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Orthostatic hypotension predicts motor decline in early Parkinson disease

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Abstract

Background—Orthostatic hypotension is increasingly reported as a risk factor for development of late-stage disease features in Parkinson disease (PD). Less is known about its significance in individuals with early PD who are often targeted for neuroprotective trials.

Methods—Using data from the CALM-PD trial (n=275), we explored whether early orthostatic hypotension predicts a decline in the Unified Parkinson's Disease Rating Scale (UPDRS) II (activities of daily living) or UDPRS III (motor) score after 102 weeks. We also explored risk factors for worsening orthostatic hypotension over a nearly 2-year period.

Results—After controlling for age, disease duration, gender, study drug, change in mini-mental status exam score, levodopa equivalent dose, and baseline UPDRS II or III score respectively, the degree of orthostatic hypotension at enrollment associated with a worsening in UPDRS motor score (t=2.40, p=0.017) at week 102 but not with UPDRS ADL score (t=0.83, p=0.409). Worsening in orthostatic hypotension during the study associated with longer disease duration (t=2.37, p=0.019) and lower body mass index (BMI) (t=−2.96, p=0.003).

Conclusions—Baseline orthostatic hypotension is a predictor of UPDRS motor decline in individuals with early PD and should be accounted for in clinical trial design. Low BMI may predict orthostatic hypotension in PD.

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Keywords

Parkinson disease; Orthostatic Hypotension; Systolic Hypertension; Body Mass Index; Clinical Trial

Introduction

Parkinson disease (PD) manifests with a variety of motor and non-motor features which collectively contribute to progressive disability with advancing disease. To date, neuroprotection trials in early PD have had only modest impact upon clinical management. One possible reason for the failure of these trials is that significant heterogeneity in the biological and clinical profiles of early PD subjects. This background variability may strongly influence longitudinal changes in the outcome parameters of interest, obscuring the effects of a therapeutic agent. Identifying clinical features associated with a more aggressive disease course may be useful trial design and performance.

Recent observational findings in PD highlight the significance of orthostatic hypotension as a risk factor for both development of progressive disability and for mortality in moderate to advanced PD.[1, 2] Using data from the CALM-PD study,[3] we conducted a retrospective longitudinal study to explore the influence of orthostatic hypotension on the Unified Parkinson's Disease Rating Scale (UPDRS) III motor exam score and UPDRS II activities of daily living (ADL) score in a cohort of subjects with early PD. We hypothesized that baseline orthostatic hypotension would associate with worsening motor function and overall disability even after controlling for relevant confounders.

Methods

Data for this longitudinal cohort study came from the CALM-PD trial: *Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomized controlled trial* (Parkinson Study Group).[3] The CALM-PD trial studied 301 subjects with early PD who were randomized to varying doses of either pramipexole or levodopa over a nearly 2-year period. The primary outcome was time to the development of dopaminergic motor complications. Within this cohort, data on orthostatic hypotension and other relevant variables sufficient for our analysis was available for 275 subjects. Inclusion criteria for the CALM-PD study are published elsewhere.[4] In general, participants were in early stages of PD and required dopaminergic therapy. Subjects were randomized 1:1 to initial doses of pramipexole 0.5mg PO TID or carbidopa/levodopa 25/100mg PO TID. Pramipexole and levodopa doses were subsequently adjusted as described previously.[4]

Baseline UPDRS assessments (week 0) occurred in the dopaminergic medication off-state. An on-state assessment was recorded at visits between week 4 and 102. We calculated the change in UPDRS II and III between weeks 4 and 102 as our outcome variables of interest. Baseline orthostatic blood pressure change was defined as the week 0 difference between supine systolic blood pressure measured after 5 minutes of quiet rest and standing systolic blood pressure measured after a 1 minute period of standing. Disease duration was calculated as the differences in years between a subject's age at enrollment and their self-

reported age in years at the time of initial diagnosis. Mini-mental Status (MMSE) exam score at week 4 and week 102 were obtained and the change in MMSE score was calculated. We used two variables to code for dopaminergic medications: study drug treatment category (bivariate) and total levodopa equivalent dose (LED) at the time of week 102.

