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Poor self-awareness of levodopa-induced dyskinesias in Parkinson's disease: Clinical features and mechanisms

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ABSTRACT

Objectives: To study the factors and possible mechanisms associated with decreased self-awareness of levodopa-induced dyskinesias (LIDs) in patients with Parkinson's disease (PD).
Methods: We enrolled 30 PD patients with LIDs. Patients were video-recorded in an "on" phase while experiencing LIDs. LIDs were objectively rated by means of the Unified Dyskinesias Rating Scale (UDyRS) by two movement disorders specialists while examining the patients. Patients were asked to rate the body site and the severity of their LIDs according to the 5-point UDyRS. Patients then rated their own LIDs while watching the video recording of themselves. Lastly, the patients rated the LIDs of other reference PD patients on a video recording. The same reference video recordings were shown to 15 healthy individuals matched for age, gender and education.
Results: Seven of the 30 PD patients investigated were subjectively unaware of the presence of their LIDs. The majority of patients, however, recognized their LIDs when watching video recording of themselves. Patients displayed a specific poor self-awareness of trunk LIDs, in both the subjective evaluation and in the video recording-based subjective evaluation. By contrast PD patients correctly recognized LIDs in video recordings of reference PD patients. Poor self-awareness correlated with predominance of motor symptoms on the left body side.
Conclusions: Poor self-awareness of LIDs is present in a proportion of PD patients as a form of anosognosia. The poor self-awareness of LIDs in the trunk is likely to be due to a complex interplay involving both anosognostic mechanisms and deficits in proprioceptive axial kinesthesia.

1. Introduction

Levodopa-induced dyskinesias (LIDs) are the most common side effects of long-term dopaminergic treatment in Parkinson's disease (PD). LIDs, which involve the face, the neck, the trunk and the limbs, may be disabling, painful and contribute significantly to the disability of PD patients [1,2].

Some studies have suggested that PD patients may be partially or even completely unaware of the presence of LIDs [3–5]. Several mechanisms have been proposed to explain this partially or totally reduced self-unawareness of LIDs in PD patients: an impairment in the experience of moving abnormally [4], the detrimental effect of dopaminergic stimulation on executive functions [5] or the inability to detect differences between intended and actual movements [6]. Previous studies on LIDs self-awareness in PD have, owing to limitations such as the small number of patients studied and the different clinical methods used to measure the presence of LIDs, left a number of questions unanswered. These questions include: i) is poor self-awareness of LIDs a common phenomenon in patients with PD? ii) does a poor self-awareness of LIDs vary depending on the body part? iii) is a poor self-awareness of LIDs in PD patients related to any demographic, clinical or neuropsychological features? iv) what are the possible mechanisms underlying the poor self-awareness of LIDs in PD? A better understanding of these issues is important because poor LIDs self-awareness may bias clinical trials based on patients' motor diaries or may result in increased doses of dopaminergic drugs being prescribed, which would in turn enhance the risk of side effects.

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To answer these questions, we studied a group of PD patients with LIDs using a clinical and a video recording procedure. An objective evaluation of LIDs was performed using the Unified Dyskinesias Rating Scale (UDysRS) [7]. The patients' subjective evaluation of LIDs was obtained by interviewing them both before and after they had watched a video recording of themselves. In order to determine whether LIDs self-awareness was correlated with any particular clinical feature, the demographic, clinical and neuropsychological variables of PD patients with LIDs self-awareness were compared with those of PD patients without LIDs self-awareness. Lastly, we correlated the LID scores assigned by the neurologists with those assigned by the patients and healthy subjects.

2. Patients and methods

We studied 30 PD patients (17 women, age: 67.4 ± 8.2 years, range: 50–86 years) with a diagnosis of idiopathic PD [8] and LIDs attending the movement disorder clinic of the Department of Neurology and Psychiatry of the "Sapienza" University of Rome. Disease stage was assessed using the Hoehn and Yahr scale (HY) and the severity of motor symptoms using the Unified Parkinson's Disease Rating Scale (UPDRS-III) [9], the axial subscore of the UPDRS-III was computed by summing items 27–30. Duration of PD symptoms was 11.5 ± 5.4 (range: 3–27) years and duration of LIDs was 3.6 ± 3.9 (range: 1–15) years. All the patients were receiving levodopa treatment (mean dose 560 ± 197 mg/day), which was combined with dopamine agonists in 18 patients and with MAO-B inhibitors in 10 patients. Patients underwent a full neuropsychological evaluation that assessed attention, memory, executive functions and language. Patients with cognitive impairment, defined as a mini-mental state examination (MMSE) score ≤26/30, were excluded from the study.

