Plasma Cholesterol and Parkinson’s Disease: Is the Puzzle only Apparent?

Recent articles (two in Movement Disorders) have provided conflicting results regarding the association between plasma cholesterol levels and risk of Parkinson’s disease (PD). In a case-control study on 124 consecutive idiopathic PD patients, blood cholesterol was significantly lower in PD patients than controls. The authors hypothesized an etiological role of low cholesterol in the development of PD. Paradoxically, they also found that 17% of cases vs. 34% of controls used statins, and further suggested that statin use may have a neuroprotective effect against PD.

It appears to us that the word “association” is being interpreted too strongly and that causes and effects are being confounded. Lower cholesterol levels and less frequent use of statins may be “associated” with PD, but this does not imply a causal relationship. In a similar case-control study, we found that PD patients had lower blood glucose and lipid levels, and lower frequency of diabetes and hypertension than controls: applying the logic of the authors cited above we would conclude that high glucose and lipids, presence of diabetes and hypertension, or even use of glucose-lowering and blood pressure-lowering drugs, were protective against PD. However, we thought it better to explain our results as an effect of the chronic illness which damages the autonomic system, resulting in reduced sympathetic activity with decrease of circulating levels of catecholamines and cortisol. Because physiologically these substances have diabetogenic and hypertensive effects and also increase plasma lipids, their reduction is likely to be an important cause of the reduced frequencies of diabetes and hypertension, and lowered glucose, cholesterol and triglycerides seen in PD patients.

Nevertheless, because cholesterol is an essential constituent of neuronal cell membranes, it is possible that cholesterol homeostasis plays an etiological role in PD. Investigation of cholesterol levels before disease onset might elucidate such a relationship, because any cholesterol alterations at that stage are unlikely to be caused by autonomic damage. Large prospective population-based studies have examined the association between plasma cholesterol and incident PD. Some found increased risk of PD in persons with high total cholesterol at baseline, others found increased risk of PD in those with low cholesterol.

In the study of Hu et al., PD cases were identified by use of anti-PD drugs reported in the National Insurance Register, which entitles patients to medications free of charge. The diagnosis of PD is often difficult, even for neurologists trained in extrapyramidal disorders, and typically requires follow-up or neuroradiological investigations for confirmation. Furthermore, free-of-charge drugs would not be denied patients with multiple system atrophy or vascular Parkinsonism, so the study may well have included such patients.

Inadequate diagnostic criteria for PD may also have been used in the study of Huang et al., where PD cases were identified from hospital records, death certificates, and self-reported histories of parkinsonism (only the latter confirmed by a neurologist). The study, confined to men, found 41 incident cases of PD, with average age at onset 79.3 years (range 73–89). The mean age at onset of PD is approximately 60 years. Since parkinsonisms and other neurodegenerative disorders are increasingly frequent over 65 years, it is likely that the authors studied the association of cholesterol with parkinsonisms, and not idiopathic PD.

In the well-conducted study of de Lau et al., the age of PD onset was not stated, but mean age at baseline was 69 years, and 87 new PD cases were diagnosed over the 9.4 years of follow-up. It is evident therefore that these patients were rather old, and late-onset PD could well differ from the common form of PD. The authors reported that high plasma cholesterol was associated with decreased risk of PD in women, but not men. Interestingly, they pointed out that: “as the intact blood-brain barrier is impermeable to cholesterol-transporting lipoproteins and most brain cholesterol is synthesized in situ, it is [...] unclear whether serum cholesterol levels reflect changes in cholesterol metabolism in the central nervous system.”

