Force overflow and levodopa-induced dyskinesias in Parkinson’s disease

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Summary
We assessed force coordination of the hand in Parkinson’s disease and its relationship to motor complications of levodopa therapy, particularly to levodopa-induced dyskinesias (LID). We studied two groups of Parkinson’s disease patients with (Parkinson’s disease + LID, n = 23) and without levodopa-induced dyskinesias (Parkinson’s disease – LID, n = 10), and age-matched healthy controls. The motor score of the Unified Parkinson’s Disease Rating Scale, a dyskinesia score and force in a grip–lift paradigm were assessed ON and OFF levodopa. A pathological increase of forces was seen in ON-state in Parkinson’s disease + LID only. In Parkinson’s disease + LID, the force involved in pressing down the object before lifting was significantly increased by levodopa (by 61%, P < 0.05). An overshooting of peak grip force by 51% (P < 0.05) and of static grip force by 45% (P < 0.01) was observed in the ON- compared with the OFF-drug condition. In contrast, no excessive force was found in Parkinson’s disease – LID. Peak grip force in ON-state was 140% (P < 0.05) higher in Parkinson’s disease + LID than in Parkinson’s disease – LID, while static grip force was increased by 138% (P < 0.01) between groups. Severity of peak-dose dyskinesias was strongly correlated with grip force in ON-state (r = 0.79 with peak force, P < 0.01). No correlation was observed between forces and the motor score as well as with the daily dose of dopaminergic medication. Force excess was only observed in patients with LID and motor fluctuations. A close relationship was seen between the overshooting of forces and dyskinesias in the ON-drug condition. We postulate that both LID and grip force excess share common pathophysiological mechanisms related to motor fluctuations.

Keywords: grip force; levodopa-induced dyskinesia; Parkinson’s disease; motor fluctuation

Abbreviations: LEDD = levodopa equivalent daily dose; LID = levodopa-induced dyskinesias; ns = non-significant; UPDRS = Unified Parkinson’s Disease Rating Scale

Introduction
Levodopa-induced dyskinesias (LID) are a serious problem in late-stage Parkinson’s disease. Two important factors are considered to promote dyskinesias in Parkinson’s disease. First, the amount of dopaminergic denervation (Blanchet et al., 1996), and secondly, a pulsatile activation of the dopaminergic system (Mouradian et al., 1990; Obeso et al., 1994; Blanchet et al., 1995; Nutt and Holford, 1996; Colzi et al., 1998). High doses of dopaminergic drugs are required to counterbalance wearing-off effects and motor fluctuations in late-stage Parkinson’s disease, but over-medication may worsen certain aspects of motor performance (Nutt et al., 1988; Merello and Lees, 1992; Johnson et al., 1996; Gordon and Reilman, 1999).

LID can cause severe disability due to interference with motor activities. Although there are several clinical scores for LID, objective measures are scarce. Amplitude and frequency of the acceleration of limbs or trunk proved to be correlated with the amplitude of LID, but these measures were of value only when obtained during rest, or when derived from body segments that were not involved in voluntary movements (Dunnewold et al., 1998; Burkhard et al., 1999; Hoff et al., 2001). Measures for the interference of LID with voluntary movements are lacking. Could the severity of LID be determined during functionally relevant movements? Such measures would be particularly valuable to evaluate the role of LID for the impairments of dexterity.
A well-established dexterous motor task is the grip–lift paradigm developed originally by Johansson’s group [for a review, see Johansson (1996)]. It provides measures for the coordination between grip force (by thumb and index finger) and load force (mainly by elbow and shoulder) when lifting a lightweight object in the precision grip. A slowness and segmentation of force development was described in the parkinsonian OFF-state (Gordon et al., 1997). Several researchers observed that while levodopa accelerates the build-up of force, it may cause an overshooting of grip force beyond the level required to prevent slips (Gordon et al., 1997; Alberts et al., 1998; Fellows et al., 1998; Gordon and Reilman, 1999). The pathophysiology of this force excess is not completely understood. In particular, the relationships between the overshooting of force and the severity of LID on the one hand, and with parkinsonian symptoms like akinesia and rigidity on the other hand have remained unclear. We hypothesized that the overshooting of force could be associated (i) with the severity of LID in patients with motor fluctuations, or (ii) other motor symptoms like akinesia or rigidity may determine the force excess.

