Statin Use and Its Association with Essential Tremor and Parkinson’s Disease

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Abstract

\textbf{Background:} Statins have potent anti-inflammatory and immunomodulating effects, and may have neuroprotective properties in patients with Parkinson’s disease (PD). There are no studies about the use of statins in the related tremor disorder, essential tremor (ET). We determined whether statin use differed in ET cases vs. controls and PD cases vs. controls. \textbf{Methods:} One hundred and thirty nine ET cases, 108 PD cases, and 124 controls participated in a research study of the epidemiology of movement disorders. They were frequency matched based on age and gender. Statin use was assessed by self-report. \textbf{Results:} In adjusted logistic regression analyses, statin use (current or ever) was inversely associated with PD (ORs 0.56–0.63), with marginal values (p values = 0.07–0.187). In similar adjusted models, ET was not associated with statin use (p values = 0.45–0.50). However, ET was inversely associated with longer-term statin use (adjusted OR 0.27, p values = 0.04–0.048). \textbf{Conclusions:} We observed a marginally significant inverse association between PD and statin use. Although in primary analyses we found no evidence that statin use was protective in ET, there was an inverse association in analyses that assessed longer term use of statins. Further observational studies are warranted.

Introduction

Statins have potent anti-inflammatory and immunomodulating effects, thereby leading to the hypothesis that these agents have neuroprotective properties [1, 2]. A sizable number of studies have examined the association between statin use and odds or risk of Parkinson’s disease (PD), and these have generated mixed results [3–6]. Thus, in a study in Denmark of 1,931 PD patients and 9,651 matched controls, there was an inverse association between PD diagnosis and short-term (≤ 1 year) statin use. However, longer duration statin use was not associated with PD [3]. There was no association between PD and statin use in a case–control analysis using the United Kingdom-Based General Practice Research Database [6]. However, long-term statin use (≥5 years) was inversely associated with PD in a sample of 312 PD patients and 342 controls from 3 rural California counties [5]. Attempting
to summarize data from eleven studies, a recent meta-analysis concluded that statin use was associated with a reduced risk of PD (summary relative risk = 0.81, 95% CI 0.71–0.92) [7].

Essential tremor (ET) is a tremor disorder that shares a number of clinical and etiological features with PD [8–11]. Furthermore, in some postmortem studies, ET cases have a preponderance of Lewy bodies compared to age-matched controls [12]. Hence, a number of studies have examined risk factors for PD among ET cases [13, 14]. Yet to our knowledge, there have been no studies of the use of statins in ET. Our goal was to determine whether statin use differed in ET cases vs. normal controls. We also enrolled a group with PD, comparing them to controls as well. These analyses capitalized on the enrollment of patients with ET and PD as well as controls in research study of the epidemiology of movement disorders [15].

Methods

Participants and Evaluation

ET cases, PD cases, and controls were enrolled in a study of the epidemiology of movement disorders at Columbia University Medical Center (CUMC; 2009–2014) [15]. All cases had received a diagnosis of ET or PD from their treating neurologist, one of the movement disorder neurologists at the Neurological Institute, CUMC. To facilitate enrollment, ET and PD cases were confined to those living in a geographical area within 2 h driving distance of CUMC [10]. One of the authors (E.D.L.) reviewed the office records of all selected ET and PD cases, and confirmed the diagnoses of PD using published diagnostic criteria [16]. ET cases also underwent a videotaped tremor examination and diagnostic confirmation as described further below.

Controls were recruited during the same time period as cases. These controls were identified using random digit telephone dialing within a defined set of telephone area codes represented by the cases within the New York Metropolitan area, and were selected from the same source population as the cases. During recruitment, controls were frequency-matched to ET cases based on age. The CUMC Internal Review Board approved all study procedures. Written informed consent was obtained upon enrollment.

During the in-person evaluation, conducted on all ET cases, PD cases and controls, the trained research worker administered clinical questionnaires (medical history and medications). This included a 10–15 min, 30-item, structured questionnaire that elicited data on history of statin use. This medication questionnaire was similar to the one used in an earlier study [17] investigating non-steroidal anti-inflammatory medications among ET cases. The questionnaire initially asked, ‘Do you currently take medications to lower your cholesterol?’ and ‘In the past did you ever take medications for cholesterol?’ If they answered ‘no’ to both questions, the questionnaire was terminated. If they answered ‘yes’ to either question, we then further asked about the prescription of the common types of statin medication, duration of use, and current and highest dose ever prescribed in mg. Also, we categorized statins into lipophilic (e.g. atorvastatin, simvastatin, and pitavastatin) and hydrophilic (e.g. rosuvastatin, fluvastatin, and pravastatin), as lipophilic statins cross the blood brain barrier and demonstrate a neuroprotective role [18, 19]. Furthermore, we investigated whether statin use for up to 12 years was associated with PD or ET; this was based on a published study demonstrating a neuroprotective role of statin use in this time frame [20].

