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Statin Use and the Risk of Parkinson's Disease

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Abstract

Objective—To investigate associations between statin (3-hxydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) use and Parkinson's disease (PD)

Methods—We used a population-based design to recruit 312 incident idiopathic PD cases and 342 controls from three rural California counties. Controls were marginally matched to cases by age, race, and gender.

Results—We observed a higher frequency of statin use among controls versus cases (OR 0.45; 95% CI 0.29 to 0.71) and a strong dose-response relation. The strongest protective association between statin use and PD was observed in long-term (≥5 years) users (OR 0.37; 95% CI 0.18 to 0.78). There was no difference by gender or age. We noted 60–70% risk reductions for each individual statin except pravastatin.

Conclusion—Ascribing causality to these associations is premature and further studies are needed to confirm a potential neuroprotective role for statins in PD.

Terms

[53] case control studies; [165] Parkinson's disease/Parkinsonism; [59] risk factors in epidemiology

Introduction

Statins (3-hxydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) are among the most widely used drugs in the United States.[1] By inhibiting hydroxyl-methyl-glutaryl Co-A reductase, which is involved in the synthesis of a substrate for cholesterol and Co-enzyme Q10, statins ultimately decrease levels of cholesterol and co-enzyme Q10.[2,3] Two studies reporting an association between low cholesterol and PD suggest that low cholesterol or low Co-enyzme Q10 increase the risk of Parkinson's disease (PD) thus raising the possibility that statin use might be harmful to the dopaminnergic system.[4,5]

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On the other hand there is considerable biological evidence suggesting that statins have neuroprotective properties. Statins scavenge oxygen-derived free radicals, which studies suggest may help ameliorate free radical injury.[6] Statins may also attenuate neuroinflammatory events that are increasingly recognized as playing a role in PD pathology.[7,8] Simvastatin inhibits microglial formation of TNFα, nitric oxide (NO) and superoxide (O_2^-), and also attenuates the dopamine depletion in MPTP-treated mice.[9] In addition, lovastatin reduces cytokine-mediated induction of iNOS and subsequent NO (nitric oxide) production in rat astrocytes, microglia, and macrophages.[10] Evidence from both humans and animal models implicate both NO and NOS, particularly iNOS, as playing an etiologic role for PD.[11]

Given the contradictory biological hypotheses proposed and the absence of epidemiologic research that evaluates statin use prior to PD diagnosis, we decided to investigate a potential role for statins in PD using our population-based case control study of incident PD.

Subjects and Methods

Study design

This study is part of the ongoing UCLA PEG (Parkinson's Environment and Genes) Study, a population based case-control study that recruits incident cases and controls from three rural California counties (Fresno, Tulare, Kern). Cases were identified through practicing neurologists in these counties who provide care for PD patients (90% of these neurologists participated), as well as through large medical groups (such as Kaiser Permanente, Kern and Visalia Medical Center, and the Veteran's Administration), PD support groups, local newspapers, and local radio stations. A age, gender, and county stratified random sample of Medicare enrollees living in the three counties and residents selected from homes identified at random from all housing units listed on parcel maps for the same tri-county area (Note this was done in proportion to each counties populations i.e. more for the larger than the smaller counties {ask Sadie if you need more info}) provided us with controls.. Controls were marginally matched to cases by age(5 year categories), race, and gender {well we attempted to do this but think we failed to some degree see my emails, so I am not sure how to express this or just not say it?} the only thing different is that we lost efficiency since we controlled for these variables anyhow (but our strata are not optimally, but I am not sure that the reviewers will understand this easily, unless they are well trained epidemiologists…on the other hand it might be time to slowly acknowledge that our matching attempt likely didn't work too well and we just got a random sample in proportion to the subjects in each county eligible in the age bracket we defined, sorry all this just became apparent when we tried to make a flow chart for PEG control recruitment with Sadie et al}. Here, we evaluated 312 incident (i.e., enrolled within 3 years of first diagnosis) idiopathic PD cases and 342 controls that were recruited between January 2001 and January 2007.

