Actigraphy Monitoring of Symptoms in Patients with Parkinson's disease

Bidve Nisha[1], Jadhav Rohini[2], Pratiksha shinde[3], Renuka R. Deshpande[4]
[1,2,3] *B.Pharmacy 2nd year Student, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India*
[4]*Assistant Professor, Department of Pharmaceutics, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India*

***Abstract*- Although the Unified Parkinson's Disease Rating Scale (UPDRS) is the "gold-standard" tool in assessing the severity of symptoms in patients with Parkinson's disease (PD), not all activity-related disease symptoms can be accurately captured by the well-established clinical rating scale. Using an alternative approach, this study examined the level of physical activity measured by actigraphy over time and whether change in physical activity was associated with disease severity assessed by UPDRS. We used a longitudinal design in which physical activity and disease severity were assessed repeatedly during a 4-month interval, over a 3-year observational period, in a sample of 61 patients with idiopathic PD and a control group of 32 neurologically intact individuals. Physical activity data during awake-time were analyzed using the power-law exponent (PLE) method. Correlational relationships between changes in maxima values of PLE and scores of total UPDRS, UPDRS—part II (Activities of Daily Living), and UPDRS—part III (Motor Examination) in patients with PD were examined. Results show an increase in maxima values of PLE and the UPDRS total score in PD patients and that there is a positive association between changes in maxima values and total UPDRS score (r=0.746, p=0.032), UPDRS—part II score (r=0.687, p=0.027), and UPDRS—part III score (r=0.893, p=0.018). There was no significant change in the level of physical activity over time for the controls. Findings from this study indicate that change in physical activity, as captured by actigraphy, is associated with increased severity in patients' clinical symptoms of PD over time. Thus, these data suggest that, when used in conjunction with the conventional UPDRS measure, an actigraphic measure of physical activity may provide clinicians an adjunct measurement approach to monitor patients' activity-based disease progression or responses to treatment in outpatient clinic settings.**

***Index terms*- Actigraphy Parkinson's disease Power-law exponent**

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease that affects millions of people worldwide. Patients with PD experience various movement-related abnormalities that significantly impact their independence and quality of life. Currently, the Unified Parkinson's Disease Rating Scale (UPDRS) [1] is considered a "gold standard" reference scale in assessing various dimensions of disease severity in patients with PD. However, daily fluctuation in disease symptoms may

0031-9384/$ - see front matter http://dx.doi.org/! 0.1016/j.physbeh.2013.05.044

not be fully captured or understood via the sole use of this clinical rating scale. Patients' symptoms of disease may well be masked by their dopaminergic medications and/or disease stages/severity [2]. In the treatment of patients with PD, the severity of symptoms is conventionally assessed using the UPDRS based on neurological examination, the patient's diary, or the caregiver's reports. These methods, however, lack quantitative aspects, thereby making them inadequate for the precise assessment of drug efficacy [3]. However, none of these studies have been successful in developing reliable analytical methods that quantitatively represent the disease progression in patients with PD [4-6]. Therefore, from a clinical standpoint, additional adjunct clinical tools that can provide an objective yet concomitant evaluation of activity-related disease symptoms manifested in daily life and during disease progression are warranted.

Research has shown that actigraphy-based observations can be useful and effective in objectively assessing activity-related disease symptoms such as tremor and motor fluctuations in patients with PD [3-7]. In our own previous work, we have shown that, by analyzing the power-law exponent (PLE; alpha) for local maxima and minima of severities in the activity time series [5,8,9], variation in physical activity captured by actigraphy was significantly correlated with the progression of PD symptoms. Our work suggests that actigraphic data, when analyzed by the PLE method, may provide clinically useful and objective information regarding PD patients' disease severity.

