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Progressive Supranuclear Palsy and Statin Use

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Abstract

Introduction: Statins were proposed to be neuroprotective; however, the effects are unknown in progressive supranuclear palsy (PSP), a pure tauopathy.

Methods: Data of 284 PSP cases and 284 age-matched, sex-matched, and race-matched controls were obtained from the environmental and genetic PSP (ENGENE-PSP) study. Cases were evaluated with the PSP Rating Scale, Unified Parkinson's Disease Rating Scale, Mattis Dementia Rating Scale, and Neuropsychiatric Inventory. Statin associations with PSP risk, onset age, and disease features were analyzed.

Results: Univariate models showed lower PSP risk for type 1 statin users (simvastatin, lovastatin, pravastatin). After adjusting for confounding variables, statin use and lower PSP risk association remained only at a trend level. For PSP cases, type 1 statins were associated with 1-year older onset age; type 2 statins (atorvastatin, rosuvastatin) were associated with the lower PSP Rating Scale and Unified Parkinson's Disease Rating Scale.

Conclusion: Statins may have inverse associations with PSP risk and motor impairment. Randomized prospective studies are required to confirm this effect.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Keywords

case-control; progressive supranuclear palsy; statins; tauopathy

Progressive supranuclear palsy (PSP) is a tauopathy presenting with postural instability, parkinsonism, ocular motor dysfunction, and executive dysfunction,[1] without any disease-modifying agents or effective treatment options.[2] Statins, primarily used for ischemic heart disease management and prevention, are one of the most commonly used drugs worldwide. In addition to reducing plasma cholesterol levels, statins may be neuroprotective through antioxidant, anti-inflammatory, and immunomodulatory mechanisms.[3] In a tauopathy animal model, using statins before neurofibrillary tangle development significantly decreased the tangle burden under both normocholesterolemic and hypercholesterolemic conditions.[4] However, statin effects on tauopathies in a clinical sample have not been investigated, apart from Alzheimer's disease (AD). As AD is a mixture of pathologies including 3R tauopathy, 4R tauopathy, and β-amyloid deposition,[5] the results cannot be generalized to PSP, a primary 4R tauopathy. Therefore, we aimed to determine whether statins are inversely associated with PSP development and symptoms using an age-matched, sex-matched, and race-matched case-control sample.

Methods

Data were obtained from the environmental and genetic PSP (ENGENE-PSP) study, previously described elsewhere.[6] The inclusion criteria for the cases were the following: (1) PSP diagnosis within the past year by the principal investigator at the screening site (based on the National Institute for Neurological Disorders and Society for PSP criteria for probable PSP[7]), (2) no other central nervous system pathology, and (3) Mini-Mental Status Examination score of >24 to exclude cognitive impairment. Controls, screening negative for parkinsonism and dementia, consisted of non–blood relatives or friends of the included PSP patients. A total of 350 incident PSP patients and 300 healthy controls meeting the inclusion criteria were recruited in 15 sites in North America between October 2006 and February 2013. Of the cases, 66 did not have a matched control and were excluded (50 without matched controls, 16 without race-matched controls), leading to 284 cases and 284 age-matched, sex-matched, and race-matched controls included in our analysis. The institutional review boards of each site approved the ENGENE-PSP, and the participants provided written informed consent prior to participation.

A list of all medications taken for more than 6 months since the age of 30, the reason of use, and the years of first and last use were collected during an in-person visit. Statin use was defined as having used statins before the onset of symptoms for cases and before the visit for controls. All PSP patients underwent clinical evaluations with standardized measures including PSP Rating Scale (PSPRS), Unified Parkinson's Disease Rating Scale (UPDRS), Mattis Dementia Rating Scale (DRS), and Neuropsychiatric Inventory (NPI).

