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Statins and Cognition in Parkinson's Disease

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Abstract

Background—The relationship between statins and cognition in Parkinson's disease (PD) is poorly understood.

Objectives—Analyses were performed to determine associations between statin use and cross-sectional and longitudinal cognitive performance in PD.

Methods—Neuropsychological tests, medication logs, and ratings of functional abilities were collected from 313 PD participants longitudinally.

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CONFLICT OF INTEREST

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Results—At baseline, statin users (SU; N = 129) were older, more likely male, and had shorter PD duration than non-statin users (NSU; N = 184). In Cross-sectional analysis, SU performed better on global cognition, Trails B, semantic fluency, and phonemic fluency tasks. Rate of long-term global cognitive (Dementia Rating Scale-2 and MoCA) decline was significantly less in SU.

Keywords

Apolipoprotein A-I; cognition; hydroxymethylglutaryl-CoA reductase inhibitors; longitudinal studies; Parkinson's disease; reactive oxygen species

INTRODUCTION

Approximately 80% of Parkinson's disease (PD) patients develop cognitive impairment [1]. HMG- CoA reductase inhibitors (i.e., statins) modulate cholesterol levels and have emerged as possible disease-modifying drugs for neurodegenerative disorders, perhaps related to their pleiotropic abilities [2]. A possible mechanism is statin-induced increases in HDL levels leading to increased Apolipoprotein A-1 (ApoA1) levels [3, 4]. PD patients have lower ApoA1 than controls or individuals with other neurodegenerative diseases, their age of disease onset is positively correlated with plasma ApoA1, and lower ApoA1 is associated with advanced PD [3, 4].

Another possible explanation is statin-mediated reduction of reactive oxygen species (ROS) may decrease vascular disease burden often comorbid in PD [5–7]. Support for potential protective effects of statins comes from two epidemiological studies [8, 9]. A US study followed both statin users (SU) and non-statin users (NSU) long-term and found that statin use was significantly associated with decreased PD incidence [8]. A Taiwanese study found that statin therapy continuation, versus discontinuation, was associated with decreased risk of PD, especially in lipophilic SU [9]. However, there are contradictory findings, including statins either raising or having non-significant effects on PD risk [10–12].

Some studies in non-PD populations suggest that statin use is associated with a lower risk of dementia [13–20], while others report no [21–24] or deleterious effects on cognition [25–28]. We report analyses from an observational study examining statin use and cognitive abilities in PD patients, hypothesizing that SU would have better cognitive performance.

METHODS

Population

Patients with idiopathic PD ($n = 313$) based on UK Brain Bank criteria [29] were enrolled from 2006–2015 at the University of Pennsylvania NINDS-funded Udall Center. The cohort was followed prospectively (from 2–6 years), with baseline (BL) and either annual (years 1–4) or biennial (after year 4) neuropsychological testing.

Participants were divided into current SU (hydrophilic or lipophilic) and NSU at their BL based on self-report, excluding patients starting statins after BL. The size of the SU sample decreases over time due to patients discontinuing statin use and variability in length of study participation (see Table 3).

Assessments

Motor disease severity was quantified using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III [30] and Hoehn & Yahr (H&Y) scale [31], and depression severity with the 15-item Geriatric Depression Scale (GDS-15) [32]. Informant impression of activities of daily living was collected by the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL) [33] and the Penn Parkinson's Daily Activities Questionnaire (PDAQ) [34].

Neuropsychological assessments

Administered cognitive tests were: global cognitive abilities (Dementia Rating Scale-2 and Montreal Cognitive Assessment [35, 36]); executive abilities/working memory (Letter-Number Sequencing (LNS) [37], phonemic fluency (FAS) [38], and Trails B [39]); attention (Symbol Digit Modalities Test [40]) and Trails A [39]); memory (Hopkins Verbal Learning Test-Revised (HVLT-R) [41]); visuospatial function (Judgment of Line Orientation (JOLO) [42] and clock drawing [43]); and language (short Boston Naming Test (BNT)[44] and semantic verbal fluency (animals) [38]).

