of an initial tremor-dominant manifestation was associated with a reduced risk of LID, independent of other risk factors such as age at the onset of PD, the duration and dose of levodopa treatment (Table 3). The development of LID was less likely in patients with tremor-dominant phenotype as the initial manifestation (odds ratio, 0.519).

4. Discussion

Several risk factors have been suggested to be associated with the occurrence of dyskinesia in PD patients [10,11]. In an exploratory study performed in Italy, female PD patients appeared to be at a higher risk for dyskinesia [12]. However, a population-based cohort study performed in the US [13] did not show the same results. Our study showed that gender does not have a significant correlation with LID. This discrepancy may be due to the difference in the characteristics of participants. Compared to patients in the two studies mentioned above [12,13], patients in our study were younger and had a shorter duration of PD. Thus, further longitudinal follow-up studies are needed to provide more comprehensive information. It has been reported that PD patients who had a younger age at the onset of the disease have a higher risk of developing dyskinesia [14]. Consistent with this report, we noted that the age at the onset of PD was a strong determinant of LID: the occurrence of dyskinesia decreased with increased age of onset. One explanation is that younger PD patients have strong plasticity mechanisms, which leaves them at an extremely high risk of developing LID even with low doses of levodopa and mild dopamine depletion [15]. As a previous study [16] suggested, chronic drug treatment and the severity of dopamine depletion associated with a long history of PD were major factors for LID. Our cross-sectional study demonstrated that the daily dose of levodopa, duration of disease and levodopa treatment, Hoehn–Yahr stage and UPDRS III score were related to the occurrence of LID. Our results support these findings. Overall, the significant risk factors for LID in multivariate logistic regression analysis were younger age at the onset of PD and the longer duration of levodopa therapy, and larger dose of levodopa.

Moreover, there was a significant association between tremor-dominant phenotype and the development of LID. Consistent with previous study [17], data from our study supported the idea that the development of LID was less likely to occur in patients who presented tremor-dominant phenotype as the initial manifestation. The idea that distinct PD subtypes involved different pathophysiological mechanisms may explain the reduced risk of LID in tremor-dominant patients. Tremor-dominant patients