Multivariable linear regression was used to test for the association between baseline orthostatic blood pressure change and the decline in on-state UPDRS II and III exam scores between weeks 4 and 102. Covariates in both models included age, disease duration, treatment arm, gender, study drug treatment arm, longitudinal change in mini-mental status exam (MMSE) score, LED at week 102, and either baseline UPDRS II or III score respectively. All analyses were performed using SAS version 9.3 (SAS institute, Cary, North Carolina).

Given that cardiovascular risk factors and orthostatic hypotension in PD have both been shown to associate with more rapid rate of disease progression[5–7], we hypothesized that cardiovascular factors may serve as risk factors for the development/worsening of orthostatic blood pressure decline in PD. In a post-hoc linear regression model, we used the mean difference in systolic blood pressure when measured supine & standing at all visits between weeks 4 and 102 as the outcome variable and used the following variables as covariates: age at baseline, disease duration, baseline orthostatic blood pressure change, LED, gender, body mass index (BMI), random measurements of both total serum cholesterol level and blood glucose level both measured at baseline, and baseline supine systolic blood pressure.

Results

The cohort consisted of 176 men and 99 women. Mean age was 60.2 years (+/− 10.3) and mean disease duration of 1.6 years (+/− 1.6). Orthostatic blood pressure differences did not vary between the levodopa vs. pramipexole treatment arms (4.57 +/−11.68 vs. 5.01 +/− 9.71; t=− 0.34, p=0.73). Table 1 presents data from two different multivariable linear regression analyses. The column in the middle and on the far right respectively are separate analyses testing the effects of the listed covariates (rows) on predicting a change in UPDRS motor and ADL scores respectively. Each model shows a statistically significant overall effect, suggesting that the combination of all covariates together collectively predict each outcome. Within each column, t-test and p-values are presented by covariate—these values represent tested correlations between the covariate in question and either the UPDRS motor or ADL score when all other covariates listed are controlled for. In the UPDRS Motor exam model (Table 1), greater baseline orthostatic blood pressure change and randomization to the pramipexole treatment arm both associated with a greater degree of decline in UPDRS Motor exam score at week 102. In the UPDRS ADL assessment model, decline in MMSE score and randomization to the pramipexole arm both associated with a greater decline in ADL function at week 102. Baseline orthostatic blood pressure change did not correlate with UPDRS ADL assessment score change.

The overall post-hoc regression model was statistically significant ($F=18.88$, $p<0.0001$). Covariates associated with a greater mean orthostatic blood pressure measurements between week 4 and 102 included baseline orthostatic blood pressure ($t=9.97$, $p<0.0001$), greater

disease duration (t=2.37, p=0.019), and lower BMI (t=−2.96, p=0.003). No associations were seen for subject age (t=0.36, p=0.719), male gender (t=−0.29, p=0.773), baseline random blood glucose (t=0.334, p=0.735), or baseline random total cholesterol (t=−0.38, p=0.704). A non-significant trend towards association was seen for higher baseline supine systolic blood pressure (t=1.70, p=0.090) and higher LED (t=1.96, p=0.051).

Discussion

Baseline orthostatic blood pressure measurements appear to be a significant predictor of motor outcomes in PD clinical trials, even after controlling for the differential effects of study drugs and other relevant confounders. Orthostatic hypotension is linked to cognitive impairment,[8] a more rapid rate of disease progression,[7] and risk for death in PD and other synucleinopathies.[1] Autonomic changes are increasingly accepted as a manifestation of early PD in the Braak staging model and more severe autonomic features in early disease phases might also be a marker for the innate aggressiveness of the underlying synucleinopathy. When looked at more broadly, autonomic changes may be part of a collective group of non-motor features that characterize early PD subtypes and variability in PD progression.[9, 10] It remains unclear which autonomic and non-motor features are most sensitive for predicting longitudinal clinical decline in PD. Understanding risk factors for the development of single-system (e.g. PD with isolated autonomic dysfunction) vs. combined multi-system non-motor features (e.g. PD with both autonomic dysfunction and mild cognitive impairment) may have important implications on understanding PD heterogeneity and on the characterization of therapeutic targets.