The study's two UCLA movement disorder specialists confirmed a diagnosis of clinically probable or possible PD for all cases using well-established, stringent diagnostic criteria,[12,13] and by making multiple patient visits to confirm diagnoses when necessary. A diagnosis of clinically probable or possible PD was confirmed if patients met the following criteria: (1) manifestation of at least two of the following characteristics: resting tremor,

bradykinesia, or cogwheel rigidity, at least one of which is resting tremor or bradykinesia; (2) no suggestion of a parkinsonian syndrome due to trauma, brain tumor, infection, cerebrovascular disease, or other known neurological disease, and no treatment in the past with dopamine-blocking or dopamine-depleting agents; (3) no atypical features such as prominent oculomotor palsy, cerebellar signs, vocal cord paresis, severe orthostatic hypotension, pyramidal signs, amyotrophy or limb apraxia; (4) asymmetric onset; and (5) if treatment with levodopa had been initiated, symptomatic improvement after treatment. Probable cases met criteria 1 through 5. Possible cases exhibited at least one characteristic from criterion 1 and fulfilled criteria described in 2 and 3. Although sometimes included under criterion 1, postural reflex impairment was excluded as a criterion because it usually occurs late in PD and may typically occur early in other parkinsonian disorders (i.e., Multiple System Atrophy and vascular Parkinsonism).[14]

Study participants completed a medical questionnaire providing information on the specific statins they took, length of treatment in months or years, and age at first and last use. Demographic and lifestyle characteristics were collected by telephone interviewers blinded to a subject's case/control status. All subjects provided informed consent and the study was approved by the UCLA Institutional Review Board.

Statistical Analysis

Participants were categorized as ever or never users of all and each individual statin. For cases, any use that occurred post-diagnosis was ignored. Odds ratios for ever versus never use of statins were calculated using unconditional logistic regression, controlling for age continuously (age at diagnosis for cases and age at interview for controls), gender, smoking packyears (0, >0 to <10, ≥10 to <40, ≥40), education (<12 yrs, 12 yrs, >12 yrs), race (Caucasian, Asian, Latino, Native American, and Black), and county of residence (Kern, Tulare, Fresno). We adjusted for these variables because previous literature indicated they could be potential confounders in the relationship between PD and statin use. A small number (n=9; 5 cases, 4 controls) of participants indicated that they used statins but did not report age at first or last use, or duration of use. We performed analyses both excluding these individuals, and also including them as statin users after assigning to them the mean duration of use for cases or controls. We also stratified statin use by duration in years, age at diagnosis/interview (≤60 yrs, >60 yrs) and gender, assessing potential heterogeneity in effect estimates using the Breslow-Day Test (BDT?) for homogeneity. We also analyzed our data after removing all cases that were diagnosed up to three years prior to 2001. This was done to account for potential temporal trends in statin prescription and usage because cases could have been diagnosed up to three years prior to the start of enrollment and interview in 2001. Finally, we performed a lagged analysis by excluding any use that had occurred during the 5 years immediately prior to the diagnosis for cases or the interview for controls.

Results

Study population characteristics are presented in Table 1. 18.7% of the population reported ever having taken statins. Among 47 cases who reported ever taking statins, 11 cases reported only post-diagnosis use and, thus, were considered non-users in all analyses.

Among statin users, specific statin use included atorvastatin (48.7%), simvastatin (26.1%), lovastatin (15.3%), pravastatin (9.9%), rosuvastatin (4.5%), and other (1.8%), with some individuals reporting the use of more than one type of statin. The average age at first use was 65.5 years (47–78 yrs) for cases and 64.6 years (40–82 yrs) for controls, with controls reporting a slightly longer mean duration of use (4.4 yrs) than cases (3.8 yrs).