Statistics were done with IBM (Armonk, NY) SPSS version 26.0. Demographics and statin data were compared between cases and controls with chi-square and *t* tests with Bonferroni correction for multiple comparisons. The association between statin use and PSP diagnosis

was evaluated by conditional logistic regression, with case/control pairs as stratum and case status as the outcome. First, univariate models were performed to identify the possible confounders, then a multivariate model was performed including confounding variables with a $P < 0.05$ from the first model. The associations between statin use and age at symptom onset, PSPRS, UPDRS, DRS, and NPI were assessed by stepwise linear regression, adjusting for potential confounders from univariate models as explained previously. The effects of different statins were analyzed by grouping the statins based on their chemical structures[8] (type 1 statins: simvastatin, lovastatin, pravastatin; type 2 statins: atorvastatin, rosuvastatin) because of the low number of participants having used individual statins. $P < 0.05$ was considered statistically significant.

Results

Demographics and clinical features are summarized in Table 1. Compared with the controls, cases had lower years of education, higher years of drinking well water and smoking, pack-years, and were less likely to have used statins. Type 2 statin use, age at first statin use, and duration of statin use were not different between cases and controls. Compared with the controls, a lower ratio of cases had used type 1 statins. Of the participants, 8.4% of the cases and 5.8% of the controls had a history of more than 1 type of statin use. More smoking pack-years and years of drinking well water were associated with increased PSP risk. More years of education and statin use—type 1 in particular (not type 2)—were associated with lower PSP risk based on univariate models (Table 1).

Multivariate model results for statin and disease parameters are shown in Table 2 (univariate model results are given in Supplementary Table 1). After adjusting for confounding variables, statin use and lower PSP risk association remained only at a trend-level ($P = 0.05$). Statin use was associated with 1-year older age at symptom onset, approximately 4-point lower PSPRS and UPDRS-Part III scores, and 7-point lower UPDRS-Total scores without any association with DRS or NPI. For controls, the association between age and statin use did not reach a significant level (B [*95*% confidence interval] = 1.83 [−0.049 to 3.71], $P = 0.056$).

After adjusting for confounding variables, type 1 statins were not associated with PSP risk. Type 1 statins were associated with 1-year older symptom onset age, without any associations with disease parameters. Type 2 statins were associated with approximately 5-point lower PSPRS and UPDRS-Part III scores and 7-point lower UPDRS-Total scores without any associations with symptom onset age, DRS, or NPI. Age at first statin use or duration of statin use were not associated with PSP risk or disease features.

Discussion

In this study, the associations between statins and PSP risk, age at symptom onset, and disease features were evaluated. Statin use was associated with lower PSP risk, although the significance remained at a trend-level once adjusted for confounding variables. For cases, statin use was significantly associated with an older symptom onset age. Although 1-year delay may not be clinically significant for some neurodegenerative disorders, it can be very

meaningful for PSP, which has a mean disease duration of 6 years before death.[9] The lack of significant age and statin association for controls may allay concerns regarding statin use patterns in this older population contributing to the association between age at symptom onset and statin use in PSP cases. Nevertheless, there was a trend for significance regarding statin use association with older age, which may temper this assertion. The association between statin use, particularly type 2 statins, with lower motor symptom severity is another important finding. The combination of a delayed onset and lower level of symptom severity as a result of statins can be promising for PSP. Different associations of type 1 and 2 statins with PSP risk, onset age, and motor symptom severity may suggest different effects of statin types.

The effects of statins on neurodegenerative disorders have mostly focused on AD, vascular dementia, and Parkinson's disease with inconsistent results, potentially because of the differences in study design, demographics of the recruited samples, definition of statin use, and heterogeneous patient groups.[10,11] However, statins have overall been suggested to lower Parkinson's disease and AD risk. In an animal model with pure tau pathology, statins had beneficial effects via anti-inflammatory mechanisms, independent of their cholesterol-lowering effects.[4] Such experimental and epidemiologic results require clinical translation to benefit patients or individuals at risk of developing PSP. Our results suggest a benefit of statin use for PSP, yet cholesterol levels or other comorbidities were not evaluated. Despite a study showing no significant association between hyperlipidemia and PSP risk,[12] it is important to acknowledge that we did not evaluate whether the associations between the statins and PSP risk are independent of the lipid profiles. Given that statin use was because of hyperlipidemia in all our participants, our results might suggest an association between hyperlipidemia and lower PSP risk. This should be addressed in a future study evaluating lipid profiles in detail. Several cytokines and microglial activation were shown to contribute to the pathologic process in PSP, suggesting a potential disease-modifying effect for cytokine inhibitors and anti-inflammatory agents.[13] The anti-inflammatory effects of statins may therefore be of value in PSP, and imaging techniques, which can visualize neuroinflammation (eg, magnetic resonance imaging and positron emission tomography[14]), may help in determining the potential neuroprotective mechanisms of statins in PSP.

