Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Suicide in Parkinson's Disease

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ABSTRACT: **Background:** Suicide is a potentially preventable event. Suicidal ideation is common in Parkinson's disease (PD), but literature on completed suicides is scarce. In this case-control study, we compared the clinical characteristics of PD subjects who completed suicide (case) with those who died from natural causes (control).

Methods: PD patients from the National Neurosciences Institute's movement disorders database from 2002 till 2012 were identified. The database was linked to the Singapore National Registry of Disease Office for mortality information, and suicide deaths were confirmed with the coroner's office. The demographic and clinical variables were compared between the cases and controls and the significant factors were further analyzed using logistic regression analysis.

Results: During the study period, 366 deaths were recorded and suicide accounted for 11 deaths. Ten subjects with suicide deaths with complete clinical information were compared with randomly selected 30 PD subjects who had died from natural causes. PD suicide patients were younger (65.9 vs. 74.48 years), had less comorbidities (CWI: 2.6 vs. 4.63), better cognition (MMSE: 25.75 vs. 21.36), lower 'ON' UPDRS motor scores (20.83 vs. 41.63), lower H &Y stage (2.16 vs. 3.86), and higher use of Entacapone than the PD non-suicide group.

Conclusion: Suicide is potentially preventable tragedy. PD patients with the identified clinical characteristics should be closely monitored for suicide ideations. Motor fluctuation is a treatable factor in such patients and should be aggressively managed.

Introduction

Parkinson's disease (PD) is a chronic, progressive, and debilitating neurodegenerative disorder. In addition to the motor symptoms and physical disability, PD is associated with a range of non-motor features contributing significantly to the overall quality of life.[1] Suicide is defined as death caused by self-directed injurious behavior with any intent to die as a result of the behavior.[2] Old age, male gender, multiple comorbidities, depression, and cognitive decline are the recognized risk factors for suicide in general populations.[3] These risk factors are also prevalent in PD. There have been, to our best knowledge, only five studies on suicide in PD. A summary of their findings may be found in Table 1.[4–8] The initial studies noted suicide to be ten times less common in PD compared to general population,[5] while in the later studies, the suicide risk was 2-5 times increased.[7,8] Suicide is a potentially avoidable tragedy and analysis of the predisposing factors can help in formulating better preventive strategies. In this regard, we undertook a case control study to ascertain the clinical profile of completed suicide patients and compared them with PD patients succumbing to the natural causes.

Methods

Data Source

The study population was selected from the National Neuroscience Institute movement disorders database during the period 2002 to 2012. Parkinson's disease was diagnosed by a movement disorders specialist according to the National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria.[9] These patients were linked to the Singapore National Registry of Disease office to obtain data on death information from January 1,

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TABLE 1 Summary of Previous Studies on Suicide in PD

Author	Year of publication	Country	Title	Population	Result
Stenager EN, et al. [4]	1994	Denmark	Suicide in patients with Parkinson's disease- An epidemiological study	458 PD patients followed-up over mean period of 5.7 years (0 to 17 years), 254 deaths with 2 suicides. Local catchment population used as reference 435,000; suicide rate = 30/100,000.	The number of expected suicide was 1.06 for men and 0.55 for women. The expected and observed suicide rates were not statistically significant for either gender.
Myslobodsky M, et al.[5]	2001	USA	Are patients with Parkinson's disease suicidal?	Total number of deaths was 12,430,473 from 1991 to 1996. Of these, 99,109 committed suicide, 144,364 of deaths were Parkinson patients of 40 years old and above. of these, 122 committed suicide	Only 0.08% (122) persons with PD died by suicide, as compared with 0.8% (99,109) in the reference population. People who committed suicide were younger than people who died from other causes (72.2 vs 81.2 years for patients with PD, $t = 13.3$, $P < .001$; 59.6 vs 74.9 years for the referent population, $t = 335.9$, $P < .0001$). PD suicide deaths were significantly older than suicide deaths in the reference population (72.2 vs 59.6 years, $t = 9.7$, $P < .001$). The rate of suicide among married patients with PD was higher than among single patients with PD.
Mainio A et al.[6]	2009	Finland	Parkinson's disease and suicide: a profile of suicide victims with Parkinson's disease in a population-based study during the years 1988–2002 in Northern Finland	546 suicide victims aged 50 and above without PD vs 9 Suicide victims with PD	Suicide occurred in 1.6% of hospital-treated Parkinson's disease patients, indicating a rather low prevalence of suicide in this group of patients. The profile of PD persons who completed suicide was as follows: male subject with recently diagnosed disease, living in rural area, having multiple physical illnesses, and having attempted suicide before.
Kostić et al.[7]	2010	Serbia	Suicide and suicidal ideation in Parkinson's disease	Suicide as outcome in PD patients 102 PD patients, followed up for 8 years, 2 patients committed suicide	The suicide-specific mortality was 5.3 (95% CI 2.1–12.7) times higher than expected. Both patient who committed suicide had major depression
Lee T et al.[8]	2016	Korea	Increased Suicide risk and clinical correlates of suicide among patients with Parkinson disease	4362 Parkinson patients (from 1996 to 2012) 29 PD suicides matched with 116 non-suicide controls	Standardised Mortality ratio for PD patients was 1.99 (95% CI 1.33 to 2.85) which was 2 times higher than the general population. Risk factors: male gender; upper extremity or generalised onset of motor symptoms; history of depressive disorder, delusion or any psychiatric disorder; and higher L-dopa dosage.