Medical comorbidity was assessed using the Cumulative Illness Rating Scale (CIRS), in which the severity of medical problems (0 (none)–3 (severe)) was rated in 14 body systems (e.g. cardiac, respiratory) and a CIRS score was assigned (range 0–42 (maximal co-morbidity)) to each participant [21]. Years since the time of last hospitalization, a measure of medical comorbidity, was also assessed. Tobacco exposure was assessed, and cigarette smoking was calculated in pack years; participants who never smoked were assigned ‘0’ for pack years. We also recorded whether the participant had a diagnosis of diabetes mellitus, which has been associated with statin use [22]. Furthermore, with the subject standing, measurements were taken of body weight to the nearest 0.1 pound using a balance scale designed for field surveys (Scale-Tronix 5600, White Plains, N.Y., USA). Height was measured to the nearest 0.5 cm using a movable anthropometer (GP Martin Type, Pfister Inc., Carlstadt, N.J., USA). Body mass index (BMI) was calculated as weight in kg divided by the square of height in meters.

All ET cases and controls also underwent a standardized videotaped tremor examination, which included tests of postural and kinetic tremors and assessments for the presence of other involuntary movements. The aim was to use the videotape to carefully validate ET diagnoses and lack thereof in controls) using rigorous research-grade diagnostic criteria [23]. Thus, each videotape was reviewed by a senior neurologist specializing in movement disorders (E.D.L.) who confirmed the ET diagnoses using Washington Heights-Inwood Genetic Study of ET (WHIGET) diagnostic criteria (moderate or greater amplitude kinetic tremor (tremor rating ≥2) during 3 or more tests or a head tremor, in the absence of PD, or another cause) [23]. The WHIGET tremor rating scale was also used to rate postural and kinetic tremor during each test: 0 (none), 1 (mild), 2 (moderate), 3 (severe). These ratings resulted in a total tremor score (range 0–36).

Final Sample Selection

To frequency match by age and gender across all 3 diagnostic groups, we excluded 82 (18.1%) of 453 enrollees. This matching was performed by selecting a group of individuals in each of the 2 remaining diagnostic groups (PD, controls) whose age and gender conformed to the distribution observed in the ET cases. This matching was performed within each diagnostic category blinded to all data other than age and gender. The final sample included 371 enrollees: 139 (100%) of 139 ET cases, 108 (80.6%) of 134 PD cases, and 124 (68.9%) of 180 controls.

Statistical Analyses

Analyses were performed using the statistical software package SPSS (version 21.0; SPSS, Inc., Chicago, Ill., USA). We compared demographic and clinical characteristics across the 3 diagnostic groups (PD, ET, controls; table 1). When variables were not normally distributed (i.e. Kolmogorov–Smirnov test statistic p value <0.05), non-parametric tests were used. When a difference was
detected across the 3 groups, we further compared each diagnostic group to controls (i.e. ET vs. controls, PD vs. controls). All tests were 2-sided, and significance was accepted at the 5% level. To assess the relationship of ET and PD to statin use we used logistic regression analyses. We first assessed whether statin use (current or ever) was associated with either ET or PD. Also, we categorized statins into lipophilic (e.g. atorvastatin, simvastatin, and pitavastatin) and hydrophilic (e.g. rosuvastatin, fluvastatin, and pravastatin), as lipophilic statins cross the blood brain barrier and demonstrate a neuroprotective role. We then assessed whether long-term statin use (i.e. for up to 12 years) was associated with ET or PD. We also used an alternative cut point for long-term statin use (i.e. for up to 10 years). In these logistic regression analyses, we began with an unadjusted model. Then, in adjusted models, we first considered variables that were associated with both the movement disorder and with statin use (‘conservative model’ (more restrictive criteria for confounding)) and then considered variables that were associated with either the movement disorder or with statin use (‘liberal model’ (less restrictive criteria for confounding)) at a p < 0.05 level. These analyses generated ORs with 95% CIs. Given the large number of comparisons in the secondary analysis of specific statin medications (n = 8; table 2), a significant p value for the secondary analysis was conservatively set at <0.006 (i.e. 0.05/8); in this analysis, p values between 0.006 and 0.05 were viewed as marginally significant. In other analyses, a Mann–Whitney U test was used to determine whether total tremor score in ET differed between categories of statin use (current or ever use – yes vs. no). Furthermore, we used a Spearman’s correlation coefficient to assess the relationship between tremor severity (i.e. total tremor score) in ET and duration of statin use in years.

Study Power
Using published data on the use of statins in PD cases vs. controls (17% of PD cases and 34% of controls used cholesterol lowering drugs) [4], we determined that a sample size of 103 per group would provide us with 80% power (assuming alpha = 0.05). Thus, our sample of 139 ET, 108 PD and 124 controls (mean = 124 per group) was adequately powered to detect case–control differences similar to those reported previously.

Results
The 3 groups were similar with respect to age, gender, education, cigarette pack years, BMI, and a variety of additional clinical features (table 1). The total number of prescription medications was significantly higher in PD and ET cases than controls (table 1).

The groups were similar with respect to the use (ever) of statins and with respect to the use (current) of statins (table 2). The duration of statin use was no different in ET and PD cases than controls. However, a significantly lower proportion of ET cases than controls had used statins for up to 12 years (chi-square test = 5.60, p = 0.018) and for up to 10 years (chi-square test = 7.34; p = 0.007; table 2). When comparing the 3 groups with respect to the proportion that used each type of statin, there were no group differences (table 2).

