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The Sequence Effect in *De Novo* Parkinson's Disease

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Background and Purpose: The sequence effect (SE) in Parkinson's disease (PD) denotes progressive slowness in speed or progressive decrease in amplitude of repetitive movements. It is a well-known feature of bradykinesia and is considered unique in PD. Until now, it was well-documented in advanced PD, but not in drug-naïve PD. The aim of this study is to know whether the SE can also be measured in drug-naïve PD. **Methods:** We measured the SE with a computer-based, modified Purdue pegboard in 4 drug-naïve PD patients, which matched our previous study with advanced PD patients. **Results:** We observed progressive slowness during movement, that is, SE. Statistical analysis showed a strong statistical trend toward the SE with the right hand, but no significance with the left hand. There was no statistical significance of SE with either the more or less affected hands. **Conclusions:** These results indicate that the SE can be identified in drug-naïve PD, as well as in advanced PD, with objective measurements and support the idea that the SE is a feature in PD observed during the early stage of the disease without medication. **Journal of Movement Disorders 2011;4:38-40**

Key Words: Parkinson's disease, *De novo*, Bradykinesia, Sequence effect, Progressive slowness, Pegboard test.

Progressive slowness in speed or progressive decrease in amplitude of repetitive movements is unique in Parkinson's disease (PD).[1,2] It is referred to as the sequence effect (SE).[3,4] Until now, it was well-demonstrated in only advanced PD.[1-3] The SE might also be observed in drug-naïve PD because the SE is a feature of bradykinesia, although measuring the SE has not been documented. Indeed, the SE might be difficult to identify in the drug-naïve, early stage of PD because the SE might be too mild to detect. The characteristics of the repetitive movements in drug-naïve PD might differ from that in advanced PD since the pattern of cerebral excitability is dissimilar between drug-naïve and advanced PD[5,6] and medication affects cortical plasticity in PD.[7,8]

With a computer-based, modified Purdue pegboard test, we reported that we measured the SE in advanced PD.[3] At that time, we also conducted similar research with drug-naïve PD, but we did not complete the study due to difficulty in recruiting drug-naïve PD patients. Although we did not complete the study with *de novo* PD, we were able to see whether the SE could be measured in drug-naïve PD.

Methods

Subjects

We collected the complete data of four patients (1 woman, 3 men). All patients were right-handed. Their mean (± SD) age was 64.3 ± 9.3 years. The mean (± SD) disease duration was 2.6 ± 1.7 years. Hoehn and Yahr stages were 2. Mini-Mental State Examination (29.3 ± 0.5), Hamilton Depression Rating Scale (3 ± 2), Fatigue Severity Scale (4.2 ± 1.1), and Multidimensional Fatigue Inventory (57.8 ± 15.0) were evaluated (Table 1). We recruited patients from the National Institute of Neurological Disorders and Stroke (NINDS) Clinics. All patients gave written informed consent for this study protocol approved by the NINDS Institutional Review Board.

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Table 1. Characteristics of patients with *de novo* Parkinson's disease

No.	Age (yr)	Sex	Duration (yr)*	H & Y	MMSE	UPDRS	HDRS	FSS	MFI
1	55	F	1.4	2	29	31	2	4.67	51
2	76	M	2	2	30	24	6	5.2	80
3	59	M	1.4	2	29	17	2	2.56	47
4	67	M	5	2	29	16	2	4.4	53

*disease duration since diagnosis, H & Y: Hoehn and Yahr, MMSE: Mini-Mental State Examination, UPDRS: Unified Parkinson's Disease Rating Scale, HDRS: Hamilton Depression Rating Scale, FSS: Fatigue Severity Scale, MFI: Multidimensional Fatigue Inventory

Procedures

The experimental details and analysis of the SE were the same as in the previous study.[3] We assessed the SE as a progressive lengthening of peg movement time for successive peg movements, using a Modified Purdue Pegboard Test and a computer-based device (part of the At-Home Testing Device, Intel, courtesy of the Kinetics Foundation).[9] The Pegboard Test had a vertical line of eight holes on both the right and left sides. The task started on the right side. We asked patients to move individual pegs from the right to the left side as quickly as possible. That constituted one run. The device could store the time of pulling-out and pushing-in of each peg. There were six runs, three with the right hand first, followed by three with the left hand. There was a 10-second pause between runs and each run began with a beep.

Data and statistical analysis

To assess the SE, we calculated differences between the times to move the first four pegs and the last four pegs for each hand. We did not calculate either the second run with the right hand or the fifth run with the left hand because the direction was opposite to the other two runs for each hand and we thought that the opposite direction might bias the data. We averaged the differences over the two runs, per hand, pegboard test, and patient. Patients were asked to visit four times and to repeat the pegboard test during each visit. Thus, we collected four sets of data. To know whether the SE in both hands was statistically significant, differences were averaged across the four visits for each hand (right, left, more affected, and less affected, respectively) and evaluated using a Wilcoxon signed rank test.

