Long-term Follow-up of Levodopa Responsiveness in Generalized Dystonia

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Objectives: To assign an accurate diagnosis to patients with dystonia based on the presence of sustained levodopa responsiveness and to determine whether motor fluctuations occur in patients with dystonia who are withheld from levodopa.

Patients and Methods: Patients with generalized dystonia who responded to treatment in the 1970s with levodopa/carbidopa were surveyed by phone and then examined during a 3-day levodopa holiday. Functional imaging with fluorodopa positron emission tomography was performed on a subset of patients.

Results: In the phone interview, 4 of 7 patients with a diagnosis of dopa-responsive dystonia reported the wearing-off effect a short while (within 4-8 hours) after missing a dose of levodopa. Five patients with dopa-responsive dystonia were examined repetitively during levodopa withdrawal, and 3 developed recurrent symptoms of dystonia as the drug was withheld. In each case, worsening of dystonia did not occur until 29 hours or more after levodopa withdrawal, providing evidence for a response profile similar to the long duration response described in Parkinson disease. No significant changes were seen in the dystonia scores of the 3 patients with idiopathic torsion dystonia who were withheld from levodopa.

Conclusions: We suggest that the subjective feeling of wearing off experienced by our patients with dopa-responsive dystonia may have been for one of the nonmotor effects of levodopa, such as mood elevation. Our data provide objective evidence for the often-repeated assertion that motor fluctuations (analogous to those in levodopa-treated patients with Parkinson disease) do not occur in patients with dopa-responsive dystonia.

Arch Neurol. 1998;55:1320-1323

PATIENTS WITH generalized idiopathic torsion dystonia (ITD) have a variable response to treatment with levodopa. Most have no response or suffer worsening dystonia. A distinct minority of patients report some improvement, which is almost always transient. A very small subset of patients with progressive idiopathic generalized dystonia, however, have a dramatic and prolonged response to relatively small doses of levodopa, leading to the designation dopa-responsive dystonia (DRD).

One of us (M.D.M.) found levodopa therapy to be effective in 12 patients with idiopathic generalized dystonia who were treated in the 1970s. Several of these patients had only a partial and transient response to levodopa, leading to the diagnosis of ITD. Others had a dramatic and prolonged beneficial response to the drug and therefore represent typical cases of DRD. One patient had otherwise typical DRD but during prolonged follow-up reported the development of motor fluctuations. This case was surprising since, according to Nygaard et al, motor fluctuations (such as the wearing-off effect) do not occur in patients with DRD. In fact, some authors have suggested that when motor fluctuations are seen in patients with presumed DRD, the correct diagnosis may in fact be juvenile-onset Parkinson disease rather than DRD. The aims of the current study were (1) to reclassify patients as having either DRD or ITD based on the presence of sustained responsiveness to low-dose levodopa therapy and (2) to determine whether motor fluctuations, such as the wearing-off effect, occur in patients with dystonia treated with levodopa.

RESULTS

Eleven patients were reached by phone and surveyed regarding their illness after a mean of 18.5 years since initiation of treatment. Table 1 shows a summary of the
PATIENTS AND METHODS

After conducting a detailed review of the medical records of the original 12 patients with dystonia who reported levodopa responsiveness in the 1970s, the patients were contacted by phone and surveyed regarding the course of their illness since their last examination, with specific attention to the issues of levodopa responsiveness and motor fluctuations. Patients were then invited to travel to the Mayo Clinic Scottsdale, Scottsdale, Ariz, for reexamination. All travel and accommodation costs were funded through the study. Those patients who agreed to visit underwent detailed clinical evaluation for dystonia and parkinsonism over a 3-day period. While we did not expect to see parkinsonism in our patients with DRD, we included scoring for parkinsonism because other investigators have suggested that these disorders can sometimes be confused.1 After providing informed consent, the patients who were still taking levodopa/carbidopa (all 5 patients with DRD and 3 of the 4 patients with ITD) were asked not to take the drug for up to 3 days, during which time they received 4 neurologic examinations for both dystonia and parkinsonism. “Off-levodopa” dystonia examinations were performed in the morning (8 AM) and in the late afternoon (5 PM) to assess for diurnal fluctuations. Dystonia was rated using the Fahn-Marsden Dystonia Scale,5 while parkinsonism was assessed using the Unified Parkinson’s Disease Rating Scale motor section (items 18-31). After the final off-levodopa clinical rating was performed on the third day, patients were given their usual dose of levodopa/carbidopa and observed for a response. Clinical ratings were repeated after maximal clinical improvement (if any) occurred, and if no improvement was seen, 90 minutes later. A second “on-state” dystonia scoring was performed 6 hours after levodopa administration in patient 1.