Using our control sample, we compared statin users vs. non statin users (table 3). Statin users are older, more likely to be male, had more cigarette pack years, took more prescription medications, had higher CIRS scores, and were marginally more likely to have diabetes mellitus (table 3).
In an unadjusted logistic regression analysis, statin use (current or ever) was not associated with either PD or ET (Table 4). In adjusted logistic regression analyses, statin use (current or ever) was inversely associated with PD (OR 0.56 (conservative model) and OR 0.63 (liberal model)), with marginal values (p-values = 0.07–0.18; Table 4). In adjusted models, ET was not associated with statin use (p-values = 0.45–0.50; Table 4). However, ET was inversely associated with statin use for up to 12 years (OR 0.28 (unadjusted model), OR 0.27 (conservative model)).
model) and OR 0.27 (liberal model), p values = 0.03–0.048; table 4). Using an alternative cut point for long-term statin use (i.e. for up to 10 years), it was found that the association with ET was even more robust (OR 0.27 (unadjusted model), OR 0.27 (conservative model) and OR 0.26 (liberal model), p values = 0.01–0.02; table 4). By contrast, PD was not associated with such long-term statin use.

Tremor severity (i.e. total tremor score) was not associated with the category of statin use (yes vs. no (current or ever)) (OR 1.10, 0.66–1.85, p = 0.71; table 4).

Table 4. Logistic regression analysis of statin use in PD and ET

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Unadjusted model</th>
<th>Liberal adjusted model</th>
<th>Conservative adjusted model</th>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>significance</td>
</tr>
<tr>
<td>Statin use (current or ever)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PD</td>
<td>1.10</td>
<td>0.66–1.85</td>
<td>0.71</td>
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<tr>
<td>ET</td>
<td>1.25</td>
<td>0.77–2.04</td>
<td>0.36</td>
</tr>
<tr>
<td>Controls</td>
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<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Statin use (current or ever) (lipophilic)</td>
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<td></td>
<td></td>
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<tr>
<td>PD</td>
<td>1.11</td>
<td>0.66–1.90</td>
<td>0.68</td>
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<tr>
<td>ET</td>
<td>0.99</td>
<td>0.60–1.63</td>
<td>0.96</td>
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<tr>
<td>Controls</td>
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<td>1.00</td>
<td></td>
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<tr>
<td>Statin use (current or ever) (hydrophilic)</td>
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<tr>
<td>PD</td>
<td>0.85</td>
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<td>0.72</td>
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<tr>
<td>ET</td>
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<td>0.63</td>
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<tr>
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<tr>
<td>Statin use for up to 12 years</td>
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<tr>
<td>PD</td>
<td>0.48</td>
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<tr>
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<td>0.09–0.85</td>
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<tr>
<td>Controls</td>
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<td>1.00</td>
<td></td>
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<tr>
<td>Statin use for up to 10 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>0.53</td>
<td>0.17–1.67</td>
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<tr>
<td>ET</td>
<td>0.27</td>
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<td>0.01</td>
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<tr>
<td>Controls</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
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</tbody>
</table>

1 Adjusted for number of prescription medications, age in years, gender, pack years (cigarettes), and CIRS.
2 Adjusted for number of prescription medications.

Values are mean ± SD (median) or number (percentage).

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differed in ET cases and controls. There was evidence that current nutritional antioxidant exposure was associated with ET. In that study, there was no hypothesis that diminished use of nutritional antioxidants was associated with ET. Conducted detailed dietary assessments and tested the hypothesis that statistical significance (p = 0.07). This inverse association between PD and statin use has been previously observed in larger studies [5, 7]. ET was not associated with statin use (current or ever); however, there was an inverse association in an analysis that assessed longer-term use of statins.

ET is a chronic, progressive neurological disease; it may even be a family of diseases. The biological mechanisms that underlie ET are not entirely clear although there is considerable evidence to support neurodegenerative mechanisms [24–26]. Whether the specific mechanisms involve oxidative stress or neuroinflammation is not known, although it was with this possibility in mind that we chose to examine the association between statin use and ET. Statins may reduce oxidative stress and neuroinflammation. Their links with PD, along with the links between PD and ET, provided a rationale to study their use in ET in these analyses [11, 27]. In our primary analyses, we did not find evidence of an association between ET and statin use; however, in an analysis that assessed longer-term use, there was an inverse association. In a prior study of 156 ET cases and 220 controls, we conducted detailed dietary assessments and tested the hypothesis that diminished use of nutritional antioxidants was associated with ET. In that study, there was no evidence that current nutritional antioxidant exposure differed in ET cases and controls [28]. Further studies are warranted.

Discussion

We investigated whether ET or PD was associated with statin use. In an adjusted model, PD was inversely associated with statin use (current or ever, OR 0.56), but with marginal statistical significance (p = 0.07). This inverse association between PD and statin use has been previously observed in larger studies [5, 7]. ET was not associated with statin use (current or ever); however, there was an inverse association in an analysis that assessed longer-term use of statins.

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References

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