We conclude that the available prospective population-based studies fail to provide compelling evidence that altered cholesterol metabolism is involved in PD genesis, and that the hypothesis should either be abandoned or be investigated by approaches that include only carefully diagnosed cases of idiopathic PD.
Neuropathy as a Potential Complication of Levodopa Use in Parkinson’s Disease: A Pharmacological and Pharmacovigilance Point of View

We read with great interest the paper from Toth et al., suggesting that long-term treatment with levodopa (l-dopa) could induce peripheral neuropathy. This conclusion derived from a study of 500 parkinsonian patients with symptomatic neuropathy, among which a relatively high number (34, i.e., 6.8%) suffered from idiopathic neuropathy. The authors suggest involvement of l-dopa in these 34 cases of peripheral neuropathy, among which a relatively high number (34, i.e., 6.8%) suffered from idiopathic neuropathy. The fact that among such a database including 1,110 case reports of neuropathy, sensory peripheral neuropathy, ‘‘sensory peripheral neuropathy,’’ and ‘‘motor peripheral neuropathy,’’ we found 1,110 case reports of neuropathy (among a total of 174,341 ADRs) notified to the French Network of Pharmacovigilance Centres between 1st January 1985 and 30th April 2005.

Among these 1,110 case reports, only three included l-dopa as a ‘‘suspect’’ drug (according to WHO definition). The first observation described a 71-year-old man suffering from Parkinson’s disease and treated by l-dopa (250 mg 4 tid) since 6 years but also receiving vinorelbine for a metastatic vesical cancer. Peripheral neuropathy occurred 6 weeks after the first administration of vinorelbine, allowing final imputation of vinorelbine [causality assessment (imputation) of levodopa = excluded]. The second case report was an 85-year-old parkinsonian woman treated by levodopa (200 mg daily) and piribedil (100 mg daily) for 1 year plus trinitrine (10 mg daily) and furosemide (20 mg daily) for angina and arterial hypertension, who developed a peripheral sensitive-motor polyneuropathy. All aetiological investigations remained negative. Causality assessment (imputation) of l-dopa was found to be ‘‘doubtful’’ (II). The third case report was a peripheral sensory neuropathy in a 76-year-old parkinsonian woman treated by l-dopa (1,000 mg daily since 14 years), bepridil (300 mg daily since 7 years), and tricalcic phosphate (2,400 mg daily as adjuvant for osteoporosis); no specific cause of neuropathy was found. Bepridil involvement was suspected; Causality assessment (imputation) of l-dopa was found to be ‘‘doubtful’’ (II).

None of these observations suggests a decisive role of l-dopa in the development, worsening, or revelation of peripheral neuropathy. The fact that among such a database including such high number of ADRs (and more than 170,000 patients) during such a long period (more than 25 years), only three cases listed l-dopa in patients suffering from peripheral neuropathy, suggest that l-dopa does not belong to drugs frequently leading to peripheral neuropathy. Moreover, level of causality assessment (imputation) remained low (excluded for the first case and “doubtful” for the two others).

In conclusion, we consider, as pharmacologists specialized in drug safety, that there is, inside the FPVD, no signal of l-dopa-induced neuropathy. Moreover, literature remained poorly informative about this putative l-dopa ADR. Finally, prevalence of l-dopa-induced neuropathy does not appear to be so elevated as related by Toth et al., but should be considered (if it really does exist) as ‘‘very rare.’’

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Author roles: ACD, GD, IL, PO, AS performed the study in the FPVD. JLM and JMS analyzed the data. JLM wrote the manuscript.

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Mortality in Parkinson’s Disease, a 20-Year Follow-Up Study

We wish to thank Dr. Rajput and coworkers1 for their interest in our article and their valuable contribution to the discussion on mortality in Parkinson’s disease.2 Based on their comments, we add here the information on disease duration at entry in our study (time of diagnosis), which was 2.11 years on average (standard deviation 2.4).

In addition, they raised two concerns with our study: First, they correctly point out that measuring survival as the difference between age at death or at a censor date and age at symptom onset can cause survival in PD cohorts to appear better than that of a control population because it does not take into account the fact that patients may have died after symptom onset but before being diagnosed at a given center performing such a study. Although this is correct in principle, there is, to the best of our knowledge, no method that would satisfactorily handle this problem.

