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Digitized Spiral Analysis is a Promising Early Motor Marker for Parkinson Disease

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Keywords

Parkinson's disease; spiral analysis; biomarkers; motor quantitative

Clinical trials of Parkinson disease (PD) are shaped by the sensitivity of the metrics used to measure dysfunction. While sequential Unified Parkinson Disease Rating Scale (UPDRS) motor scores reflect disease progression [1], objective quantitative motor assessments may be more sensitive in detecting early disease and may supplement the UPDRS. Spiral analysis is a graphonometric method of assessing upper limb kinematics by digitizing and analyzing Archimedean spirals drawn on a digitized graphics tablet [2] that correlates with the motor UPDRS score [3]. It has the advantage of being non-invasive and relatively easy to perform. To test if spiral analysis could detect changes not clinically measurable by UPDRS, we assessed whether spiral analysis could identify abnormalities on the unaffected side in a unique population of early and clinically unilateral PD (i.e. normal motor UPDRS scores on one side of the body).

Methods

Patients for this report were obtained from a prospective observational study of early PD. All subjects were rated using the UPDRS 3.0 Part III [1], and were tested with spiral analysis along with 40 age-matched normal controls. All provided written consent, and the study was conducted in accordance with the respective Institutional Review Boards. Twenty spirals were drawn by each subject (10 per hand) with an inking pen for full visuomotor feedback on a digitizing tablet (Intuos 2, Wacom Inc., Saitama, Japan) connected to a computer. Subjects were allowed to draw freely without constraints, attachments, or traceable templates, and they

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were asked to neither anchor nor rotate their drawing hand so that collection was standardized across all subjects. They also were instructed to sit with shoulders parallel to the front edge of the tablet, and not let their arms rest on the tablet.

Quantification of handwritten spirals was derived from graphonometric methods assessing curvature, drawing speed and other kinematic measures of spiral execution. The assessment included mathematically “unraveling” and averaging multiple spiral drawings to capture a range of spatial attributes not based on a single sample, and provided data for computation of an overall spiral severity score. This five-point (0–4) score correlated with clinical phenomena associated with PD [3].

Spiral severity scores on affected and unaffected sides of PD patients were compared with an averaged control scores from both hands using the Mann-Whitney test for non-parametric data.

Results

Nine subjects in the larger cohort of 104 met the stringent criteria of completely unilateral motor features, were not on anti-parkinsonian medication, and are reported here. All nine subjects were right hand dominant as were 87.5% of controls. Each subject's total UPDRS-III was zero on the asymptomatic side. Table 1 shows demographic, clinical and spiral analysis findings. Median spiral severity on the unaffected side was greater in patients [1.18 (interquartile range 1.07–1.30)] compared to controls [0.87 (0.64–1.08)] ($p=0.04$) and in the affected side of patients compared to controls [1.54 (1.10–1.78)] ($p=0.001$).

Discussion

We suggest that the graphonometric spiral analysis test may be more sensitive in detecting early changes in motor performance than the UPDRS. Drawing on a graphics tablet is used to elucidate mechanisms of basal ganglia dysfunction in PD[5]. Thus, spiral analysis might be useful to complement the UPDRS, and shows promise as an early marker for PD. However, our sample size is small and limited to very early PD, and additional studies to replicate and further examine the utility of this test are needed. We postulate that spiral drawing abnormalities reflect subtle disturbances in motor pathways, likely due to early contralateral nigral degeneration. It is also possible that abnormalities on the asymptomatic side are due to ipsilateral brain changes exerting bilateral effects.

While the primary focus of this report was to determine whether spiral analysis shows potential to be more sensitive than the UPDRS in patients with unilateral findings, we also reviewed the clinical data of unilateral individuals who were selected based on UPDRS criteria, to determine whether there were ”soft” features, such as decreased armswing, on the unaffected side which were not captured with UPDRS but might reflect subtle motor changes. However, none of the subjects were noted to have these features, suggesting that they indeed were clinically completely asymmetric.

Our unique study design provides a window to assess very mild disease. An important possible application of these findings could be in the detection of subjects without clinically manifest PD on either side (“pre-clinical PD”), but who may be on the trajectory to clinical PD. For neuroprotective clinical trials on pre-clinical PD, individuals at high risk for conversion to PD must be identified, and screens to detect pre-clinical parkinsonism established. Our study shows that spiral execution abnormalities may have the potential to discern pre-clinical disease, and might be considered in a combined or staged battery of tests including imaging, olfactory, autonomic, sleep, and other motor tests.

Combining the spiral test with these others in a cohort of at-risk individuals would lend further insight into this potential use. However, as only 8% of our overall early PD cohort met the stringent inclusion criteria of hemi-PD not on anti-parkinson medication, further study to expand on this pilot sample in a larger population is warranted. Spiral analysis may have broader utility in diagnosis of PD, and may be useful as a supplemental outcome measure in proof of concept clinical trials. Before considering spiral analysis for these applications, sensitivity and specificity should be established, and the ability of spiral analysis to assess longitudinal change determined.

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Table 1

Clinical and Spiral Data

Patient	Age (years)	Sex	Disease duration (years)	Affected side	UPDRS motor score*	Spiral Severity Unaffected side**	Spiral Severity Affected side**	Spiral Severity Both Sides Average
1	57.2	F	1.7	Left	15.0	1.36	2.61	1.98
2	61.0	F	0.2	Left	5.5	1.30	1.54	1.42
3	63.6	F	0.1	Right	7.0	1.07	1.78	1.42
4	54.3	F	2.6	Right	8.5	1.55	1.68	1.62
5	59.0	M	0.7	Left	8.0	.76	1.10	0.93
6	63.1	F	0.03	Right	10.0	1.28	.92	1.10
7	51.6	M	1.3	Left	6.0	1.18	1.44	1.31
8	53.7	F	0.0	Right	7.5	1.15	.59	0.87
9	62.6	M	0.4	Left	7.5	.58	3.61	2.10
Patients (n=9)	57 (54.5– 61)	33% men	0.79 (0– 2.6)	44% Right	8.3 (5.5 – 15)	1.18 (1.07–1.30)	1.54 (1.10–1.78)	1.42 (1.11–0.62)
Controls (n=40)	61 (57.2 – 62.6)	40% men	-----		---	.87 (.64 – 1.08)	.87 (.64 – 1.08)	.87 (.64 – 1.08)
p-value***	NS	NS	---	---	---	.04	.002	.001

* UPDRS Part III Total

** Control spiral severity score averaged from both hands

*** Mann-Whitney test based on comparison of medians (as reported above, with interquartile range)