A worsening in orthostatic hypotension over the duration of the study period seemed to be predicted by lower BMI. It is possible that declining BMI is an independent staging marker for PD reflecting the onset of clinically significant frailty. Correlation between lower BMIs and progression on the Hoehn and Yahr scale[11] along with incident cognitive impairment[12] have been previously described. Low BMI may also be a marker for lower levels of plasma urate,[13] which may be a surrogate for diminished ability to manage the enhanced oxidative stress speculated to be involved in PD pathogenesis.

Limitations of this study include the absence of more precise estimates of blood pressure. For example, many studies in cardiovascular literature use continuous ambulatory blood pressure monitoring systems to more precisely estimate the burden of hypertension or orthostatic hypotension. In our post-hoc analysis, we attempted to improve the precision of our estimate of orthostatic hypotension over time by taking the mean value over several study visits. It also should be noted that subjects randomized to levodopa showed less change in UPDRS III score than subjects randomized to pramipexole. In terms of comparative LED scores, the pramipexole doses that were used in the CALM-PD trial were less potent than the corresponding doses of levodopa. We attempted to control for the possibility of differential dopaminergic medication strength influencing our outcomes by not only controlling for subject randomization arm, but also controlling for subject LED, the latter of which summarizes the combined effects of open-label levodopa and other PD medications on change in motor/ADL performance. Even after controlling for both, orthostatic hypotension remained a significant predictor of change in UPDRS motor score.

Idiopathic PD can be challenging to diagnose early in the disease course and it is possible that some of the subjects in our cohort with severe autonomic dysfunction may have progressed overtime to fit more closely with a clinical diagnosis of MSA. This issue has been previously explored in the DATATOP trial cohort where a PD misclassification rate of 8.1% was determined after subsequent follow-up.[14] Although this limitation is important it does, however, exist in nearly all PD clinical research and is offset slightly by the relatively large sample size available in this multicenter trial.

Randomization techniques in PD trial design might benefit from incorporating baseline prognostic markers—including demographic factors like age and disease duration in addition to clinical markers like REM sleep behavior disorder, orthostatic hypotension, mild cognitive impairment, or medical comorbidities--in treatment arm allocation through either stratified or covariate adaptive randomization. Natural history studies in PD moving forward could benefit from more detailed evaluations of blood pressure fluctuations which may lead to improved understanding of their prognostic significance.

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- Baseline orthostatic hypotension predicted a 2 yr decline in the UPDRS motor exam.
- Disease duration and low BMI predicted the development of orthostatic hypotension.
- Orthostatic hypotension should be factored into PD trials randomization techniques.

Table 1

Multivariable Regression Models

	Model 1: Change in UPDRS Motor Exam (F = 3.44, p = 0.0009)	**Model 2: Change in UPDRS ADL assessment (F = 2.26, p =0.024)**
Covariate predictors	**t-test and p-value**	
Baseline UPDRS Motor exam	t = −1.22, p = 0.223	NA
Baseline UPDRS ADL assessment	NA	t = −0.28, p = 0.779
Disease Duration	t = −0.54, p = 0.588	t = 0.45, p = 0.652
Baseline Orthostatic blood Pressure change	**t = 2.40, p = 0.017**	t = 0.83, p = 0.409
Age	t = −1.38, p = 0.167	t = −1.73, p = 0.085
Change in MMSE score	t = −1.75, p = 0.082	**t = −2.33, p = 0.021**
Levodopa equivalent dose	t = −1.89, p = 0.061	t = −0.78, p = 0.435
Male Gender	t = 1.94, p = 0.053	t = 0.34, p = 0.733
Levodopa treatment arm	**t = −2.25, p =0.025**	**t = −2.65, p = 0.008**