Subsequently, 6 patients underwent positron emission tomography (PET) scans with fluorodopa F 18 and raclopride labeled with carbon 11 (11C) at the University of British Columbia, Vancouver. All PET studies were performed (using an ECAT 953B/31 tomograph) after a 12-hour withdrawal of medication. The fluorodopa F 18 PET scans were performed dynamically over a 2-hour period. The analysis was performed using regions of interest that covered the heads of the caudates and 3 regions of interest per slice that covered the putamen. The analysis was performed using a graphical method and metabolite-corrected blood input according to the method described by Patlak and Blasberg.6 The full details of the method have been described elsewhere.7 The 11C-raclopride scans were performed using the same sets of regions of interest placed manually on the raclopride scans. After an injection of 5 mCi, data were collected for 60 minutes. The analysis was the ratio of striatum to background for the period from 30 to 60 minutes. The definition of normal for both the fluorodopa and raclopride scans was based on the 95% confidence limits of age-matched normal controls. The control subjects had no history of neurologic disease and were normal on neurologic examination. None were taking medication that influenced the dopaminergic system.

Table 1. Clinical Features Based on Chart Review and Phone Interview

<table>
<thead>
<tr>
<th>Patient No./ Age at Onset, y</th>
<th>Initial Symptom</th>
<th>Daily Levodopa Dose, mg</th>
<th>Effect of Levodopa</th>
<th>Wearing-Off Effect</th>
<th>Duration of Response to Levodopa, h</th>
<th>Diurnal Fluctuations?</th>
<th>Diagnosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/7</td>
<td>Foot inversion when walking</td>
<td>100</td>
<td>Dramatic</td>
<td>Yes</td>
<td>29</td>
<td>Yes</td>
<td>DRD</td>
</tr>
<tr>
<td>11/5</td>
<td>Foot inversion when walking</td>
<td>100</td>
<td>Dramatic</td>
<td>Yes</td>
<td>8</td>
<td>Yes</td>
<td>DRD</td>
</tr>
<tr>
<td>8/7</td>
<td>Torticollis and dystonic posturing of arms</td>
<td>150</td>
<td>Dramatic</td>
<td>Yes</td>
<td>4</td>
<td>Yes</td>
<td>DRD</td>
</tr>
<tr>
<td>5/6</td>
<td>Involuntary movements of hands</td>
<td>300</td>
<td>Dramatic</td>
<td>Yes</td>
<td>6</td>
<td>No</td>
<td>DRD</td>
</tr>
<tr>
<td>4/5</td>
<td>Inversion of feet and flexion of toes</td>
<td>200</td>
<td>Dramatic</td>
<td>Yes</td>
<td>7</td>
<td>Yes</td>
<td>DRD</td>
</tr>
<tr>
<td>10/3</td>
<td>Foot inversion when walking</td>
<td>100</td>
<td>Dramatic</td>
<td>Yes</td>
<td>24</td>
<td>Yes</td>
<td>DRD</td>
</tr>
<tr>
<td>2/2</td>
<td>Foot inversion when walking</td>
<td>100</td>
<td>Dramatic</td>
<td>Yes</td>
<td>17-25</td>
<td>Yes</td>
<td>DRD</td>
</tr>
<tr>
<td>7/10</td>
<td>Truncal dystonia with retrocollis</td>
<td>None</td>
<td>Modest</td>
<td>No</td>
<td>Not applicable</td>
<td>No</td>
<td>ITD</td>
</tr>
<tr>
<td>6/9</td>
<td>Torticollis</td>
<td>500</td>
<td>Modest</td>
<td>No</td>
<td>Not applicable</td>
<td>No</td>
<td>ITD</td>
</tr>
<tr>
<td>9/12</td>
<td>Torticollis, right arm tremor</td>
<td>1000</td>
<td>Modest</td>
<td>Yes</td>
<td>24</td>
<td>Yes</td>
<td>ITD</td>
</tr>
<tr>
<td>3/43</td>
<td>Eyelid and facial twitching</td>
<td>1600</td>
<td>Modest</td>
<td>Yes</td>
<td>4</td>
<td>No</td>
<td>ITD</td>
</tr>
</tbody>
</table>