**Methods**

**Subjects and experimental conditions**

A total of 33 patients with idiopathic Parkinson’s disease were recruited for the study, which was approved by the Ethics Committee of The Christian–Albrechts University, Kiel. Written informed consent was given by all patients. The 23 patients with peak dose dyskinesias. All suffered from varying severity (see Table 1). Mild to severe OFF-period dystonia was present in 10 patients of the Parkinson’s disease + LID subgroup. Ten patients at an earlier stage of Parkinson’s disease were also included who had no evidence for LID according to observations during the levodopa challenge and according to items 32–35 of the Unified Parkinson’s Disease Rating Scale point IV (UPDRS IV) (Fahn and Elton, 1987) (Parkinson’s disease – LID subgroup, see Table 1). A group of 10 age-matched healthy controls was also included for grip force analysis [mean age 62.7 ± 15.2 (standard deviation) years versus Parkinson’s disease total of 59.4 ± 6.9 years, non-significant (ns), Mann–Whitney U-test].

The influence of dopaminergic medication on the level of force and dyskinesias was studied. The following conversions (extended from Krack et al., 1998) were applied to calculate the levodopa equivalent daily dose (LEDD): dihydروergocryptin × 5; bromocriptine and apomorphine × 10; ropinirole × 20; lisuride, pergolide, pramipexole and cabergoline × 100; levodopa with decarboxylase inhibitor × 1; controlled release levodopa with decarboxylase inhibitor × 0.7; levodopa with decarboxylase and COMT inhibitor × 1.3.

Patients were tested in two conditions. The OFF-drug condition was assessed following a 12 h overnight withdrawal of dopaminergic treatment. The ON-drug state was examined at the time of best motor response following a challenge with a suprathreshold dose of levodopa, exceeding the usual morning dose by 100 mg (Krack et al., 1998). Patients were videotaped during the entire levodopa test.

The motor score (UPDRS III) (Fahn and Elton, 1987) was rated in the OFF and ON conditions, and the difference between these conditions was considered as the amplitude of motor fluctuation. Subscores of akinesia (items 23–26) and rigidity (item 22) were also derived from the UPDRS (Lozano et al., 1995). OFF-period dystonia and peak-dose dyskinesias were rated from the videotape by a rater who had no knowledge of the results from force coordination. This rating

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parkinson’s disease – LID</th>
<th>Parkinson’s disease + LID</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>58.5 ± 8.6</td>
<td>59.8 ± 6.2</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>5.3 ± 1.6</td>
<td>16.3 ± 5.4*</td>
</tr>
<tr>
<td>Motor score OFF</td>
<td>22.2 ± 7.6</td>
<td>20.8 ± 9.5**</td>
</tr>
<tr>
<td>(0–108) ON</td>
<td>11.2 ± 5.4**</td>
<td>27.1 ± 12†</td>
</tr>
<tr>
<td>Δ OFF – ON</td>
<td>6.5 ± 3.5</td>
<td>19.3 ± 6.1†</td>
</tr>
<tr>
<td>Akinesia score OFF</td>
<td>2.7 ± 2.3**</td>
<td>8.4 ± 5.2**</td>
</tr>
<tr>
<td>(0–32) ON</td>
<td>4.2 ± 1.6</td>
<td>9.7 ± 3†</td>
</tr>
<tr>
<td>R rigidity score OFF</td>
<td>1.8 ± 1.1**</td>
<td>4.6 ± 2.5††</td>
</tr>
<tr>
<td>(0–20) ON</td>
<td>491.5 ± 334.7</td>
<td>1263.3 ± 708.3††</td>
</tr>
<tr>
<td>LEDD</td>
<td>2 ± 4 (range 0–18.5)</td>
<td>7.2 ± 5.1 (range 1–16.5)</td>
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</table>

Akinesia (items 23–26) and rigidity (item 22) are subscores of the motor score (UPDRS III, score range in parentheses). Δ OFF–ON depicts the fluctuations of the motor score. LEDD is given in mg. OFF-phase dystonia was present in 10 patients of the Parkinson’s disease + LID subgroup. Mean values ± standard deviation are given. *P < 0.001, **P < 0.01 compared with Parkinson’s disease – LID (between subgroups). *P < 0.001, **P < 0.01 compared with Parkinson’s disease OFF-drug (levodopa effect).
of LID encompassed the face, neck, trunk and each of the upper and lower limbs (sum of all seven regions, range 0–28) (Marconi et al., 1994; Krack et al., 1999). Sense of position and light touch was rated according to the subjects’ perception of passive movements of the distal joint of the index and the touch with a swab: not disturbed/disturbed.

