ORIGINAL RESEARCH

The Association Between Frailty and Parkinson's Disease in the ReSPOnD Trial

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ABSTRACT

Background

Frailty and Parkinson's disease (PD) are both highly prevalent in older people, but few studies have studied frailty in people with Parkinson's. Identifying frailty in this population is vital, to target new interventions to those who would most benefit.

Methods

Data were collected as part of the double-blind randomised controlled rivastigmine to stabilise gait ReSPonD trial in 130 people with Hoehn and Yahr 2-3, idiopathic PD who had fallen in the year prior to enrolment. Individuals were assessed at baseline and followed up at eight months, including determination of frailty status.

Results

120 patients attended for follow-up. At follow-up, the mean (SD) age was 70.2 years (8.0), MDS-UPDRS total score 91.5 (29.1), and MDS-UPDRS motor score (Part III) 42.7 (14.8). Median disease duration was 9.2 years (IQR 4.6 to 13.1), Geriatric Depression Score 4 (IQR 2 to 6). Using the Fried frailty criteria, 31 (26%) were frail and 70 (58%) pre-frail. In univariable analysis, being female, higher depression score, and MDS-UPDRS score were associated with greater frailty. Using ordinal regression, in the multivariable model, being female (odds ratio [OR] 3.10, 95%CI 1.53 to 6.26, p=.002), higher total MDS-UPDRS score (OR 2.02, 95%CI 1.42 to 2.87, p<.0001) and higher depression (OR 1.47, 95%CI 1.05 to 2.06, p=.03) were associated with higher number of frailty markers.

Conclusion

There was a high prevalence (84%) of pre-frail and frail individuals in patients participating in this RCT. Future research should determine the optimum tool to assess frailty in this at-risk population, and delineate the association between Parkinson's, frailty, and health outcomes.

Key words: Parkinson's disease, frailty, ageing

INTRODUCTION

Frailty and Parkinson's disease (PD) are conditions that are highly prevalent in older people, and share common features. However, few studies have described frailty in people with Parkinson's.

Frailty is recognised as a state of increased vulnerability to stressors through loss of physiological reserve and function.[(1)] Whilst it has eluded a consensus definition,[(2)] there have been two approaches to quantifying frailty. The phenotype model first developed by Fried[(3)] defines frailty as the presence of three or more out of five criteria: weakness, weight loss, slow walking speed, fatigue, and low physical activity. An alternative approach proposed by Rockwood and Mitniski[(4)] measures acquired deficits of symptoms, diseases, and disability to describe an overall frailty burden. This is expressed as an index measure, but has subsequently been developed into more usable clinical scales.[(5)]

The pathophysiology of frailty is not fully understood, but it is thought that chronic inflammation and immune system activation result in multisystem dysfunction affecting the musculoskeletal, endocrine, haematological, and cardiovascular systems.[(6)] Reserve is diminished, such that the body becomes incapable of adapting to acute and chronic stressors. The aetiology of PD is similarly not fully understood, but immune system activation, oxidative stress, abnormal protein processing, and mitochondrial disruption converge and contribute to the complex cascade of dysfunction that result in cell loss in the substantia nigra, dopamine deficiency in the neostriatum, and disruption of other neurotransmitter pathways.[(7,8)] PD confers an increased risk of various negative health outcomes, including falls,[(9)] fractures, and cognitive impairment.[(10)]

Frailty and PD are clinical syndromes resulting from multisystem disorders which result in increased vulnerability to stressors. Identifying frailty in this population may offer an opportunity to identify those at increased risk of negative outcomes and, thus, intervene to reduce the mortality and morbidity associated with both conditions.[(11)]

METHODS

Population

Data for this analysis were collected as part of the ReSPonD trial, a double-blind randomised controlled trial of rivastigmine vs. placebo to stabilise gait in people with PD, the methods of which have been previously described.[12,13] One hundred and thirty people were enrolled at a single UK site, with Hoehn and Yahr stage 2–3 idiopathic PD. All participants had fallen in the last year, could walk 18 metres unaided, and had been stable on anti-Parkinsonian medication for two weeks prior to enrolment. Patients were excluded if they had neurological, visual, or orthopaedic problems that interfered with balance or gait, were non-English speaking, or had PD-dementia. Ethical approval was granted from the South West Central Bristol Research Ethics Committee and written informed consent was obtained from participants.