Consensus cognitive diagnosis

Cognitive status (normal cognition, mild cognitive impairment or dementia) was determined annually or biennially by a consensus of movement disorders specialists or psychiatrist affiliated with the Penn Udall Center as described previously [45].

Modified framingham heart study cardiovascular risk factor scale (mFRF)

The scale [46] weighs vascular risk factors based on age and sex. We modified the scale to include self-identification of high blood pressure as a substitute for measured systolic blood pressure (a score of "3" for women and a score of "2" for men).

Plasma ApoA1 analysis

As previously described [4] plasma was collected in a subset of participants (N = 93). Levels of ApoA1 were measured via enzyme-linked immunosorbent assay (ELISA; catalog no 0462; Abnova, Taipei, Taiwan) [47]. Duplicate samples were run (<1% of samples had a coefficient of variation of >0.2). ELISA was used to process all samples, on the same day, via the same operators.

Statistical analyses

T-tests were used to compare SU and NSU demographic variables. Significant ($p < 0.05$) variables associated with statin use were included as co-variables in linear regression and linear mixed-effects model analyses. Linear regression models analyzed group differences in baseline data, while linear mixed-effects models analyzed group differences in rates of long-term cognitive decline. Since our study was exploratory rather than confirmatory, multiple testing was not performed [48].

RESULTS

Participant demographics

There were 129 participants on HMG-CoA reductase inhibitors with the mean duration of statin use prior to baseline visit = 7.26 years (SD = 6.3). At baseline SU were significantly older ($t(295) = -2.06$; $p = 0.04$), had shorter duration of illness ($t(311) = 1.96$; $p = 0.05$), scored higher on mFRF (denoting greater vascular risk) ($t(203.5) = -2.99$; $p = 0.003$), and had lower UPDRS motor scores ($t(296.4) = 2.03$; $p = 0.04$) than NSU ($n = 184$). As higher mFRF scores in SU would not bias results in support of our hypothesis, we did not include it as a co-variate in subsequent analyses. Demographic and clinical variables are summarized in Table 1.

Statin classification

Frequency of statin type (hydrophilic or lipophilic) and mean dosage for SU can be found in Table 4.

Baseline neuropsychological assessments

Baseline cognitive scores are listed in Table 2. After controlling for UPDRS motor score, age, and disease duration, SU performed significantly better than NSU on the MoCA ($F(4,121) = 11.41$; $p = 0.04$), FAS ($F(4, 225) = 5.08$; $p = 0.02$), animal fluency ($F(4, 263) = 22.65$; $p = 0.04$), and Trails B ($F(4, 80) = 22.12$; $p = 0.008$).

Longitudinal neuropsychological assessments

After controlling for baseline age, baseline UPDRS motor score, baseline cognitive assessment scores, and disease duration at baseline, we found that MoCA ($F(1, 402.9) = 6.19$; $p = 0.013$) and DRS-2 total scores ($F(1, 706.1) = 3.95$; $p = 0.05$), DRS-2 initiation/perseveration ($F(1, 817.2) = 9.5$; $p = 0.002$), concept ($F(1, 896.2) = 4.3$; $p = 0.039$), and memory ($F(1,874.8) = 7.5$; $p = 0.006$) subscores declined at a significantly slower rate over time in SU group compared with NSU group. These results were supported by near-significant findings on LNS and JOLO. Longitudinal neuropsychological scores are listed in Table 2.

Lipophilic statin-users vs. non-statin-users

Upon removal of hydrophilic SU, lipophilic SU performed significantly better on MoCA ($F(4,107.3) = 10.94$; $p = 0.04$) at baseline. Longitudinally, lipophilic SU declined at a significantly slower rate than NSU on DRS total score ($F(1,684.2) = 5.99$; $p = 0.02$).