Statin use was associated with less severe motor symptoms (4-point decrease in PSPRS and UPDRS-Part III and 7-point decrease in UPDRS-Total) without any associations with cognitive or behavioral symptoms. Motor symptoms and nonmotor symptoms may be associated with tau pathologies in different brain regions or other comorbid pathologies, which can respond differently to agents. Although statins have been shown to affect neurofibrillary tangles,[4] the extent of correlations between symptom profile and neurofibrillary tangle burden in PSP is currently unknown. Lack of any association between the disease features and age of starting statins or duration of statin use should also be considered while interpreting our significant findings. In addition, data on disease onset age and prior statin use was collected retrospectively. To prevent recall bias regarding the information gathered from cases and controls, caregivers were allowed to correct if cases recalled any information inaccurately. However, it is not possible to strongly argue for a beneficial statin effect in PSP based on our cross-sectional case-control findings without studies evaluating controlled statin intake in patients with PSP.

Our results showed that type 1 statins are associated with reduced risk and delayed onset, whereas type 2 statins were associated with less motor impairment. Previously, comparisons of multiple statin types suggested that simvastatin (a type 1 statin) might provide most efficacy for neuropathological conditions considering blood–brain barrier penetration, safety, cholesterol reduction in neurons, and neuroprotection in cell cultures.[15] Although our sample size of statin users did not allow us to assess each statin type individually, certain statins may be more or less effective in PSP. In addition, some participants had a history of more than 1 type of statin use, suggesting a cautious interpretation of our findings. We did not have detailed information on the dosage of statins to evaluate dose-dependent effects. Considering that the participants were on statins for hypercholesterolemia, the beneficial effects of statins in PSP may require different doses or specific types of statins given that blood–brain barrier permeabilities and effects on low-density and high-density lipoprotein cholesterols differ between statin types.[15]

To conclude, statins were associated with potentially lower PSP risk, delayed symptom onset, and less severe motor symptoms, with different effects found for type 1 and 2 statins. The potential statin effects require future investigations, as there is an urgent need for efficient therapeutic approaches in PSP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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TABLE 1.

Demographics and clinical features

Features	Cases, n = 284	Controls, n = 284	Cases vs. Controls, *P* Value	Odds Ratio (95% CI) for PSP Risk*
Age	68.8 (7.01)	69.0 (7.44)	1.00	–
Sex, female	50.4	50.4	1.00	–
Race			1.00	–
White or European American	97.5	97.5		
Black or African American	0.7	0.7		
Asian or Pacific Islander	1.8	1.8		
Income			0.067	–
<$50,000/year	36.4	27.1		
$50–80,000/year	27.1	28.6		
>$80,000/year	36.4	44.3		
Years of education	14.7 (4.21)	16.2 (4.07)	**<0.001**	0.89 (0.84–0.93)
Smoking, pack-years	15.7 (25.1)	10.5 (19.5)	**0.032**	1.01 (1.01–1.02)
Years of drinking well water	11.4 (17.0)	7.10 (12.4)	**0.003**	1.02 (1.01–1.04)
Age at symptom onset	65.03 (7.01)	–		
PSP symptom duration, years	3.68 (1.76)	–		
PSP Rating Scale	36.3 (11.3)	–		
UPDRS-Total	51.7 (17.9)	–		
UPDRS-Part III	30.0 (12.3)	–		
Dementia Rating Scale	127 (10.8)	–		
Neuropsychiatric Inventory	10.1 (9.11)	–		
Statin use	20.8	30.6	**0.011**	0.61 (0.41–0.91)
Type 1 statins	10.9	17.6	**0.023**	0.56 (0.34–0.92)
Type 2 statins	11.6	14.8	0.27	–
Age at first statin use	59.2 (8.08)	62.1 (8.08)	0.19	–
Duration of statin use, years	7.48 (5.66)	6.24 (5.69)	0.97	–
Reason for statin use			0.80	–
Hypercholesterolemia	97.7	98.3		
Hypercholesterolemia & hypertension	2.3	1.7		

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Variables are reported as mean (standard deviation) or percentage. Bold indicates statistical significance.