Procedure

Frailty status was determined at a 32-week follow-up visit, using the original 5 Fried criteria.[3] The following information was collected to determine the frailty score: 1) Weakness, measured as a grip strength below published cutoffs;[3] 2) Slow walking speed, below published cutoffs;[3] 3) Self-reported weight loss of >4.5 kg in the past year; 4) Self-reported exhaustion, measured using two questions from the Centre for Epidemiological Studies Depression Scale;[14] and 5) Low physical activity, defined as those scoring in the lowest quintile on the Physical Activity Scale for the Elderly (PASE; Low score <52 for women and <64 for men).[15] A score of 3 or more features were defined as frailty, while the presence of 1 or 2 factors indicated pre-frailty. Those with 0 frailty features were defined as non-frail. Duration of PD was defined as years since diagnosis. Patients were assessed using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), which ranges from 0 to 265, with higher score indicating greater disease severity. They also completed the Geriatric Depression Scale, which scores people's mood, with higher scores indicating greater depressive symptoms (range 0 to 15).

Statistical Analysis

Baseline data are described as mean ± Standard Deviation (SD) if normally distributed or as median interquartile range (25^{th} percentile, 75^{th} percentile) if skewed. We used ordinal logistic regression to look at the association between demographic factors and PD factors, and number of positive frailty criteria. Stata/MP 15.1 was used to perform statistical analysis. We analysed both the MDS-UPDRS and depression scale as continuous variables. However, we tested the linearity assumption by creating an ordinal variable (tertiles) and repeating our models using both ordinal and nominal categories to compare the effect estimates. As these appeared to be consistent with a linear pattern, we have used the original continuous variable in the final models. We standardised both variables in our analysis (z-scored), to facilitate the description of the effects on frailty.

RESULTS

One hundred and thirty participants were enrolled in the study, of which 120 attended for the 32-week follow-up assessment. Of the 10 lost to follow-up, 3 died, 4 withdrew, and 3 were too unwell to attend.

Table 1 presents the demographic data of the patients included. 37.5% were women. At follow-up, the mean age was 70.2 years (SD 8.0), MDS-UPDRS total score 91.5 (SD 29.1), and mean MDS-UPDRS Part III (motor score) 42.7 (14.8). Median disease duration was 9.2 years (IQR 4.6 to 13.1), Geriatric Depression Score 4 (IQR 2 to 6). Using the Fried frailty criteria, n=31 individuals (26%) scored as frail, with 3 or more positive frail criteria, and 70 (58%) were pre-frail, as they had 1 or 2 features.

In univariable analysis, being female, higher depression score and higher MDS-UPDRS score were associated with greater number of frailty criteria (all p values <.05). Age was included in the univariate model, but did not reach significance and was therefore not included in the final model. In the multivariable ordinal logistic model (n=120), we found that being female (OR 3.10, 95%CI 1.53 to 6.26, $p = .002$), higher total MDS-UPDRS score (OR 2.02, 95%CI 1.42 to 2.87, $p < .0001$), and higher depression score (OR 1.47, 95%CI 1.05 to 2.06, $p = .03$) were associated with higher number of frailty markers (see Table 2).

TABLE 1.
Demographic data for patients attending follow-up visit[a]

Number (%) of women	45 (37.5%)
Number (%) of men	75 (62.5%)
Age (yrs)	70.2 (8)
IQR for age (yrs)	65.4 – 75.9
Median (IQR) Montreal Cognitive Assessment score	25 (22.5-27)
Median (IQR) Geriatric Depression Scale score	4 (2 to 6)
MDS-UPDRS score (SD)	91.5 (29.1)
Part III MDS-UPDRS score (SD)	42.7 (14.8)
Median (IQR) years since Parkinson's disease diagnosis	9.2 (4.6 to 13.1)
Number of frail patients	31 (26%)
Number of pre-frail patients	70 (58%)
Number of non-frail patients	19 (16%)
Fried Frailty Criteria	
Number of weak patients	61 (50.8%)
Number of slow patients	17 (14.1%)
Number of patients with weight loss	26 (21.7%)
Number of exhausted patients	66 (55%)
Number of inactive patients	33 (27.5%)

[a]Data are presented as mean (SD) unless stated.
MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; IQR = inter-quartile range.