There have been, however, limited accelerometer-based studies that examine patterns of daily physical activity among independently living adults and how variation in movement-related activities may be correlated with change in clinically identified symptoms of severity over time. Addressing these issues could be clinically important in providing a comprehensive evaluation of patients' disease status on a range of symptoms. Their severity information can be subsequently used by clinicians in aiding their clinical decisions about patients' treatment options and/or evaluation of their responses to intervention modalities.

The purpose of this study, therefore, was to examine whether daily physical activity among independently living adults' physical activity would be associated with clinically rated symptoms over time in patients with PD. On the basis of our prior work [5,8-11], we hypothesized that variation in actigraphic recordings of patients' kinematics of movement disorder symptoms during awake-time would be correlated with PD symptoms assessed by UPDRS over time.

MATERIALS AND METHODS

Study design

We used a longitudinal design in which study participants were contacted and assessed with the planned study outcome measures every 4th month over a period of 3 years.

Participants

A total of 61 outpatients with idiopathic PD and 32 control participants were recruited from the department of Neurology of Shuguang Hospital Affiliated with Shanghai University of TCM. Eligibility criteria for patients with PD included individuals who were (a) at least 40 years of age, (b) diagnosed on two of the cardinal symptoms (bradykinesia, tremor, rigidity, or postural instability) assessed by the UPDRS [1], (c) on dopaminergic medications (i.e., levodopa), (d) showing no sign of mental deficit (e.g., dementia) and major depressive disorder, and (e) not affected by unstable cardiovascular disease or extrapyramidal syndromes due to other central nervous diseases identified by the investigators. Inclusion criteria for the control participants included neurologically intact and healthy community-dwelling adults. The study protocol was approved by the Ethics Committee of Shuguang Hospital Affiliated with Shanghai University of TCM according to the principles outlined in the Declaration of Helsinki. An informed consent was obtained from each participant.

CONTROL OF MEDICATIONS

Patients' anti-Parkinson drugs were administered per the international medication guidelines [12] and monitored throughout the study period. Patients were instructed to adjust their medications for at least 14 days (mean ± SD, 30.6 ± 15.7) until their symptoms of PD approached a steady state.

OUTCOME ASSESSMENT

The study included two outcome measures: (a) the UPDRS [1] and (b) actigraphy. Each is detailed below. Measures were taken at 4-month intervals across a 3-year period.

The UPDRS with two subsections (part II—Activities of Daily Living [ADL] and part III—Motor Examination [Motor]) was used. Items contained in UPDRS were rated on a 5-point (0-4) scale, with higher scores indicating severity of the disease. The UPDRS assessment for patients with PD was made during an "on" medication status by a neurologist. All assessments were conducted before actigraphy recordings (described below).

Patients with PD and the controls were given an actigraphy (MicroMini-Motionlogger®, Ambulatory Monitoring, Inc.) in which they were instructed to wear the device on their dominant wrist for 24 h per day during a 7-day period. Zero-crossing activity

counts [11,12] were recorded every minute to register and quantify participants' physical activity.

Once the actigraphy was returned, the wrist activity data recorded during awake-time were then transmitted to the program software provided by the manufacturer, and the data were aggregated into 1-minute epochs for analysis using the Action-W (version 2, Ambulatory Monitors Inc.). The power-law (scaling) exponent (a), obtained as the slope of a straight line fit in the double-logarithmic plot of time scales vs. magnitudes of fluctuation, was used to emphasize the level of such correlation [9]. As Ohashi et al. [9] demonstrated, physical activity data have different power-law exponents in periods with higher and lower activity levels, corresponding to qualitatively different physiological states. The actual procedures we used are as follows: First, a daytime physical activity time series was integrated, as in DFA, and wavelets with different time scales (S) were slid along the time series and correlated with the data to obtain the wavelet coefficients (W(S)) at each point. We used the third derivative of the Gaussian function as the so-called "mother wavelet":

m = t(3-t2)e"a5t2

where t is time. This is equivalent to using the Gaussian second derivative (so-called "Mexican hat") wavelet to examine the raw signals, though the integration approach automatically removes the local

Table 1

Demographic and clinical profiles of the study population at baseline.