* Only significant variables from the univariate regression models are shown.

CI, confidence interval; PSP, progressive supranuclear palsy; UPDRS, Unified Parkinson's Disease Rating Scale.

TABLE 2.

Multivariate regression model results for associations between PSP features and statin use (model with 284 PSP cases), age at first statin use, and duration of statin use (model with 59 statin user PSP cases)

Statin parameters	PSP risk,[1] odds ratio (95% CI)	Age at symptom onset,[2] B (95% CI)	PSP Rating Scale,[3] B (95% CI)	UPDRS-Total,[4] B (95% CI)	UPDRS-Part III,[4] B (95% CI)	Dementia Rating Scale,[5] B (95% CI)	Neuropsychiatric Inventory,[4] B (95% CI)
Statin use	0.65 (0.43–1.00), *P* = 0.050	1.00 (0.31–1.70), ***P* = 0.005**	−3.80 (−7.03 to −0.56), ***P* = 0.022**	−7.16 (−12.17 to −2.14), ***P* = 0.005**	−4.48 (−7.89 to −1.06), ***P* = 0.010**	1.43 (−1.64 to 4.50), *P* = 0.36	0.55 (−2.42 to 3.53), *P* = 0.71
Type 1 statin use	0.60 (0.35–1.03), *P* = 0.064	1.09 (0.18–1.99), ***P* = 0.049**	−1.47 (−5.69 to 2.76), *P* = 0.50	−5.61 (−12.14 to 0.92), *P* = 0.092	−3.10 (−7.55 to 1.35), *P* = 0.17	−0.16, (−4.11 to 3.80), *P* = 0.94	1.82 (−1.99 to 5.63), *P* = 0.35
Type 2 statin use	0.81 (0.47–1.37), *P* = 0.43	0.61 (0.003–0.03), *P* = 0.17	−4.87 (−8.95 to −0.80), ***P* = 0.019**	−6.83 (−13.18 to −0.48), ***P* = 0.035**	−4.66 (−8.98 to −0.35), ***P* = 0.034**	2.34 (−1.55 to 6.23), *P* = 0.24	0.56 (−3.13 to 4.25), *P* = 0.77
Age at first statin use	0.84 (0.67–1.05), *P* = 0.12	0.06 (−0.003 to 0.13), *P* = 0.061	0.03 (−0.31 to 0.36), *P* = 0.88	−0.19 (−0.69 to 0.30), *P* = 0.44	−0.11 (−0.54 to 0.32), *P* = 0.61	−0.04 (−0.42 to 0.34), *P* = 0.84	−0.03 (−0.49 to 0.43), *P* = 0.90
Duration of statin use	1.04 (0.88–1.22), *P* = 0.67	−0.02 (−0.10 to 0.06), *P* = 0.59	0.13 (−0.35 to 0.60), *P* = 0.59	0.61 (−0.08 to 1.30), *P* = 0.083	0.36 (−0.12 to 0.85), *P* = 0.14	−0.12 (−0.55 to 0.32), *P* = 0.59	0.01 (−0.55 to 0.57), *P* = 0.97

Bold indicates statistical significance. B values show the amount of increase in outcome measure with statin use (overall, types 1 and 2), and 1-year increase in age at first statin use or duration of statin use.

[1]Confounding variables in the model: years of education, smoking, pack-years, years of drinking well water.

[2]Confounding variables in the model: age, smoking, pack-years.

[3]Confounding variable in the model: ethnicity.

[4]Confounding variables in the model: age, years of education.

[5]Confounding variables in the model: age, sex, years of education, years of drinking well water.

PSP, progressive supranuclear palsy; CI, confidence interval; B, unstandardized beta coefficient; UPDRS, Unified Parkinson's Disease Rating Scale.