2002 to December 31, 2012. The cause of death for suicide was confirmed by coroner's certificate from the coroner's court in Singapore. The Centralized Institution Review Board of the Singapore Health Services approved the study.

Case and Control Selection

The study population comprised of PD patients with completed suicide and randomly selected PD patients with non-suicide deaths as controls. The suicide patients were included in the study after the verification of Coroner's certificate. In both groups, clinical information obtained from the last clinic visit within two years from the date of death was included for analysis. In order to obtain reliable information on vital status, only Singaporean citizens and permanent residents were included. Control subjects were selected randomly from pool patients who had a non-suicide death in a 1:3 case-to-control using the following web-help: http://www.uwec.edu/help/excel107/randamizationdata.htm/.

Data Collection

The demographic and clinical characteristics were reviewed by the authors (LW, AMM) from medical records. Demographic variables, such as age, gender, ethnicity, education, employment, and marital status were recorded. The clinical data comprised the presence of other comorbidities, date of PD diagnosis, Hoehn and Yahr stage, part III (motor component) Unified Parkinson's Disease Rating Scale (UPDRS) during the "ON" state, and Mini-Mental State Examination (MMSE). Depression and hallucinations were determined by the reviewers based on the clinical history and use of antidepressants and antipsychotics, respectively, in the clinical record as well as a score of 2 and above in UPDRS part I (1.2 and 1.3). Clinical history and UPDRS part IV were utilized to assess motor fluctuations and wearing-off phenomenon. The total levodopa dose and the anti-Parkinson's medications during the last visit were noted; the levodopa equivalent dose was calculated. The Charlson Weighted Index (CWI) score was utilized as a measure of co-morbidities.[10] CWI is a method of classifying comorbidities and provides an estimate of the risk of death from comorbid diseases for a patient who may have a range of comorbid conditions, such as heart disease, AIDS, or cancer. Each condition is assigned a score of 1, 2, 3, or 6 depending on the risk of dying from each condition. In addition, a factor for age is included by assigning 1 point for each decade above 40 years (40 years taken as 0 rank for age). These scores are added together to compute a total score that ranges from 0 to 41, with higher scores indicating greater comorbidity.

Statistical Analysis

SPSS version 22 was used for the data analysis. Distribution of demographic and clinical characteristics of the study population was summarized. Categorical variables were presented with simple frequency, along with percentages, and were compared between cases and control subjects using Fisher's exact tests. Continuous variables were summarized using mean ± SD and compared using non-parametric Mann-Whitney U test. Statistical significance was set at 5%. Univariate logistic regression was used to estimate the odds ratios (OR) along with 95% confidence interval (CI) to study the individual effect of the demographic and clinical characteristics. The variables associated with nature of death in the univariate analysis at 10% statistical significance level were further included in a multivariable logistic regression model and backward variable selection procedure was applied.

Results

The total cohort comprised of 2012 PD subjects during the 11-year study period; 366 (18.1%) deaths were observed and suicide was the cause of death in 11 (3%) of deceased patients (cases). One patient was excluded from analysis due to insufficient data and the remaining 10 PD suicide patients were analyzed. Thirty non-suicide deceased PD subjects served as controls.

The demographic and clinical profiles of cases and controls are summarized in Table 2. The demographic features were similar in both the groups, except the cases were more likely to be younger (mean age: 65.9 ± 13.12 years). The cases had a higher mean MMSE and a lower mean Charlson's weighted index score compared to control subjects. The other significant clinical differences were a lower mean UPDRS motor score, lower Hoehn & Yahr stage, and more frequent use of Entacapone. Depression (40%) and motor fluctuations (67%) were frequent and the mean levodopa equivalent dose (820.88mg) was higher in the cases than the control subjects, although these did not reach statistical significance (Table 2).