* DRD indicates dopa-responsive dystonia; ITD, idiopathic torsion dystonia.

clinical features of each case gathered from chart review and telephone interview. An important finding from the survey was that all patients with DRD admitted to having experienced the wearing-off effect from levodopa, usually when a dose of the drug was inadvertently skipped. Three of the 7 patients with DRD had a relatively long duration response to a given dose, noting wearing off of the effects 24 hours or more after the dose was missed. Four of the 7, however, had short duration responses by history and developed a feeling of uneasiness that they thought presaged the recurrence of dystonic posturing within a mean of 6 hours after taking the last dose of levodopa.

Nine patients traveled to Mayo Clinic Scottsdale for detailed examination over a period of 3 days. Those still taking levodopa remained off the drug for up to 83 hours (mean, 55.8 hours). Dystonia scores for each patient at each of the assessment examinations are shown in Figure 1 and Figure 2. Consistent with our expectations, parkinsonism was not observed in any patient at any time during drug withdrawal. Diurnal fluctuation of dystonia severity (operationally defined here as a low-
Fig 1. Dystonia scores of patients with dopa-responsive dystonia during withdrawal from levodopa therapy and after rechallenge. Day 3 Off indicates the period before levodopa was taken; Day 3 On, the period after response was seen. Patient 1 was given a late examination 6 hours after levodopa was administered (Day 3 Late). No dystonia was detected in patients 5 and 8 during the levodopa holiday.

Fig 2. Dystonia scores of patients with idiopathic torsion dystonia during withdrawal from levodopa therapy and after rechallenge. Day 3 Off indicates the period before levodopa was taken; Day 3 On, 90 minutes after the administration of levodopa. Patient 7 had discontinued taking levodopa years before the present study was begun.

Table 2. Subjective/Objective Data Comparison for Drug Latency and Duration in Patients With Dopa-Responsive Dystonia for Whom Complete Data Are Available

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Duration of Response to Levodopa, h</th>
<th>Latency to Onset of Drug Effect, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone Interview Observed</td>
<td>Phone Interview Observed</td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>17-25</td>
<td>38.5</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>29</td>
</tr>
</tbody>
</table>

COMMENT

A beneficial response to levodopa is uncommon in generalized dystonia but, when present, is of enormous diagnostic and therapeutic significance. Dopa-responsive dystonia can be easily diagnosed when childhood-onset dystonia responds completely and persistently to small daily doses of levodopa. This disorder has been shown to be due to mutations in the gene coding for guanosine triphosphate cyclohydrolase I, which leads to a deficiency of tetrahydrobiopterin.8 Since tetrahydrobiopterin is a key cofactor for tyrosine hydroxylase, this gene defect results in impaired synthesis of dopamine by nigral neurons. An autopsy study was published recently that showed normal numbers of nigral neurons associated with marked dopamine deficiency.6 findings that confirm the nondegenerative nature of DRD.