	Baseline	3-Year follow-up
Age (years)	61.2 ± 7.9	
Sex (male/female)	32/24	
Duration (years)	6.8 ± 5.7	
Hoehn & Yahr	2.8 ± 1.4	3.3 ± 1.2
Levodopa/DCI (mg/day)	416.8 ± 209.7	482.4 ± 174.6
Pramipexole (mg/day)	1.63 ± 0.78	2.35 ± 1.17
Entacapone (mg/day)	169.74 ± 76.68	185.73 ± 56.35
Selegiline hydrochloride(mg/day)	8.22 ± 3.53	11.98 ± 6.87
Adamantanamine (mg/day)	57.31 ± 36.7	79.66 ± 34.86
Artane hydrochloride (mg/day)	2.86 ± 2.37	3.93 ± 2.61

mean and the local linear trend, as in DFA. By changing the scale of different time scales. The transient increases (low-high-low activity the wavelet, this "hat-shaped" template dilates or contracts in time, patterns) yield local maxima of the wavelet coefficients at their probing transient increases or decreases in activity records in time points, while the decreases (high-low-high activity patterns)

1.15 1.0 0.95 0.9 0.85 0.8
Ï PD UPDRS Î PD a 2 Ctr c
-3>..g>..-5E..3E...^...j|>..
16 20 Duration(M)
0.08 0.04 0
J PD a 5 Ctr a J PD UPDRS
4.....Ï.....-Ï-
--Ï.....-I.....I----Ï----------$--
12 24 36 Duration(M)
^ 0.9 E
! 0.06 S
< 0.03
r = 0.746
0 1.3 2.6 3.9 5.2 6.5 A UPDRS scores/y (Total)
0.9 0.06 0.03 0
r = 0.687
"0 1.3 2.6 3.9 5.2 A UPDRS scores/y (Part II)
E 0.12 0.9
< 0.03
r = 0.839
sj,.r ° s s
„•-t"!« I
0 1.6 3.2 4.8 A UPDRS scores/y (Part III)
I baseline
I 3-year follow-up
UPDRS II UPDRS III UPDRS Total

Fig. 1. Changes in UPDRS scores and power-law exponent (PLE) values in patients with PD and controls during 3-year follow-up and the relationship between UPDRS scores and PLE values (A-E). UPDRS indicates Unified Parkinson's Disease Rating Scale and PLE value indicates power-law exponent a (F). Д, compared with baseline of UPDRS scores (A,p < 0.05; ДД, p < 0.01); #, compared with baseline of PLE (#, p < 0.05; ##, p < 0.01); *, compared with baseline (*, p < 0.05; **, p < 0.01).

yield local minima of the wavelet coefficients. Second, the squared wavelet coefficients at the local maxima or minima were averaged for all the available days. As the coefficient gives the magnitude of local fluctuations matching the shape of ^(t) with different time scales, the squared W(S) was used, again as in DFA. Finally, the power-law exponent (a) was obtained separately for local maxima and minima as the slope of a straight line fit in the double-logarithmic plot of S vs. W(S)2. In this

study, the range of S corresponding to 8 to 35 min, where acceptable linear relationships between log S and log W(S)2 were observed for all the records, was used [2,10,11]. This range is also approximately the same as that used in Ohashi et al., and this method yields the same a-values as does DFA, but separately for periods with higher and lower activity levels. In other words, a lower value for local maxima or minima of activity recordings reflects more frequent switching behavior from low to high or high to low physical activity, respectively, and the switching behavior from lower to higher activity levels is considered to be related to akinesia in patients with PD.

In patients with PD, the PLE a-values for local maxima did not differ between the arms with tremor and those without tremor, but were significantly lower in both of the patient groups than in the control arms, indicating that, although the presence of tremor greatly influenced the actigraphic counts, the presence of tremor did not yield false positive results in the PLE for maxima [2]. In this study, we analyzed the local maxima for the awake-time of each record in the series of time windows observed.

