Early Morning Off-Medication Dyskinesias, Dystonia, and Choreic Subtypes

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Background: Abnormal involuntary movements (dyskinesias) are common in patients with Parkinson disease (PD) as a consequence of the disease and dopaminergic replacement therapy. Early morning off-medication choreic dyskinesias have been recently reported after fetal dopaminergic cell transplantations in patients with advanced PD.

Objective: To determine the frequency and severity of the early morning off-medication dyskinesias in consecutive patients with advanced PD and an insufficient response to medical management before they undergo neurosurgery.

Methods: Consecutive patients with advanced idiopathic PD were examined and videotaped before undergoing neurosurgery that included pallidotomy, fetal transplantation, or deep brain stimulation. The examination took place in the morning in the practically defined off state, at least 12 hours after the last dose of dopaminergic drugs. Parkinson disease was characterized using the Unified Parkinson's Disease Rating Scale and the Hoehn and Yahr stage. Dyskinesias were rated with the Abnormal Involuntary Movements Scale and the Rush Dyskinesia Rating Scale. Patients’ characteristics and medications were compared using the Wilcoxon rank sum and the Fisher exact tests.

Results: Of 68 consecutive patients (44 [65%] men and 24 [35%] women), 11 (16%) had early morning off-medication dyskinesia, with a 95% upper confidence limit of 24%. Focal dystonia was the most common off-medication dyskinesia, and occurred in 10 patients (15%), with a 95% upper confidence limit of 22%; and off-choreic dyskinesia occurred in 1 patient (1.5%), with a 95% upper confidence limit of 4%. There was no difference in PD medications between the patients with and those without dyskinesias.

Conclusions: The most common form of off-medication dyskinesia seen in patients with advanced PD is dystonia. Early morning off-medication choreic dyskinesias are rare but do occur in patients with advanced PD before surgical intervention. The presence and type of off-medication dyskinesias should be monitored in clinical and surgical studies in patients with PD as part of the safety and evaluation of clinical benefits.

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Dyskinesias in patients with Parkinson disease (PD) have various forms, related in part to the underlying dopaminergic denervation and to drugs.1 Dyskinesias are usually classified into 2 categories, off-period dyskinesias and on-period dyskinesias, based on the patient’s clinical state (on or off) and relationship with the medication intake (before the first dose of morning medication, at peak medication intake, and at the end of the dose). On-period dyskinesias, such as levodopa peak-dose dyskinesias, occur during the period of maximal relief of parkinsonian symptoms and are predominantly choreic, usually involving the upper more than the lower limbs, the face, and the trunk.2,3 Peak-dose on-period dystonia may also occur.

Off-period dyskinesia include dystonia, usually seen in patients when they are akinetic and rigid before the first daily dose of levodopa, and end-of-dose dyskinesias, seen during the day as drug effects wear off, which predominate in the lower extremities.4-6 Recently, a third type of off-period dyskinesia, which is primarily choreic, has been reported before the intake of morning medication following fetal dopaminergic cell transplantations in patients with advanced PD. This type of dyskinesia was posited to be the result of transplantation.7 The occurrence of off-medication dyskinesias before surgical intervention in patients with advanced PD has not been systematically studied. This
PATIENTS AND METHODS

Consecutive patients with advanced idiopathic PD who underwent neurosurgery, including pallidotomy, deep brain stimulation, and fetal transplantation, at the Movement Disorder Section of the Department of Neurological Sciences, Rush-Presbyterian-St Luke’s Medical Center, Chicago, Ill, and at the Mt Sinai Medical Center, New York, NY, were examined preoperatively with a standardized videotape. The taping protocol documented the patients’ scores on the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS), following the recommendations of the Core Assessment Program for Intracerebral Transplantations, at baseline in the morning (no PD medications for at least 12 hours). Parkinson disease motor impairment and therapy motor complications were characterized by using the motor section of the UPDRS; the Hoehn and Yahr stage; and the fourth section of the UPDRS, focusing on dyskinesias. Dyskinesias were rated using the modified Abnormal Involuntary Movements Scale during the UPDRS motor subscale filming and using the Rush Dyskinesia Rating Scale. Information on patients’ levodopa and agonist (equivalent pergolide mesylate) doses was also collected.

Patient characteristics were analyzed as percentages or as means ±SDs, with results expressed with 95% confidence limits for the percentage of patients with dyskinesias. To compare medications and characteristics in patients with and without dyskinesias, we used Wilcoxon rank sum tests for continuous variables and Fisher exact tests for discrete variables.