Patients were studied in an "on" phase while experiencing LIDs, ∼30–60 min after their usual first levodopa dose of the day. An "*objective evaluation*" of LIDs was performed according to the UDyRS by two neurologists with experience in movement disorders while patients were videotaped. The neurologists performed the evaluation at the same time and next to each other. Patients rated their LIDs at the same time than the neurologists. A "*subjective evaluation*" was then performed by asking the patients whether they were aware of the presence of LIDs and, if so, in which site of their body (face, neck, trunk, right and left upper limb, right and left lower limb). They were also asked to rate the severity of the LIDs (according to the 5-point UDysRS) for each body part. All the patients were video-recorded in a well-lit room according to a standardized protocol. Patients were then shown the video recordings of themselves and were asked whether they saw LIDs and, if so, in which body part; they were asked to rate the severity of the movement for each body part ("*video-based subjective evaluation*"). LIDs scores assigned by the patients were compared with those assigned by the two neurologists. The inter-rater agreement of the two neurologists was almost absolute. The ratings of dyskinesias differed only in less than 5% of evaluations (in these cases, the scores were averaged). In the last part of the investigation, video recordings of two reference PD patients (one with mild LIDs and another with severe LIDs) were shown to the patients who participated in the study. PD patients were asked whether they saw any abnormal movements and, if so, to rate the body sites affected by LIDs and the severity of each site ("*reference patient evaluation*"). The same reference video recordings were shown to 15 healthy individuals (unrelated to the patients in the study) who were matched for age, gender and education (8 women, age: 66.8 ± 9.9 years; education: 9.9 ± 4.2 years).

The study was approved by the local ethics committee and signed informed consent was obtained from all the patients and healthy individuals after full disclosure of its purposes.

2.1. Statistical analysis

The inter-rater agreement during the assessment of LIDs severity and topography (by neurologists, patients and healthy individuals) was calculated using the intraclass correlation coefficient (ICC) [10]. Frequency distribution of categorical variables was compared by means of the chi-square test with Yates correction. Continuous variables were preliminarily compared by means of Kruskal–Wallis ANOVA and, in case of significance, post-hoc analyses were performed by means of Mann–Whitney *U* test for between groups and by means of Wilcoxon matched test for within groups comparisons. Continuous variables were correlated using Spearman Rank Order coefficient. The analysis of covariance (ANCOVA) was then applied by entering the independent variables found by the explorative analysis and assuming as dependent variable the ICC between neurologist and patients. The normal distribution of this variable was confirmed by mean of the Shapiro Wilks Test for Normality ($W = 0.94$, $P = 0.09$). Values are expressed as mean ± 1 standard deviation (range). Statistica 7.0 (StatSoft, Tulsa, OK) software was used for the analysis. All tests were two-tailed, with the level of significance set at $P < 0.05$. Bonferroni's correction was applied in case of multiple comparisons.

3. Results

The mean HY stage of the 30 patients enrolled in the study was 2.3 ± 0.5 (1.5–4), while their mean total score and axial sub-score of the UPDRS-III on medication were 21.1 ± 7.5 (7–34) and 3.8 ± 2.6 (1–8), respectively. Symptoms were clearly asymmetric in 24 out of 30 patients, with the left hemi-body more severely affected in the majority of cases (16 vs. 8). The mean MMSE score was 28.1 ± 2.1 (26–30). The score of historical section of UDysRS was 20.7 ± 9.6 (4–40) and that for the disability was 4.9 ± 2.3 (0–10).