ApoA1 analyses

Statin use did not significantly correlate with baseline ApoA1 plasma levels (all $p > 0.05$) and baseline ApoA1 levels did not significantly correlate with any baseline neuropsychological measures (all $p > 0.05$).

DISCUSSION

In this examination of the impact of statin use on cognition in PD we observed that SU performed better on assessments of global cognition, verbal fluency, and executive processing in cross-sectional analysis when controlling for important covariates. In addition, in longitudinal analyses rates of cognitive decline were less for SU on global scales and initiation/perseveration, concept, and memory subscores of DRS-2.

Results of our analysis on ApoA1 yielded non-significant results and leads us to believe that statins are not modulating cognition through increasing levels of ApoA1. Thus, our findings suggest that statin use-mediated cognitive reserve occurs via a different mechanism. A possible explanation relates to findings that, on autopsy, PD brains compared to matched controls have significantly larger blood vessel size, with vessel degeneration particularly in substantia nigra, medial frontal gyrus, and caudate nucleus [49]. PD cases were also found to have decreased number of capillaries and more small arterioles/veins, causing significant reduction in the ratio of small to large vessels in these brain regions [49]. Decreases in small blood vessels alter vascular networks and may lead to decreased vascular performance.

Statins may decrease effects of this vascular remodeling by removing ROS, and a reduction in ROS has been shown to delay cell death in the brain *in vivo*, animal models, and humans [5–7]. Simvastatin reduces mitochondrial stress in myocytes [50], yet effects on neurons is unknown. Statins may contribute to cognitive reserve in PD by reducing ROS in the medial frontal gyrus/cortex, an area found to exhibit increased vascular burden in PD [49].

In terms of study limitations, SU might have had better cognitive performance due to a healthier lifestyle and less medical comorbidity that could be associated with the decision to take statins. We addressed this by including a mFRF composite score, although this could introduce bias because hypertension was self-reported. We found that SU actually had more vascular risk factors typically associated with cognitive impairment in PD [51], thus making it less likely that there were other, unrelated factors explaining improved cognitive performance in SU. Another limitation is made apparent by a recent study that PD symptoms may worsen with statin use, which could have biased use of statins in our population (10). A further limitation was an inability to provide a proxy biomarker for statin use, e.g. fasting cholesterol levels. Additionally, our study had variable duration of follow-up, which can be addressed in future analyses of this cohort.

An ongoing, prospective, multi-site study known as “PD Stat” is examining use of simvastatin as a disease-modifying drug (<https://penctu.psmd.plymouth.ac.uk/pdstat/Default.aspx>). This and other studies will determine if statins truly have neuroprotective effects, with impact on both motor and non-motor symptoms.

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Table 1

Demographics

Variables	Percentage or Mean, SU (SD)	Percentage or Mean, NSU (SD)	P-Value
Age	70.5 (7.5)	68.6 (8.6)	0.04 *
Sex	72.9%	27.1% Male	0.09
modified-Framingham Heart Study Vascular Score	16.6 (3.6)	15.2 (3.4)	0.003 *
UPDRS-motor score	20.2 (9.7)	22.7 (11.6)	0.05 *
Geriatric Depression Scale-15 score	2.5 (2.5)	3 (2.9)	0.12
PD Disease duration	6.7 (5.1)	7.9 (5.2)	0.05 *
PD age of onset	63.8 (9.1)	60.7 (9.0)	0.004 *
Hoehn & Yahr stage	2.2 (.66)	2.3 (.67)	0.63
Activities of Daily Living Inventory (total score)	71.3 (12.7)	69.5 (12.3)	0.34
Number of Participants Follow-up (In Years)	65.00 (30.4)	90.7 (40.0)	0.29

* Denotes that significance $p < 0.05$.