RESULTS

Sixty-eight patients were included (44 [65%] men and 24 [35%] women), and underwent different neurosurgical procedures for PD. These procedures included pallidotomy in 30 patients, the fetal transplantation program in 34, and deep brain stimulation in 4. The mean age of the patients was 60 ± 9 years (range, 39-75 years), and the mean PD duration was 14 ± 7 years (range, 2-41 years). All received levodopa (mean dose, 962.02 ± 507.00 mg), and 51 patients (75%) received agonist (mean dose, 2.18 ± 2.10 mg). In accordance with the guidelines of the Core Assessment Program for Intracerebral Transplantations, all subjects were videotaped in the morning at least 12 hours after the last dose of medication, in the “practically defined” off state. At the time of the videotape, the patients’ mean total score on the motor section of the UPDRS was 50 ± 13 (range, 37-65), and the patients’ median Hoehn and Yahr stage was 4 (range, 2-5).

The mean score on the fourth section of the UPDRS was 9 ± 3 (range, 2-19), taken on the day of the videotape. Based on the videotape examinations, 11 patients (16%) were found to have early morning dyskinesias in the off state, with a 95% upper confidence limit of 24% (Table 1). Dystonia occurred in 10 patients (15%), with a 95% upper confidence limit of 22%. Focal and segmental dystonias, including foot (5 patients), arm (2 patients), and cervical (3 patients) dystonias, were the more common form of off-medication dyskinesia. The mean Abnormal Involuntary Movements Scale score was 2 ± 1, and the mean Rush Dyskinesia Rating Scale score was 1 ± 1. There were no differences in patients’ characteristics or scores on the fourth section of the UPDRS between the group of patients with and the group without off-medication dyskinesias (Table 1). There was also no difference in the levodopa dose between the group of patients with and the group without off-medication dyskinesias, nor was there a difference in the proportion of patients taking levodopa and agonist between the 2 groups (Table 2).

Off-medication choreic dyskinesias involving the orofacial muscles, the trunk, and the lower extremities occurred in 1 patient (1.5%), with a 95% upper confidence limit of 4% (Table 1), despite confirmed abstinence from dopaminergic drugs for 12 hours. The patient experienced repetitive lifting of the right leg off the ground with the foot inverted and the knee flexed. He also showed mild but continuous pouting, smacking, and sucking movements of the lips and rocking movements of his back. His Abnormal Involuntary Movements Scale score was 7, and his Rush Dyskinesia Rating Scale score was 1. The patient was clinically in the off state otherwise, with a total score on the motor section of the UPDRS of 48. Although our study’s focus was on off-medication dyskinesias, because of the particularly choreic character of these dyskinesias, we also looked at the on-medication videotape assessment. At peak medication effect, his score on the motor section of the UPDRS was 35, the dyskinesias were more intense than the dyskinesias in the off state, and there was spread to the contralateral side and neck.

COMMENT

Dyskinesias in patients with PD are difficult to assess because they are phenomenologically variable, transient, and often poorly appreciated by the patient. We restricted our study to objective examinations based on videotapes focused on the practically defined off state, defined by the recommendations of the Core Assessment Program for Intracerebral Transplantations. Although we maximized the rigor of our examinations, we only had one preoperative videotape for each subject. To our knowledge, no publications have reported on the temporal stability of dyskinesia assessments in the off state using videotapes taken at repeated time points. Therefore, although we document both off-medication dystonia and choreo-dystonic movements in this group of patients with PD who have severe motor impairment, we cannot comment on whether these behaviors would be reproducibly seen in frequency or severity on other days or during other off cycles.
Limb dystonia is a well-characterized form of early morning off-medication dyskinesia, occurring in 20% to 30% of patients with PD receiving long-term treatment with levodopa, usually documented by the patient's report. It takes the form of a static posture, involving the feet and, less often, the whole leg, the upper limb, and the neck, and usually disappears on withdrawal of levodopa for more than 24 hours. Other studies have found that those patients with early morning off-medication dyskinesias have taken levodopa for 5 to 12 years, have coexisting peak-dose and diphasic dyskinesias, and exhibited dystonia before the initiation of levodopa treatment. In our sample, dystonia was the most frequent off-medication dyskinesia.

Choreic movements with dystonic features, especially involving the legs, can be seen typically in patients with PD during the day, after they have taken at least one dose of medication and before their next dose, as medication effects wane. These dyskinesias often are a component of the dyskinesia–improvement dyskinesia syndrome, and are most prominent on the more parkinsonian side. They typically improve with dopaminergic drugs and are not a regularly described feature in the early morning before the first dose of medication.