Controls reported a higher frequency of statin use {Angelika, do you mean in dosage or a higher proportion of ever users ?? this is not clear here} compared to cases, thus suggesting a 55% reduction in PD risk among ever statin users. When evaluating duration of use, we noted a strong dose-response relation, with long-term users (≥5 years) showing the strongest protective association (Table 2). Results were similar when including subjects with missing statin duration/age data (ever vs. never use, OR 0.46; 95% CI 0.30 to 0.71) and when lagging/excluding use within 5 years before diagnosis (cases) or interview (controls) (OR 0.33; 95% CI 0.14 to 0.80). When excluding cases diagnosed before 2001, we still noted a strong protective effect for ever versus never statin users (OR 0.49; 95% CI 0.29 to 0.82) as well as for short and longer-term users (≥1 year, OR 0.43; 95% CI 0.15 to 1.20; ≥ 5 years, OR 0.50; 95% CI, 0.23 to 1.10). We noticed no difference in effect estimates between men (OR 0.48; 95% CI 0.27 to 0.86) and women (OR 0.41; 95% CI, 0.20 to 0.84). A protective effect was evident for both younger (≤60) and older age at diagnosis/interview, with a slightly stronger protective effect in the younger age group (≤60, OR 0.25; 95% CI 0.07 to 0.88; >60, OR 0.47; 95% CI 0.29 to 0.76), although the confidence intervals largely overlap (B-D test p=0.90). Similarly, we noticed a slightly stronger protective association among never smokers (OR 0.35; 95% CI 0.17, 0.70) compared to ever smokers (OR 0.57; 95% CI (0.32, 1.02) (B-D test p=0.25). When evaluating use of each individual statin we noted 60–70% risk reductions for all statins except pravastatin (atorvastatin OR 0.39; 95% CI 0.21 to 0.71, simvastatin OR 0.38; 95% CI 0.16 to 0.91, lovastatin OR 0.27; 95% CI 0.09 to 0.87, pravastatin OR 1.78; 95% CI 0.43 to 7.42).

Discussion

In our population-based case control study of incident PD, we observed a protective association between statin use and PD risk and a strong dose-response relation with increasing duration of use. Adjustment for potential confounders did little to change the magnitude of the observed association. Excluding cases whose diagnosis occurred before 2001 – the year we started enrollment of our population controls - demonstrated that the inverse associations observed were not solely due to recent trends in the use of these drugs or in medical prescription practices.

Non-differential misclassification of disease is expected to be minimal due to our study's stringent diagnostic criteria and (repeated if necessary) clinical examination of every PD case by the study's movement disorder specialists (JB and YB). There is a possibility of non-differential misclassification because statin use was self-reported, especially when asking participants to recall specific drugs and duration of use. However studies have demonstrated fair recall of prescription drug use with consistently high specificity[15] and recall is likely even better because statins are fairly new drugs with use occurring at most 15–20 years ago and most users continuing to currently use their prescribed statin. Lastly,

while this is a population-based study with matched controls having been selected at random from a well-defined source population, the possibility of selection bias in our study cannot be ruled out. Specifically, access to healthcare may affect statin use and may have also influenced the self-selection and participation of patients in our study different from controls, i.e. PD patients were generally in regular contact with medical providers. Thus, PD patients might have been more likely than population controls to be evaluated and receive treatment for high cholesterol conditions and the expected bias would have been towards finding no association i.e. PD patients would be expected to be prescribed more statins than controls.

All statins were inversely associated with PD except for pravastatin, although small size of each subgroup limited these comparisons. A possible explanation for pravastation being the exception might be postulated differences in statins' lipophilic properties. There is a general consensus in the literature that pravastatin is the least lipophilic statin resulting in its difficulty in crossing the blood-brain barrier and thus its ability to affect the central nervous system (CNS); yet, another report claims that atorvastatin also has low CNS penetration.[16]

Interestingly, the only previous study to examine associations between statins and prevalent PD also reported a protective effect, even after adjustment for LDL-C concentration.[4] However this study heavily relied on statin use for the post-diagnosis period and prevalent PD cases with a moderately to long duration of disease. Post-diagnosis statin use may not properly reflect pre-diagnosis use. For example in our study population, 23% of cases who reported ever taking statins reported only post-diagnosis use; we considered all such individuals as non-users in our analyses of pre-diagnosis statin use.