Measuring survival from the time of diagnosis only leads to an opposite bias where observed person-years at risk in the PD cohort would be underestimated, thus inflating SMR’s for PD—as illustrated in Rajput and coworkers own data.3 In fact, most previous studies4-6 on mortality and survival in PD have used a similar approach as was used in our study.

Secondly, Rajput and coworkers point out that it is hard to explain why PD patients should have a survival advantage over the general population. Again, we agree, in fact, the SMR of 0.6 observed in our cohort after the first 5 years of disease has a wide confidence interval ranging between 0.4 and 1.0 and considering an SMR of 0.9 after 10 years of disease duration, our conclusion was that patients with PD had similar survival compared with the general population up to a disease duration of 10 years. We never made a claim of “supernormal” life expectancy in early PD.


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Mixed Tremors with Integrity of Nigrostriatal System: A Clinical and DAT-SPECT Follow-Up Study

Mixed tremor, i.e., the combination of postural and resting tremor, may occur either as the sole clinical manifestation (isolated mixed tremor) or as predominant feature associated with other mild extrapyramidal signs (mixed tremor plus), posing diagnostic challenges.

A normal DAT scan in patients with mixed tremor supports the diagnosis of essential tremor (ET) but it is still unknown whether these patients may develop Parkinson’s disease (PD) over time. In this study, a sample of patients referred to our movement disorders clinic with isolated mixed tremor or with mixed tremor plus, and normal DAT-SPECT imaging were followed-up for a long period of time to assess their disease course and the possible evolution into PD. This study is part of a more extensive research project on mixed tremors; data concerning differential diagnosis among patients with mixed tremors have already been published.1

Study population consisted of 15 patients with mixed tremor, including 7 patients with isolated mixed tremor and 8 patients with mixed tremor plus, and of 15 age and sex-matched control subjects. Clinical characteristics of tremor and other extrapyramidal signs were accurately assessed by specialists in movement disorders. Family history was considered positive when a first-degree relative was reported to have a diagnosis of ET or PD. Iatrogenic or metabolic causes of tremor and additional dystonic features were excluded in all patients, as well as any history of cerebrovascular diseases, other degenerative neurological diseases or intracranial lesions in brain MRI. Demographic and clinical data were collected when patients performed DAT-SPECT for the first time (baseline evaluation), according to a standardized procedure, and at follow-up examinations. All patients were evaluated clinically every 6 months, up to 60 months, by the same physician, blinded to the DAT-SPECT results. In addition to the baseline, a second imaging study was performed in all patients after an interval period of 40±13.66 months (mean ± SD; range: 18–60 months). The study was approved by the Institutional Ethics Committee, and all participants gave written informed consent.

Demographic and clinical characteristics of the patients with mixed tremor, isolated or plus, and of the control subjects, at baseline evaluation, are listed in Table 1. DAT-SPECT binding values were within the normal range of values at baseline in both groups of patients with mixed tremor and in control subjects. Duration of follow-up, expressed as mean ± SD, was 37.43 ± 14.1 months in isolated mixed tremor patients and 42.25 ± 13.8 months in mixed tremor plus patients (P = 0.480). Clinical and DAT-SPECT findings of both mixed tremor groups did not significantly differ between baseline and follow-up evaluation (Table 2).