Off-medication choreic-dystonic dyskinesias have been described by Freed et al as a phenomenon in patients who previously underwent fetal transplantation. They described disabling dyskinesias including dystonia in 15% of the patients, and suggested that fetal transplantation may play a role in causing or enhancing this phenomenon. In one subject from our series of patients with advanced PD, early morning off-medication choreic-dystonic dyskinesias occurred in one leg, closely resembling the movements seen in the wearing-off dyskinesias during the day (although these usually occur in both legs), but this subject also had choreic-dystonic dyskinesias in the face and trunk, which are not typically described in patients with the wearing-off dyskinesias. They occurred before surgery, demonstrating that this phenomenon cannot be solely ascribed to surgical intervention. This form of off-medication dyskinesias was uncommon and much less frequently encountered than dystonia. It was not reported or appreciated by the patient and, because it was not painful like dystonia in the off state, we doubt that patients can reliably report these choreic movements. There was no difference in the total score on the fourth section of the UPDRS between the group of patients with and the group without dyskinesias, supporting the idea that the patient's accuracy of perception of the presence of dyskinesias, especially when mild, is poor.

Off-medication choreic-dystonic dyskinesias are not likely to be addressed outside of research protocol because patients are rarely seen in clinical practice before taking their first dose of medication. Because they occurred so rarely in our series, the higher prevalence of 15% in the report by Freed et al suggests that surgical intervention may exacerbate or produce these movements. Comparisons of films before surgery and afterwards would be necessary to permit more solid conclusions.

In treatment trials for PD, continued improvement in bradykinesia, tremor, rigidity, and gait impairment function is usually the primary outcome variable of interest. Information about dyskinesias, including dystonia in the off state and choreic dyskinesias in the on state, is usually collected by patient report or investigator examination, and choreic-dystonic movements in the off state are not specifically sought. Surgical protocols such as the Core Assessment Program for Intracerebral Transplantations and the Core Assessment Program for Surgical Interventional Therapies in Parkinson’s Disease include videotape as-

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Table 1. Early Morning Dyskinesias in the Off State

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (N = 68)</th>
<th>Patients With Dyskinesias (n = 11)</th>
<th>Patients Without Dyskinesias (n = 57)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60 ± 9</td>
<td>57 ± 9</td>
<td>60 ± 9</td>
<td>.30</td>
</tr>
<tr>
<td>Male-female ratio</td>
<td>44/24</td>
<td>7/4</td>
<td>37/20</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>PD duration, y</td>
<td>14 ± 7</td>
<td>13 ± 5</td>
<td>14 ± 7</td>
<td>.90</td>
</tr>
<tr>
<td>UPDRS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor section</td>
<td>50 ± 13</td>
<td>47 ± 7</td>
<td>50 ± 13</td>
<td>.50</td>
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<tr>
<td>Fourth section</td>
<td>9 ± 3</td>
<td>10 ± 5</td>
<td>9 ± 3</td>
<td>.50</td>
</tr>
<tr>
<td>Hoehn and Yahr stage†</td>
<td>4 (2-5)</td>
<td>3 (2.5-5)</td>
<td>4 (2-5)</td>
<td>.20</td>
</tr>
</tbody>
</table>

*Data are given as the mean ± SD unless otherwise indicated. The off state is defined as being at least 12 hours after the last dose of dopaminergic drugs. PD indicates Parkinson disease; UPDRS, Unified Parkinson’s Disease Rating Scale.
†Data are given as median (range).

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Table 2. Patients’ Therapy

<table>
<thead>
<tr>
<th>Type of Medication</th>
<th>Overall (N = 68)</th>
<th>Patients With Dyskinesias (n = 11)</th>
<th>Patients Without Dyskinesias (n = 57)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agonist, mg</td>
<td>2.18 ± 2.10</td>
<td>2.60 ± 2.60</td>
<td>2.09 ± 2.00</td>
<td>.60</td>
</tr>
<tr>
<td>Levodopa, mg</td>
<td>962.02 ± 507.00</td>
<td>963.60 ± 457.60</td>
<td>961.70 ± 520.00</td>
<td>.91</td>
</tr>
<tr>
<td>Levodopa and agonist†</td>
<td>51 (75)</td>
<td>9 (82)</td>
<td>42 (74)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD dose of medication unless otherwise indicated.
†Data are given as number (percentage) of patients taking levodopa and agonist.
essment of patients at baseline and after treatment in the on and off states. Our observations on consecutive patients being treated with neurosurgical intervention for PD cannot be extrapolated to all subjects with PD. These patients were relatively young and had severe motor impairment poorly controlled with available pharmacological therapies. Nevertheless, because the group included all patients from 2 centers that enrolled patients from 2 neurosurgical programs, we consider them representatives of the population undergoing neurosurgical treatments for PD. Our data document that choreic-dystonic dyskinesias, partially resembling wearing-off dyskinesias, can occur in the early morning before medication ingestion in patients with advanced PD, and should be recorded as a form of dyskinesia in the off state. Baseline prevalence rates will permit a safety-and-benefit assessment of the role of interventions like fetal transplantation in the induction, exacerbation, or amelioration of these dyskinesias in patients with PD.

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REFERENCES