STATISTICAL ANALYSIS

A repeated-measures analysis of variance (ANOVA) was performed to evaluate longitudinal changes from baseline to 3-year follow-up in UPDRS total score, UPDRS part II—ADL score, UPDRS part III—Motor score, and PLE alpha values. Pearson's bivariate correlations were analyzed to examine the relationship between changes in the UPDRS total score and subscale scores and changes in the PLE alpha values. The alpha (a) level for significance was set at $p < 0.05$. Analysis of the data was carried out using SPSS (Version 17.0), and the resulting data are presented in mean ± stand deviation.

RESULTS

In all, five patients with PD withdrew from the study, three because of medical complications and two because of loss to follow-up. Fifty-six patients with PD and all control subjects completed the study. Patients' demographic and clinical profiles at baseline are presented in Table 1.

At the end of 3-year follow-up, there was a significant increase, from baseline, in patient's UPDRS total score, subscales scores (part II—ADL, part III—Motor, data not shown), and PLE alpha values observed during awake-time (Fig. 1A), with 5 points per year in UPDRS score and 0.04 points per year in the PLE maxima alpha values, respectively. The average alpha values of local maxima, however, were not changed over time in the control participants (Fig. 1B). Changes in UPDRS total score and its subscale scores (UPDRS part II—ADL, UPDRS part III— Motor) were found to be significantly correlated with changes in local maxima alpha values over time; 0.746 ($p = 0.032$) (Fig. 1C), 0.687 ($p = 0.027$) (Fig. 1D), and 0.839 ($p = 0.018$) (Fig. 1E), respectively.

DISCUSSION

This is the first study that uses an actigraphic recording approach to physical activity over time to evaluate the development of symptom severity in patients with PD. Through the PLE analytic method, we found that there was a significant increase in patient's wrist activity during awake-time and that the increase was associated with the clinically rated PD severity over time.

Previous studies have reported that lower PLE values for local maxima of activity were related to more frequent switching behavior from low to high physical activity [2,10,11]. However, these studies have significant limitations, such as small sample sizes and limited follow-ups. By using a longitudinal design with repeated measures and a larger sample size, this study extends the previous analyses by showing a higher auto-correlation pattern of physical activity over time compared with the healthy controls. The increase in the local maxima PLE values may thus indicate the sensitivity of actigraphy in capturing symptoms of movement disorders seen in PD patients. Our correlational analyses further show that changes in these movement symptoms were related to changes in UPDRS part II and III scores, which reflect severity in day-to-day activities and motor severity.

Although there has been an increasing use of actigraphy to quantitatively evaluate symptoms of PD, such as tremor and sleep disorders [4-7] and other chronic disease conditions [13-16], few studies

have undertaken evaluation of PD severity by actigraphy [7]. Thus, this study contributes to a deeper understanding of actigraphy and monitoring of symptoms of PD. Our study, however, has limitations. For example, our data do not capture symptoms of patients underlying Parkinsonism during their wearing-off period of medications or alteration between periods "on" and "off" medications. Our local maxima of PLE activity data may simply reflect the overall trend and/or patterns of changes in movement activities over time rather than short-term moment-to-moment motor fluctuations (medication off time) and dyskinesia (drug-induced involuntary movements) experienced during on- and off-medication periods. Accordingly, future efforts are needed to evaluate the relationship between wrist activity and levodopa-induced motor complications.

CONCLUSION

In conclusion, we show that actigraphy can be used as an ambulatory device to monitor symptoms associated with PD over time and that changes in physical activity are associated with increased fluctuations in patients' clinical symptoms of PD over time. Our findings suggest that, when used in conjunction with the conventional UPDRS measure, actigraphy may be useful for clinicians to monitor and track patients' activity-based disease progression or responses to treatment in outpatient clinic settings.