In light of the reports suggesting that motor fluctuations are not seen in DRD,4,10-12 we were surprised by the results of our phone interviews, in which several patients with DRD reported a short duration response to levodopa. We predicted that if a true short duration response was present in these cases, we would observe recurrent dystonia within several hours as patients were withdrawn from levodopa. Our data showed that this was not the case, indicating that the subjective feeling of wearing off reported in the phone interview did not represent recurrent dystonia. Patients with ITD, on the other hand, who by history had a modest or transient benefit from levodopa therapy, were expected to maintain relatively constant dystonia scores during the time of levodopa withdrawal, and our data confirmed this.

Our results demonstrated that all patients with DRD who developed dystonia during levodopa withdrawal experienced continued deterioration in dystonia scores during the second day off the drug. As such, this clinical observation is analogous to the long duration response described in patients with Parkinson disease in whom pro-
gressive deterioration in motor scores was observed over several days of levodopa withdrawal.\textsuperscript{13} Since we terminated the levodopa holiday on the third day, it is unknown whether further worsening of dystonia would have been observed with a longer period of observation off levodopa.

Improvement in dystonia scores occurred within several hours of levodopa rechallenge in our patients with DRD, which parallels the short duration response to levodopa seen in patients with Parkinson disease. That the dystonia score of patient 1 improved and then worsened again by 6 hours after administration echoes previous observations in Parkinson disease that a single dose of levodopa may be insufficient to restore the long duration response.\textsuperscript{14} These findings in our patients with DRD are thus consistent with an intact population of nigral neurons capable of storage and release of dopamine in a physiologic fashion. A similar presynaptic dopamine storage mechanism may partly explain the long duration response seen in patients with Parkinson disease. However, since Parkinson disease involves progressive loss of presynaptic nigral neurons with a gradual diminution of the long duration response, we would expect significant differences in the clinical deterioration rate during levodopa withdrawal in patients with DRD compared with those with Parkinson disease. A detailed comparison of these 2 disorders with respect to rate of deterioration during a levodopa holiday is desirable, but would require more detailed studies with a much larger number of patients with DRD.

We had hoped to obtain PET scans on all patients participating in the clinical phase of the study, but for a variety of personal reasons, 3 patients (all with DRD) were unable to schedule their scans in Vancouver. Since only 2 patients with DRD underwent scanning, limited conclusions can be drawn from the data. The normal fluorodopa uptake is consistent with the nondegenerative nature of DRD, and may help to distinguish DRD from juvenile Parkinson disease (in which low uptake is expected). The finding of high raclopride binding in 1 patient with DRD is supported by similar findings in a recent study of 6 patients with DRD and 4 obligate carriers of DRD,\textsuperscript{15} and suggests that striatal D\textsubscript{2} receptor up-regulation occurs in this disorder. However, since this finding conflicts with a that of a previous study of treated DRD in which the patients showed normal raclopride binding,\textsuperscript{16} further studies will be necessary to clarify this issue. The normal fluorodopa uptake in the 2 patients with ITD suggests that nigral dysfunction is not the key feature of this disorder, although the results of previous PET studies in ITD have been inconsistent.\textsuperscript{17}

In summary, while some patients with DRD may report a wearing off of the effects of levodopa 6 to 8 hours after taking the last dose, our clinical scoring of patients with DRD during 3 days of levodopa withdrawal provides objective evidence of a long duration response to levodopa in this disorder. That some patients subjectively perceived a wearing off of the effects within hours after taking their last dose is undeniable and might be due to the wearing off of a non–motor effect from levodopa, such as its mood-elevating effect.\textsuperscript{18} An alternative explanation is that the concept of wearing off may be understood differently by different patients, resulting in wide variability with regard to how this question was answered in the phone interview. When querying patients about wearing off, the physician must delve deeply into exactly what is meant by this term to avoid misunderstanding. The PET studies revealed normal fluorodopa uptake in cases of DRD and ITD, a finding that provides further evidence that neither disorder is due to degeneration of nigral neurons. Clinical differentiation of DRD from ITD can be accomplished with a trial of levodopa therapy, which should be used in all patients with childhood-onset dystonia.

Accepted for publication April 20, 1998.

This study was supported in part by a grant from Mayo Clinic Scottsdale.

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ARCH NEUROL / VOL 55, OCT 1998

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