In the univariate regression analysis, age (OR 0.90; 95% CI: 0.81-0.98), CWI score (OR 0.39; 95% CI: 0.18-0.69), MMSE (OR 1.38; 95% CI: 1.08-1.92), UPDRS motor score (OR 0.89; 95% CI: 0.80-0.96), H &Y staging (OR 0.06; 95% CI: 0.01-0.34), and Entacapone use (OR 19.33; 95% CI: 2.37-417.05) were significantly associated with nature of death (Table 3). However, nothing remained statistically significant in the multivariable model.

Discussion

In the present study, we reviewed the clinical profile of PD patients who committed suicide and compared them with randomly selected PD subjects who died from natural causes. In our present cohort, 3% of all deaths in PD were due to suicide. These patients were younger, had less comorbidities (lower CWI score), better cognition, lower motor scores, and more frequent use of Entacapone than non-suicide controls. Male gender, depression, motor fluctuations were frequent and levodopa equivalent dose was higher in the PD suicide patients; but, these did not reach statistical significance. Our results are in contrast to the clinical correlates of suicide in normal population; wherein old age, cognitive decline, presence of multiple comorbidities, and depression play a major role.[3,11]

We observed that PD suicide cases accounted for 3% of PD deaths in our study. The suicide rate of the Singapore resident

TABLE 2 Demographic and Clinical Profile of PD Suicide Cases and Non-Suicide Controls

Variables	PD Controls (n = 30)	N* = 30	PD Suicide (n = 10)	N* = 10	p Value
Age (years)	74.48 (+7.16)	30	65.9 (+13.12)	10	0.015
Gender (male)	14 (47%)	30	7 (70%)	10	0.281
Race (Chinese)	24 (80%)	30	10 (100%)	10	0.307
Married	27 (96%)	28	8 (100%)	8	1
Education (years)	5.23 (+4.33)	26	6.88 (+4.39)	8	0.413
Employed	1 (4%)	25	2 (25%)	8	0.139
CWI	4.63 (+1.54)	30	2.6 (+1.43)	10	0.001
Duration of disease (years)	6.81 (+4.56)	30	6.82 (+4.13)	10	0.842
MMSE	21.36 (+4.41)	22	25.75 (+3.28)	8	0.012
Hallucinations	11 (37%)	30	1 (11%)	9	0.228
Depression	4 (13%)	30	4 (40%)	10	0.089
UPDRS III (motor score)	41.63 (+17.7)	30	20.83 (+8.28)	9	0.002
Hoehn & Yahr stage	3.86 (+1.09)	30	2.16 (+0.35)	9	0.000
Motor fluctuation	11 (37%)	30	6 (67%)	9	0.142
Dyskinesia	5 (60%)	30	2 (22%)	9	0.653
Levodopa equivalent dose (mg)	631.65 (+355.46)	30	820.88 (+425.86)	10	0.173
Entacapone	1 (3%)	30	4 (40%)	10	0.01
Trihexyphenidyl	2 (6%)	30	2 (20%)	10	0.256
Selegiline	1 (3%)	30	2 (20%)	10	0.149
Dopamine agonists	4 (13%)	30	4 (40%)	10	0.089
Antidepressants	3 (10%)	30	1 (10%)	10	1
Antipsychotics	4 (13%)	30	0 (0%)	10	0.556

Abbreviations: CWI- Charlson's Weighted Index, MMSE-Mini Mental State Examination; N*, valid numbers; UPDRS-Unified Parkinson Disease Rating Scale.
Note: values are expressed in mean (+standard deviation) or frequency (percentage)

TABLE 3 Univariate Logistic Regression Analysis Results

Variables	Odds ratio (95% CI)	P value
Age	0.90 (0.81, 0.98)	0.024
Gender	2.67 (0.61, 14.26)	0.209
Education	1.09 (0.91, 1.34)	0.348
Employed	8.0 (0.66, 190.36)	0.112
CWI	0.39 (0.18, 0.69)	0.005
Disease duration	1.02 (0.85, 1.21)	0.839
MMSE	1.38 (1.08, 1.92)	0.025
Hallucination	0.22 (0.01, 1.41)	0.174
Depression	4.33 (0.82, 23.86)	0.081
UPDRS Motor Score	0.89 (0.80, 0.96)	0.011
Hoehn &Yahr stage	0.06 (0.01, 0.34)	0.021
Motor fluctuation	3.45 (0.75, 19.09)	0.122
Dyskinesia	1.43 (0.18, 8.40)	0.704
Levodopa equivalent dose	1.00 (0.99, 1.00)	0.181
Entacapone	19.33 (2.37, 417.05)	0.014
Trihexyphenidyl	3.5 (0.37, 33.23)	0.245
Selegiline	7.25 (0.62, 168.38)	0.124
Dopamine agonists	4.33 (0.82, 23.86)	0.081
Antidepressants	1.00 (0.05, 9.01)	0.999