REFERENCES

[1] Goetz CG, Poewe W, Rascol O, et al. Movement disorder society task force on rating scales for Parkinson's disease. UPDRS: status and recommendations. Mov Disord 2003;18:738-50.

[2] Pan W, Ohashi K, Yamamoto Y, Kwak S. Power-law temporal autocorrelation of activity reflects severity of parkinsonism. Mov Disord 2007;22(9):1308-13.

[3] Katayama S. Actigraph analysis of diurnal motor fluctuations during dopamine agonist therapy. Eur Neurol 2001;46(Suppl. 1):11 -7.

[4] van Someren EJ, van Gool WA, Vonk BF, et al. Ambulatory monitoring of tremor and other movements before and after thalamotomy: a new quantitative technique. J Neurol Sci 1993;117:16-23.

[5] Van Someren EJ, Vonk BF, Thijssen WA, et al. A new actigraph for long-term registration of the duration and intensity of tremor and movement. IEEE Trans Biomed Eng 1998;45:386-95.

[6] Van Someren EJ, Pticek MD, Speelman JD, et al. New actigraph for long-term tremor recording. Mov Disord 2006;21:1136-43.

[7] Perez Lloret S, Rossi M, Cardinali DP, Merello M. Actigraphic evaluation of motor fluctuations in patients with Parkinson's disease. IntJ Neurosci 2010 Feb;120(2):137-43.

[8] Pan W, Soma R, Kwak S, Yamamoto Y. Improvement of motor functions by noisy vestibular stimulation in central neurodegenerative disorders. J Neurol 2008; 255 (11) : 1657-61.

[9] Ohashi K, Nunes Amaral LA, Natelson BH, Yamamoto Y. Asymmetrical singularities in real-world signals. Phys Rev E Stat Nonlin Soft Matter Phys 2003;68(6 Pt 2):065204.

[10] Pan W, Kwak S, Liu Y, et al. Traditional Chinese medicine improves nocturnal activity in Parkinson's disease. Park Dis 2011;2011:789506.

[11] Pan W, Liu Y, Fang Z, Zhu X, Kwak S, Yamamoto Y. A compound belonging to traditional Chinese medicine improves nocturnal activity in Parkinson's disease. Sleep Med 2011;12(3):307-8.

[12] Voelker R. Parkinson disease guidelines aid diagnosis, management. JAMA 2006;295(18):2126-8.

[13] Jean-Louis G, Kripke DF, Cole RJ, Assmus JD, Langer RD. Sleep detection with an accelerometer actigraph: comparisons with polysomnography. Physiol Behav 2001;72(1-2):21-8.

[14] Jean-Louis G, Mendlowicz MV, Gillin JC, Rapaport MH, KelsoeJR, Zizi F, et al. Sleep estimation from wrist activity in patients with major depression. Physiol Behav 2000;70(1-2):49-53.

[15] Comella CL, Morrissey M, Janko K. Nocturnal activity with nighttime pergolide in Parkinson disease: a controlled study using actigraphy. Neurology 2005;64(8): 1450-1.

[16] Yamamoto Y, Struzik ZR, Soma R, Ohashi K, Kwak S. Noisy vestibular stimulation improves autonomic and motor responsiveness in central

neurodegenerative disorders. Ann Neurol 2005;58(2):175-81.

AUTHOR DETAIL

Bidve Nisha Sanjay
Student of B.pharmacy 2nd year,
College of Pharmacy, Hasegaon

Jadhav Rohini Pandurang
Student of B.pharmacy 2nd year, College of Pharmacy, Hasegaon

Pratiksha hanumant shinde
Student of B.pharmacy 2nd year, College of Pharmacy, Hasegaon

Renuka R. Deshpande,
Assistant Professor, Department of Pharmaceutics, Latur College of Pharmacy, Hasegaon