3.1. Objective vs. subjective LIDs evaluation

A significant proportion of patients (7/30 = 23.3%) had no awareness of their LIDs (UDysRS scale overall score = 0), (neurologists vs. patients: $X^2 = 5.8$; $P = 0.02$). The neurologists objective evaluation of LIDs (UDysRS) was 7.6 ± 4.2 and the patients' subjective evaluation of LIDs was significantly lower (5.5 ± 4.7) ($P = 0.006$). When watching the video recording of themselves, a higher percentage of patients (28/30 = 93.7%) recognized LIDs on the video recording (neurologists vs. patients: $X^2 = 0.5$; $P = 0.47$) but their UDysRS score was still lower than the objective UDysRS score (5.5 ± 4.3 vs. 7.6 ± 4.2, $P = 0.016$).

The comparison of the severity scores for each body part (Fig. 1) given by neurologists (objective evaluation) with those assigned by the patients (subjective evaluation) disclosed that patients underestimated the severity of trunk LIDs ($U = 171.0$, $Z = -4.5$, $P = 0.001$; Fig. 1). When watching the video recording of themselves, patients again underestimated the severity of trunk LIDs ($U = 189.0$, $Z = -4.1$, $P = 0.001$ for comparison with neurologists' evaluation). Finally, there were no differences in the severity scores assigned to each body part between the patients' subjective evaluation and video-based subjective evaluation (Fig. 1); notwithstanding, the ICC between the these two evaluations was poor (0.34 ± 0.53).

3.2. Evaluation of reference PD patients' video recording

When asked to identify LIDs while watching video recordings of reference patients with severe and mild LIDs, all the patients and healthy subjects recognized the presence of LIDs. When rating the reference PD patient with severe LIDs, all the patients and healthy subjects assigned a maximal score to the severity of the LIDs regardless of body distribution, and therefore we did not perform any further evaluation. When we compared the scores assigned by the PD patients, healthy subjects and neurologists to the patient with mild LIDs, we found that patients and healthy subjects assigned a higher score to LIDs of the trunk (+80.0%; $U = 375.0$, $Z = 2.3$, $P = 0.02$; +100% $U = 45.0$, $Z = 2.8$, $P = 0.005$) and of the right upper limb (+50.0%; $U = 330.0$, $Z = 2.8$, $P = 0.003$; +210%; $U = 22.5$, $Z = -3.7$, $P = 0.001$), and a lower score to LIDs of the neck (−33.3%; $U = 225.0$, $Z = -3.7$, $P = 0.001$; −80%; $U = 22.5$, $Z = -3.7$, $P = 0.001$) and of the left upper limb (−123.7%; $U = 120.0$, $Z = 5.5$, $P = 0.001$). The ICC between the evaluations made by the neurologists and patients was 0.41 ± 0.32, while that between the evaluations made by the neurologists and healthy subjects was 0.46 ± 0.32. The ICC between healthy controls and patients was greater, though not significantly, than that between healthy controls and neurologists (0.46 ± 0.32 vs. 0.39 ± 0.18).

3.3. Features associated with poor LIDs self-awareness

No gender-related differences were found. In patients with a clearly asymmetric involvement of motor symptoms, the ICC was consistently lower (indicating a lower level of agreement between patients and neurologists) in patients with predominantly left hemi-body symptoms. However, the difference in ICC only reached statistical significance when objective evaluations were compared with video-based subjective evaluations ($U = 142.0$, $Z = 2{,}1$, $P = 0.031$, Fig. 2).

The explorative correlation analysis found a number of significant associations (with UPDRS-III, LLR LIDs and the neuropsychological tests MMSE, TMT A-B, False recognition and Raven CPM), which did not survive after Bonferroni correction for multiple comparisons (Table 1). The ANCOVA entering these independent continuous variables plus trunk LIDs and the more affected side as independent categorical variable found no significant correlation with the dependent variable ICC between the subjective and objective evaluations.

4. Discussion

In this study, we found that 23.3% of the PD patients investigated were unaware of the presence of their LIDs, though most of these patients were able to recognize their own LIDs as well as those of reference PD patients when watching videos recordings. We also found that patients had a poor awareness particularly for trunk LIDs, in both the subjective and video-based subjective evaluations. The only clinical feature which correlated with the poor self-