Abbreviations: CWI, Charlson's Weighted Index; MMSE, Mini Mental State Examination; UPDRS, Unified Parkinson Disease Rating Scale.

population over the same period as our study was 2.3% (4332 suicide cases/185,905 number of deaths).[12,13] Statistically, they were not significantly different. Although the PD suicide rate in our study was similar to the Singapore resident population, suicide is an important preventable cause of death in Parkinson's disease. A recent American study observed PD as one of the major health conditions among 2,674 individuals committing suicide (age and gender adjusted OR: 1.87; 1.20- 2.91).[14] Suicidal ideation is common in PD patients and occurs in 17-30% of patients;[7,15] however, the literature on completed suicides is scarce. Our study is only the second to analyze the clinical profile of these subjects. In a previous study of clinical correlates in 29 PD suicide patients, the presence of psychiatric disorders and a higher levodopa use, but not PD related variables like motor scores, were significantly associated with suicides in PD patients.[8] However, motor fluctuations were not analyzed in that study and the motor scores were noted during the entry into the PD registry, but not at the last visit as in our study.

PD patients with younger age (Mean 65.9 ± 13.12, median 63.8) were noted to be more likely to commit suicide in our study. The mean age is similar to a previous population-based study on profile of PD suicide victims in Northern Finland.[6]

In the present study, the PD suicide group had lower motor scores compared to controls, more frequent motor fluctuations, and significant Entacapone use. Entacapone is the only COMT inhibitor in Singapore and is indicated for use in patients with motor fluctuations. Our findings suggest that it is the motor fluctuations that occur more frequently amongst younger PD patients,[16] that has such an adverse impact that it drives these relatively young, cognitively well patients with few comorbidities towards suicide. A previous multi-center study noted that motor complications, primarily on/off fluctuations significantly impact the quality of life in PD patients.[17] Our findings highlight the importance of better management of motor fluctuations to avoid this disastrous outcome. In addition to the medical management of motor fluctuations, deep brain stimulation should be considered in PD patients with early motor fluctuations.[18,19]

Our findings, that PD patients who committed suicide had better motor function, contrasts with the suicidal behavior in older adults and other neurological illnesses where physical disability is a significant risk factor.[3,20] In a study on treatment preferences at the end-of-life in PD patients, we observed that PD patients were more tolerant of greater motor impairment in regards to end-of-

life treatment preferences. Patients with greater motor impairment were more likely to accept care that would result in further physical disability rather than face death.[21]

Dementia is associated with a higher suicide risk in the elderly;[22] however, there are no studies on the cognitive profile of PD suicide patients. Similar to our study, better cognitive scores were observed in PD patients with suicidal ideation in previous studies.[7,15] Suicide is a heterogeneous behavior, with interplay of individual vulnerability, state related brain changes, and environmental factors playing a role. The predisposing factors might differ across the lifespan. The poor decision-making abilities due to cognitive decline in old age might be contributory.[11]

In our present study, depression was more frequent in the suicide group, although the difference did not reach statistical significance. Depression was a significant determinant of both suicidal ideation and completed suicide in the previous studies.[8,15] In another study, suicidal thoughts were noted in more than two-thirds of depressed PD and major depression patients. However, very few PD depressed (4%) patients made suicidal attempts compared to major depression (42%) subjects.[23]

The strengths of our study is the uniformity of data, with each patient in the two groups regularly reviewed by the movement disorders specialists, and suicide cases were only included after proper verification with coroner's certificates. Our study also had several limitations. The major limitation was the small sample size of the PD suicide group. This is a retrospective study and the number of suicides was limited. As such, no statistically significant relationship with the suicide status could be established in the multivariable setting. The other limitations were the absence of detailed neuropsychological evaluation and history of previous suicidal ideation or attempts.

In conclusion, suicide is a potentially preventable cause of death amongst PD patients. These subjects are significantly younger with fewer comorbidities, better cognition, lower motor scores, and significant motor fluctuations as demonstrated by their more frequent Entacapone use. These results suggest that motor fluctuations, rather than disease severity, is an important contributor to suicide deaths. Motor fluctuations should therefore be more aggressively managed with medical and surgical therapies. Future studies with larger pooled patient groups will be helpful to further validate these findings in the hope of preventing such catastrophic deaths.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

L.W.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B
A.M.M.: 1C, 2A, 2C, 3A, 3B
A.S.: 2B, 2C, 3A, 3B
N.H.L.: 1A, 2C, 3B
T.K.Y: 1A, 2C, 3B
A.W.L.: 1A, 2C, 3B
L.C.S.T.: 1A, 1B, 1C, 2A, 2C, 3B

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Disclosures

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