**Grip force measurement**

The experimental procedure for the analysis of grip force coordination was similar to that described previously (Johansson and Westling, 1984; Odergren et al., 1996; Ingvarsson et al., 1997) and therefore is only described briefly. All subjects washed their hands before the experiment and the table was positioned such that the forearm was parallel to the floor when the object was grasped between the thumb and index finger (Fig. 1A). The object weighed 220 g and the sandpaper-covered grip surfaces (granulation 320, diameter 17 mm) were 5.5 cm apart. Horizontal grip forces and vertical load forces were measured from thumb and index finger using 3D sensors (Assurance F/T, ATI Industrial Automation, Apex, USA) and digitized at 400 Hz using SC/ZOOM software (Umea, Sweden). Subjects were instructed to perform the task at a normal pace, i.e. no instructions were given regarding speed, accuracy or force. The hand was held open at the level of the object, and the subject grasped and lifted the object at a beep. After 5 s of holding the object, subjects were told to replace it on the table. Fifteen repetitions were recorded with a 5–10 s pause in between. To minimize the influence of learning effects, the first five trials were regarded as practice trials and were not considered for data analysis. The more dyskinetic side was analysed in Parkinson’s disease + LID (right side in 18 patients, left side in five patients). All patients of the Parkinson’s disease – LID subgroup were affected bilaterally. The right (dominant side) was analysed in these patients and in the controls.

We focused on four force measures (Ingvarsson et al., 1997; Gordon and Reilmann, 1999). (i) Peak negative load force ($N_{LF\text{PEAK}} =$ pushing down the object before lifting) was determined before the onset of positive load force (at the zero crossing of the load force curves, Fig. 1B). (ii) The grip force of thumb was measured at the onset of the positive load force ($GF_{LOAD}$). (iii) The grip force of thumb was measured at its peak ($GF_{PEAK}$). (iv) The grip force of thumb was measured at its peak ($GF_{PEAK}$).

![Fig. 1](image)

**Fig. 1** (A) The horizontal direction of the grip force ($GF$) and the vertical direction of the load force ($LF$). If the object is pressed down, $LF$ becomes negative ($NLF$). (B) Temporal and force variables of the grip–lift paradigm. The object is contacted typically first by the thumb ($T_0$) and then by the index finger ($T_1$). Temporal variables were calculated as follows: duration of grip preparation ($DUR_{GPREP} = T_1 - T_0$), preload phase duration ($DUR_{PLoad} = T_2 - T_1$), and load phase duration ($DUR_{LOAD} = T_3 - T_2$). Generally, the object is pressed down before the onset of lifting ($NLF_{PEAK} =$ negative LF peak). Grip force at start of loading ($GF_{LOAD}$) was measured at onset of positive LF (at $T_2$). $GF$ and $LF$ increase in parallel during the loading phase until lift-off ($T_3$, $Vel =$ velocity in vertical direction). $GF$ was also measured at its peak ($GF_{PEAK}$).
measured during the early static phase (GF\text{STATIC} = \text{mean GF during a 200 ms period in the static phase, beginning 500 ms after the GF peak}).

The load force was the sum of the vertically acting forces, measured at the thumb and index sensors. In addition, the following temporal variables were derived: duration of grip preparation (DUR\text{GPREP}); duration of preload phase (DUR\text{PLLOAD}); and of load phase (DUR\text{LOAD}). These were the latencies between four discrete events: first contact of a finger; definite grip by thumb and index; onset of positive load force; and movement of the object (for details, see Fig. 1B). Lift-off of the object was assumed at the last zero crossing of the vertically directed velocity, which was computed as the change of vertical position over time. This method allowed us to pick up accurately the moment of lift-off and to skip preceding movements of the object due to tremor or slow tilting. Peak vertical acceleration (ACC\text{PEAK}) was computed as LF\text{PEAK} ± (object weight × 9.81)/object weight according to Odergren et al. (1996). The peak vertical position (HEIGHT\text{PEAK}) during lifting was also determined. Mean values from 10 trials were used in the statistical analysis.