At this point we are reluctant to ascribe causality to the observed protective association with statin use prior to PD diagnosis. There is some suggestion that low LDL cholesterol may increase the risk of PD.[4,5] If low LDL cholesterol levels indeed increase risk of PD etiologically, we could be observing a lower risk of PD among subjects who were prescribed statins because of their higher cholesterol levels i.e. statin use would serve as an indicator of high LDL cholesterol level which would be preventative of PD. Statin use may also be serving as an indicator of high levels of serum co-enzyme Q10, for which serum cholesterol is an important determinant. Co-enzyme Q10 acts as an antioxidant and electron acceptor for complex I and II in the mitochondrial respiratory chain.[5] The observed protective association when statins were only used for one year or less may be suggestive of a biological mechanism other than statins acting truly protectively. On the other hand, it is plausible that statins are themselves causally associated with PD or at least contribute to the observed protective effect. The possibility of a causal association is supported by our finding of a dose-response relation with duration of use and considerable biologic evidence that statins can be neuroprotective through a variety of mechanisms including NOS and NO regulation, anti-oxidant effects, and reducing the induction of pro-inflammatory mediators such as cytokines.

Further investigation of the potential role for statins, cholesterol, and coenzyme Q10 in PD etiology is warranted given our study findings. Due to the nature of the relationship between LDL cholesterol, statin use (an intermediate) and PD, a longitudinal study design, including

measures of cholesterol levels over time, is necessary to further investigate this potential causal chain.

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Table 1

Study Population Characteristics

	Cases n=312	Controls n=342
Age in years (median (SD))	70.0 (10.6)	69.0 (12.7)
Men, n (%)	166 (53.2)	168 (49.1)
Race/Ethnicity, n (%)		
White	254 (81.4)	277 (81.0)
Black	3 (1.0)	11 (3.2)
Latino	36 (11.5)	30 (8.8)
Asian	4 (1.3)	10 (2.9)
Native American	15 (4.8)	14 (4.1)
County of Residence, n (%)		
Fresno	146 (46.8)	132 (38.6)
Kern	99 (31.7)	136 (39.8)
Tulare	67 (21.5)	74 (21.6)
Education, n (%)		
< 12 years	58 (18.6)	35 (10.2)
12 years	80 (25.6)	69 (20.2)
>12 years	174 (55.8)	238 (69.6)
Smoking packyears[1], n (%)		
0	167 (53.5)	147 (43.0)
>0 to <10	62 (19.9)	75 (22.1)
≥10 to <40	53 (17.0	77 (22.7)
≥40	30 (9.6)	40 (11.8)

[1]Missing packyear data for smokers (n=3)

Table 2

Association between statin use and Parkinson's disease

	Cases n (%) n=312	Controls n (%) n=342	Odds Ratio[1] (95 % CI)	Odds Ratio[2] (95% CI)
Statin Use				
Never	276 (88.5)	267 (78.1)	1	1
Ever	36 (11.5)	75 (21.9)	0.43 (0.28, 0.66)	0.45 (0.29, 0.71)
Duration of Statin Use				
0 yrs (nonusers)	276 (88.5)	267 (78.1)	1	1
≤1 year	11 (3.5)	19 (5.6)	0.54 (0.25, 1.17)	0.55 (0.25, 1.21)
1<x <5 years	14 (4.5)	27 (7.9)	0.45 (0.23, 0.88)	0.47 (0.23, 0.94)
≥5 years	11 (3.5)	29 (8.5)	0.33 (0.16, 0.68)	0.37 (0.18, 0.78)
p- trend			<.01	<.01

[1] Odd ratios adjusted for age, sex, and race

[2] Odds ratios adjusted for age, sex, smoking packyears, race, education, county