Results

There was progressive slowing (SE) during movement of the last four pegs. A Wilcoxon signed rank test showed a strong statistical trend toward the SE with the right hand, but no significance with the left hand (right hand, 7745.3 ± 513.7 ms. vs. 8082.8 ± 455.7 ms, $p = 0.068$; left hand, 7797.3 ± 887.8 ms. vs. 8144.8 ± 937.5 ms, $p = 0.465$) (Figure 1A). A Wilcoxon signed rank test did not show statistically significant SE with either the more or less affected hands (more affected hand, 7700.0 ± 465.0 ms. vs. 8186.3 ± 629.8 ms, $p = 0.144$; less affected hand, 7842.5 ± 912.7 ms. vs. 8041.3 ± 828.9 ms, $p = 0.144$) (Figure 1B).

Discussion

These results indicate that the SE can be identified in drug-naïve PD, as well as in advanced PD. Additionally, the data

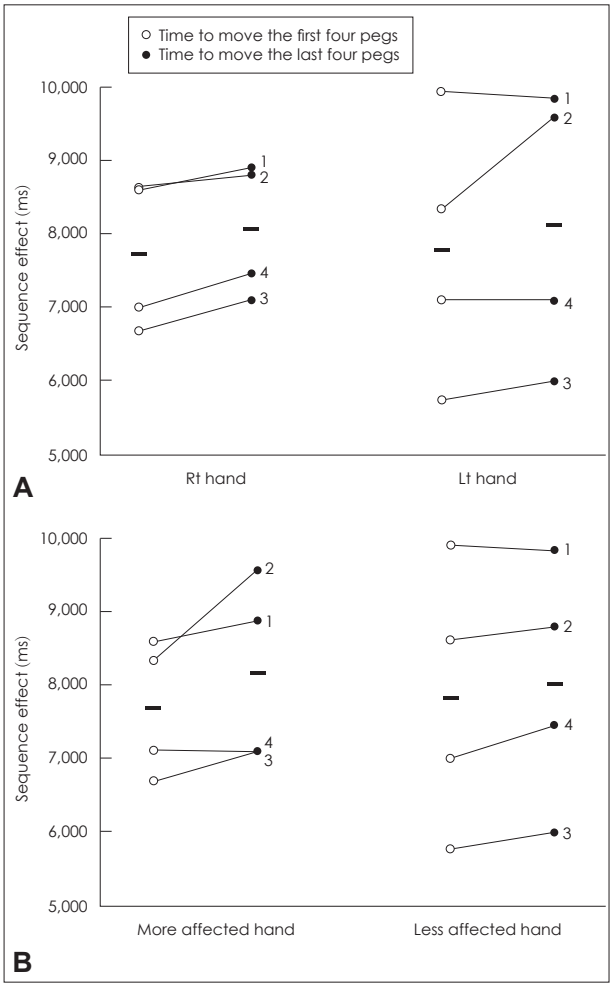

Figure 1. Sequence effect (SE) in four drug naïve patients during four visits. Circles indicate time to move the first four pegs (1st-4th) (open circles) and time to move the last four pegs (5th-8th) (closed circles) (individual data as circles, group averages as bars). Increased mean value in closed circles indicates SE (progressive slowing during peg movements) and decreased mean value indicates the opposite (speeding up during peg movements). A: There was a strong statistical trend for SE in peg movements with the right hand, but no significance with the left hand (right hand, $p = 0.068$; left hand, $p = 0.465$; Wilcoxon signed rank test). B: There was no significance with the more and less affected hands, respectively (more affected hand, $p = 0.144$; less affected hand, $p = 0.144$; Wilcoxon signed rank test).

show that the SE is a feature in PD and is observed during the early-stage of the disease without medication.

The SE is well-known in PD.[1,4,10,11] Patients with PD were especially slow while they performed complex or repetitive movements.[2,11] The patients needed considerably more time to perform one task and exhibited a longer pause between one task and the next, compared with healthy volunteers.[2,11] Patients with basal ganglia disorders also showed these abnormalities, but only PD patients needed progressively increased time to complete individual movements during repetitive movements.[1] That is, the SE was observed in only PD patients.

To date, the SE has only been measured in advanced PD with medication. In clinical practice, we can observe the SE from several types of repetitive movements such as finger tapping, writing, and gait in early, drug-naïve as well as advanced PD. Thus, one can assume that the SE would be measured during early, drug-naïve PD.

It might be asked why the SE should be measured separately from other motor symptoms. It appears that the cause of all motor symptoms is not the same and dopaminergic medication does not improve all such symptoms.[12-14] The clinical significance of the SE remains to be investigated. It has been suggested that it contributes to freezing of gait in PD.[15] It was also postulated that the SE may be related to cognition[3,16] and fatigue.[1]

There are some limitations in this study. First, the sample size was small. The mean value of the SE was higher in the more affected hand than in the less affected hand, but there was no statistical significance. Second, we did not provide data from healthy volunteers; but because the SE has been demonstrated in various types of sequential movements in PD, and not in healthy volunteers,[11] it is less likely that the healthy volunteers would show the same SE.

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