**Statistical analysis**

One way analysis of variance (ANOVA; SPSS Inc, Chicago, Ill., USA) was used to examine the differences between groups (Parkinson’s disease – LID, Parkinson’s disease + LID, control). *Post hoc* contrasts between groups were corrected according to Bonferroni (Norman and Streiner, 1994). ANOVA for repeated measurement was calculated to compare OFF and ON states with a level of significance of *P* < 0.05. The Spearman rank correlation was calculated for those measures which differed between groups and significance was assumed if *P* < 0.01.

**Results**

**Clinical data**

The UPDRS motor score in the levodopa test decreased by 50% in Parkinson’s disease – LID (*P* < 0.01) and by 57% in Parkinson’s disease + LID (*P* < 0.001). The amplitude of motor fluctuations in Parkinson’s disease + LID was more than twice as high as in Parkinson’s disease – LID (*P* < 0.001, see Table 1 for akinesia and rigidity subscores). LEDD was 61% lower in Parkinson’s disease – LID than in Parkinson’s disease + LID. Sense of position and light touch was not disturbed in any patient.

**Force profiles**

Control subjects produced a smooth, unimodal force output when grasping to lift the object (Fig. 2A). The build-up of forces in the OFF state was slow in both the Parkinson’s disease – LID and Parkinson’s disease + LID subgroups with a high variability between trials, and a stepwise increase of

![Fig. 2 Force profiles in a control subject (A) and two representative individuals from the group without LID (B: PD – LID) and with LID (C: PD + LID) in OFF-drug (dashed lines) and ON-drug (solid lines) conditions. The thick lines depict mean grip force of thumb (GF) and mean load force of thumb and index (LF). The thin lines show the standard error of the mean of 10 repetitions. The figure illustrates the overshooting of grip force in Parkinson’s disease patients with LID both in OFF-drug and ON-drug conditions, whereas there is no force excess in patients without LID.](image-url)
grip force and load force (Fig. 2B and C). An increased negative load force was observed mainly in the subjects with severe OFF-phase dystonia (Fig. 2C). In the ON-drug condition, the force profiles in Parkinson’s disease – LID appeared almost similar to the controls, without an excess of forces (Fig. 2B). In Parkinson’s disease + LID, in contrast, an overshooting of grip force and a pushing of the object downwards before lifting (negative load force) was observed, while the timing appeared almost normal in the ON-state (Fig. 2C).

Comparison of forces, acceleration and lifting height between groups

A significant influence of group on the peak negative load force (NLF\textsubscript{PEAK}) in the ON-drug condition was observed \([F(1,12) = 5.86, P < 0.01]\). Post hoc tests revealed an overshooting of NLF\textsubscript{PEAK} by 72\% in the ON-state of Parkinson’s disease + LID compared with Parkinson’s disease – LID, and an excess of 100\% in Parkinson’s disease + LID over controls (\(P < 0.05\) in both, Fig. 3A). In the OFF-drug condition, no significant differences of NLF\textsubscript{PEAK} between Parkinson’s disease subgroups and in Parkinson’s disease + LID compared with controls emerged (Table 2).

GF\textsubscript{LOAD} was influenced by group in the ON-state \([F(1,12) = 6.05, P < 0.01]\). GF\textsubscript{LOAD} overshot by 127\% in Parkinson’s disease + LID compared with Parkinson’s disease – LID, and by 98\% compared with the controls (\(P < 0.05\) in both; Fig. 3B). No significant difference was seen between the groups in the OFF-state (Table 2).

The influence of group on GF\textsubscript{PEAK} in the ON-drug state was significant \([F(1,12) = 6.24, P < 0.01]\). Post hoc comparisons revealed an increase in GF\textsubscript{PEAK} by 140\% in Parkinson’s disease + LID in the ON-state compared with Parkinson’s disease – LID, and by 74\% compared with the
A pathological force excess in a grip–lift paradigm was observed in patients with Parkinson’s disease and LID. This failure of force generation was very marked on levodopa, but was also seen in patients in the OFF-state in Parkinson’s disease + LID. In the parkinsonian group without LID, no overshooting of forces was observed.
Levodopa-induced dyskinesias and force overflow