TABLE 2.
Univariable and multivariable regression analysis of relationship between gender, MDS-UPDRS total score, GDS score, and the number of positive frailty criteria

	Univariable			*Multivariable*		
	Odds Ratio[a]	*95% Confidence Interval*	*p value*	*Odds Ratio*[a]	*95% Confidence Interval*	*p value*
Female gender	2.25	1.14, 4.43	0.019	3.10	1.53, 6.26	.002
MDS-UPDRS (z-score)	1.97	1.41, 2.76	<.0001	2.02	1.42, 2.87	<.001
GDS (z-score)	1.64	1.18, 2.28	.003	1.47	1.05, 2.06	.03

[a]Odds ratio for one standard deviation increase from the mean for UPDRS and GDS.
MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; GDS = Geriatric Depression Scale; SD = standard deviation.

DISCUSSION

In this study of 120 ambulatory patients with well-controlled PD who had fallen in the past year, we found that frailty was highly prevalent, with 26% classified as frail, and 58% pre-frail. This estimate exceeds that which we would have expected in a non-PD population of similar age,[16] consistent with previous research suggesting PD patients have higher frailty rates.[17,18]

Our study included a selected trial population, and may not be generalizable to the wider population of PD with early or very advanced disease. Our study sample also had a relatively narrow range of ages, which may explain why no effect was seen for age on frailty. Given that our participants had a history of past fall(s), we will have excluded earlier milder cases of PD who would be expected to have less frailty, and hence these results may have over-estimated frailty rates in the broader PD population. However, our study excluded participants who could not walk 18 metres without an aid, which will counter this bias to some degree in the opposite direction so that our results would be better than expected.

These results confirm a high pre-frailty rate in this PD population despite only moderate length disease duration (median 9.2 years). Identification of pre-frailty is attractive because it may offer an opportunity to intervene before a frailty syndrome is fully established and decompensation might be irreversible. Our findings, that patients with higher MDS-UPDRS scores have more positive frailty criteria, also aligns with previous research.[17] Accurately identifying the two clinical syndromes in at-risk patients is crucial, as the presence of frailty may be misidentified as a decline in PD.

This growing evidence of higher frailty in patients with PD, as well as research identifying similar inflammatory processes occurring in both frailty and PD, have prompted suggestions of a shared pathophysiology between frailty, PD, and ageing.[17,18,19] Large longitudinal cohort studies studying the onset and progression of PD and frailty would help inform whether one precedes the other, or if the two, at least for some patients share a pathogenesis.

We have shown that the Fried frailty model can easily be applied to PD patients, and is useful in identifying frailty and pre-frailty. The model has its weaknesses, notably its exclusive focus on physical attributes, which neglects the psychosocial elements of frailty. Its approach to categorising continuous variables, which are dichotomised according to a cut-off, also risks potentially losing valuable data. Although simple in its categorisation of individuals, it cannot be used to differentiate between different degrees of frailty. Several of the Fried criteria also overlap with motor and non-motor symptoms of PD (e.g., slow walking, fatigue) and, therefore, risk over-diagnosing frailty in people with PD. This would depend on whether age-related frailty phenotypes have the same significance as disease-related features. There is increasing recognition that refining the approach to measuring frailty is necessary. The more comprehensive frailty models, such as electronic frailty indices[20] or the SHARE frailty instrument,[21] include deficits in multiple domains, and may thereby better reflect the complexity of the frailty syndrome. Other measures can be more easily applied in clinical settings—such as the nine-point Clinical Frailty Scale which incorporates pictographs[5]—can be used with relatively little training, and does not focus exclusively on physical frailty.

CONCLUSION

We found a high prevalence of pre-frailty and frailty in patients with PD who had a history of having fallen. Future research should use representative longitudinal cohorts, studying the onset and progression of PD and frailty, as this would help delineate unique and overlapping aspects of pathogenesis. This would also usefully inform which tool is optimal to assess frailty in this vulnerable population.

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CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

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