Mixed types of tremor are not uncommon and evidence that resting tremor may also be part of the manifestations of ET raises clinical diagnostic difficulties.3 It has been speculated whether resting tremor in a proportion of patients with ET may represent an early symptom of PD. DAT-SPECT imaging allows differential diagnosis between ET and PD helping in the accurate diagnosis of these tremor disorders. Some studies have investigated the usefulness of DAT-SPECT in patients with isolated mixed tremor showing that about a half of them had an intact nigrostriatal system.4,5 Interestingly, isolated mixed tremor patients investigated in the aforementioned study,4 continued to present only tremor at a 2-years clinical follow-up, thus, suggesting a diagnosis of ET but a DAT-SPECT imaging follow-up evaluation was lacking. The presence of other neurologic signs in patients with mixed tremor increases the diagnostic uncertainty raising the chances of misdiagnoses of ET with PD and vice versa. A very few studies investigated the integrity of the nigrostriatal system in patients with mixed tremor plus showing a normal putaminal uptake in a proportion of these patients.1,6 Lack of follow-up studies, however, makes the clinical evolution of mixed tremor plus over time still unknown. Our study demonstrates that patients with mixed tremor, either isolated or plus, maintained the integrity of nigrostriatal system even after 5 years of follow-up, suggesting that the diagnosis of ET is not ruled out by the presence of resting tremor, or other additional extrapyramidal signs such as mild bradykinesia, or rigidity.

There are several possible explanations for the presence of resting tremor or other extrapyramidal signs in ET patients with integrity of the dopaminergic striatal system. First, the pathological process that is responsible for their ET features, such as postural and kinetic tremor, may spread into motor systems outside of the cerebellum/cerebellar outflow connections and, more specifically, into the basal ganglia and/or their connections.

Second, the extrapyramidal features in ET may be the only clinically detectable signs of basal ganglia involvement due to a coexistent Lewy body pathology. Indeed, the reported presence of Lewy bodies in some ET cases7 is intriguing and may explain the apparent clinical links between ET and PD.8

Additional studies in a larger cohort of patients with mixed tremor isolated or associated with mild extrapyramidal features and with a longer period of follow-up are warranted.

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TABLE 1. Clinical characteristics of patients with mixed tremor and control subjects at baseline evaluation

<table>
<thead>
<tr>
<th>Findings</th>
<th>Mixed tremor (n = 15)</th>
<th>Isolated (n = 7)</th>
<th>Plus (n = 8)</th>
<th>Control subjects (n = 15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at examination</td>
<td>66.14 ± 10.9</td>
<td>68.00 ± 7.5</td>
<td>63.47 ± 7.2</td>
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<td>0.443b</td>
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<tr>
<td>Male n (%)</td>
<td>5 (71.4)</td>
<td>3 (37.5)</td>
<td>8 (53.3)</td>
<td></td>
<td>0.500c</td>
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<tr>
<td>Age at onset</td>
<td>43.29 ± 19.0</td>
<td>57.00 ± 8.0</td>
<td>–</td>
<td></td>
<td>0.240b</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>19.14 ± 17.4</td>
<td>8.13 ± 6.7</td>
<td>–</td>
<td></td>
<td>0.314a</td>
</tr>
<tr>
<td>Familial history of ET n. (%)</td>
<td>5 (71.4)</td>
<td>3 (37.5)</td>
<td>–</td>
<td></td>
<td>0.312a</td>
</tr>
<tr>
<td>DAT-SPECT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left putamen</td>
<td>2.42 ± 0.1</td>
<td>2.54 ± 0.2</td>
<td>2.44 ± 0.2</td>
<td>0.263b</td>
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</tr>
<tr>
<td>Right putamen</td>
<td>2.43 ± 0.1</td>
<td>2.44 ± 0.1</td>
<td>2.45 ± 0.2</td>
<td>0.974b</td>
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</tbody>
</table>

DAT-SPECT = (123)I-FP-CIT-SPECT.

*Values are expressed in years as mean ± SD.

bOne-way ANOVA.

cMonte Carlo exact test.

dPutamen specific to non specific (occipital area) uptake ratio; values are expressed as mean ± SD.

ET: Essential tremor.

TABLE 2. Baseline and follow-up characteristics of patients with isolated mixed tremor and patients with mixed tremor plus

<table>
<thead>
<tr>
<th>Findings</th>
<th>Isolated mixed tremor</th>
<th>Mixed tremor plus</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Age at examination*</td>
<td>66.14 ± 10.9</td>
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