Table 2

Neuropsychological assessments

Neuropsychological Assessment (N)	SU Baseline Mean (SD)	NSU Baseline Mean (SD)	P-value	Annual change (SE) in SU group	Annual change (SE) in NSU group	P-value for group difference of annual change
MoCA total score (128)	25.52 (3.99)	25.05 (3.45)	0.04 *	-0.262 (0.064)	-0.435 (0.061)	0.01 *
DRS-2 total score (313)	135.04 (10.00)	134.00 (11.83)	0.22	-0.732 (0.212)	-1.64 (0.203)	0.001 *
Attention subscore	35.62 (1.57)	35.47 (2.04)	0.61	-0.070 (0.054)	-0.150 (0.048)	0.35
Initiation subscore	34.83 (4.46)	34.20 (5.20)	0.95	-0.458 (0.085)	-0.783 (0.082)	0.002 *
Construction subscore	5.87 (0.60)	5.72 (0.85)	0.05 *	-0.065 (0.020)	-0.096 (0.019)	0.201
Concept subscore	36.40 (2.99)	36.12 (3.43)	0.48	-0.015 (0.066)	-0.189 (0.063)	0.04 *
Memory subscore	22.33 (3.32)	22.48 (3.10)	0.95	-0.135 (0.055)	-0.326 (0.053)	0.006 *
LNS (279)	9.38 (3.17)	9.04 (3.02)	0.14	-0.223 (0.043)	-0.328 (0.042)	0.06
FAS (231)	41.96 (15.79)	37.96 (15.38)	0.02 *	-0.878 (0.164)	-0.961 (0.160)	0.69
Animals (269)	17.70 (5.83)	16.72 (5.90)	0.04 *	-0.461 (0.090)	-0.487 (0.088)	0.82
Trails A total time (85)	49.34 (47.37)	45.94 (25.47)	0.21	0.237 (0.577)	0.815 (0.594)	0.27
Trails B total time (85)	101.34 (59.11)	103.94 (63.57)	0.008 *	4.05 (1.23)	5.50 (1.23)	0.24
Symbol Digit Modalities Test (85)	37.97 (9.43)	37.44 (11.10)	0.11	-0.714 (0.191)	-0.885 (0.186)	0.37
BNT (274)	54.99 (6.06)	55.14 (4.91)	0.97	-0.106 (0.048)	-0.0872 (0.049)	0.77
Clock Drawing Scale (291)	5.75 (1.43)	5.32 (1.84)	0.07	-0.084 (0.028)	-0.093 (0.028)	0.80
JOLO (271)	22.41 (5.67)	22.05 (5.33)	0.71	-0.106 (0.094)	-0.335 (0.097)	0.06
HVLT-R Total (295)	19.77 (6.24)	19.63 (5.84)	0.48	-0.374 (0.088)	-0.387 (0.086)	0.91
HVLT-R Delayed Recall	5.93 (3.22)	5.98 (3.39)	0.86	-0.197 (0.053)	-0.224 (0.052)	0.69
HVLT-R Retention %	68.73 (29.93)	69.47 (33.09)	0.92	-1.15 (0.638)	-1.63 (0.627)	0.54
HVLT-R Recognition Discrimination	8.88 (2.62)	8.82 (2.43)	0.58	-0.097 (0.042)	-0.093 (0.041)	0.94

* Denotes that significance p 0.05.

Table 3

Number of participants assessed longitudinally

Visit	SU	NSU
Baseline	129	184
V01	99	155
V02	89	125
V03	75	103
V04, V05	67	85
V06, V07	43	53
V08	17	23

Table 4

Statin classification

Hydrophilic	Frequency (# participants)	Mean dosage in mg (SD)
Pravastatin	5	30 (11.5)
Rosuvastatin	12	13.3 (10.3)
Lipophilic		
Lovastatin	5	20.0 (12.2)
Atorvastatin	44	21.4 (17.3)
Simvastatin	63	31.8 (19.0)