The present study identified the severity of peak dose dyskinesias and OFF-period dystonia as the main factors in the pathophysiology of force excess. Overshooting of grip force, mainly exerted by distal muscles, was most pronounced on levodopa in the patients with LID (Parkinson’s disease + LID subgroup). Negative load force (pressing down before lifting the object) was also increased in Parkinson’s disease + LID, an action particularly involving proximal muscles (Lemon et al., 1995). We assume that parkinsonian patients with LID have problems with smooth coordination of the grip and therefore reduce the degrees of freedom by using the object as a support. Overshooting of forces was not observed in the patients without levodopa-induced dyskinesias (Parkinson’s disease – LID). This cannot be explained by the lower daily dosage of dopaminergic medication (LEDD) in this subgroup because of lacking correlations.

Our results extend earlier reports where single Parkinson’s disease patients with dyskinesias exhibited a similar increase of grip force in the ON-state, whereas no force abnormalities were found in the OFF-drug condition (Ingvarsson et al., 1997; Gordon and Reilmann, 1999).

The influence of motor symptoms on grip force

Besides dyskinesias, motor symptoms related to akinesia and rigidity affect coordination in the OFF-state and could potentially induce a compensatory overshooting of grip force. This hypothesis is not supported by the present data because no correlation was observed between the clinical scores and force excess. These findings argue against a compensatory overshooting of grip force in the ON-state.

However, the disability due to peak dose dyskinesias was clearly related to the overshooting of grip force.

Pathophysiology of force overflow and LID

LID usually occur in patients with motor fluctuations. They are not primary parkinsonian symptoms, but develop secondary to treatment with levodopa (Blanchet et al., 1996; Nutt, 2000). We found a close relationship between the severity of LID and force excess, and hypothesize therefore that both share common pathophysiological mechanisms.

The observation of force excess in parkinsonian patients might appear counter-intuitive. Indeed, reduced peak muscle force has been described previously in parkinsonian patients OFF-drug. This weakness has been related to the lack of Piper rhythm in the OFF-state, which was restored by levodopa, allowing for a tetanic muscle contraction (Brown et al., 1997). In the grip–force paradigm used in the present study, forces decreased ON levodopa in patients with little motor fluctuations (Parkinson’s disease – LID), whereas they increased in the group with severe fluctuations and LID (Parkinson’s disease + LID). Paresis or reduced peak torque and excessive force, not adapted to a dexterous motor task are not mutually exclusive because optimized coordination requires economical regulation, rather than a fast build-up of peak force.

Which other factors could possibly contribute to the grip force excess in Parkinson’s disease? An influence of the levodopa challenge on sweating might have determined the grip force necessary to prevent slips, but the dose was the same in both Parkinson’s disease – LID and Parkinson’s disease + LID, whereas force excess was observed in the latter group only and we observed no consistent hyperhidrosis after levodopa. Theoretically, a disturbance of sensory feedback could contribute to force abnormalities because overshooting of force in a grip task has also been observed in neuropathy (Thonnard et al., 1997) and in healthy subjects following local anaesthesia (Johansson and Westling, 1984, 1987; Hager-Ross and Johansson, 1996). Fellows et al. (1998) hypothesized, therefore, that a loss of kinaesthetic sense could underlie the force excess in Parkinson’s disease, but they assessed their patients only in ON-drug state. The clear influence of levodopa on grip force, but not on sensation, renders unlikely the possibility that sensory dysfunction was a major factor of force excess, and there was no evidence for a disturbance of sensory functions in our patients. In recent studies, Parkinson’s disease patients adapted their grip forces properly to changes of the objects’ surface texture and weight (Gordon et al., 1997; Ingvarsson et al., 1997), which is a second strong argument against a role for sensory deficits in the force excess of parkinsonian patients.
Hypothetically, overshooting of grip forces could be a compensatory mechanism for akinesia or paresis to hasten and stabilize the grip. In this case, however, force excess should be higher in the OFF-drug than in the ON-drug condition, but the reverse was the case.

Excess force relates to the motor fluctuations resulting from both the severity of the motor handicap and the levodopa sensitivity. We speculate that oscillations in gain between the ON- and OFF-drug conditions may lead to difficulties in calibrating the correct force and timing adapted to a specific task. Problems of force regulation may underlie the syndrome of LID and could possibly be a general phenomenon in dyskinesias of other origins such as the force excess in writer’s cramp (Odergren et al., 1996).

Acknowledgements

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