Published in final edited form as:
Mov Disord. 2007 February 15; 22(3): 377–381.

Lower low density lipid cholesterol levels are associated with Parkinson's disease

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Abstract

The apolipoprotein E (APOE) ε2 allele has been associated with both Parkinson's disease (PD) and lower low density lipoprotein cholesterol (LDL-C). The study is to test the hypothesis that lower LDL-C may be associated with PD. This case-control study used fasting lipid profiles obtained from 124 PD cases and 110 controls, the PD cases recruited from consecutive cases presenting at our tertiary Movement Disorder Clinic, and controls recruited from the spouse populations of the same clinic. Multivariate odds ratios (OR) and 95% confidence intervals (CI) were calculated from unconditional logistic regressions, adjusting for age, gender, smoking status, and use of cholesterol-lowering agents. Lower LDL-C concentrations were associated with a higher prevalence of PD. Compared with participants with the highest LDL-C (≥139 mg/dL), the OR was 2.2 (95% CI 0.9–5.1) for participants with LDL-C of 115–138, 3.5 (95% CI 1.6–8.1) for LDL-C of 93–114, and 2.6 (95% CI 1.1 – 5.9) for LDL-C ≤ 92. Interestingly, use of cholesterol lowering drugs or just statins was related to lower PD prevalence. Our data provide preliminary evidence that low LDL-C may be associated with higher occurrence of PD, and/or that statin use may lower PD occurrence; either of which findings warrant further investigations.

Keywords

Parkinson's disease; LDL cholesterol; apolipoprotein E; statin; case control study

Parkinson's disease (PD) is an age-related progressive neurodegenerative disorder affecting 1–2% of the population over the age of 60 years. The lifetime risk for PD is higher in men than in women.[1] Although a few PD cases are due to several known genetic mutations, the disorder is largely idiopathic, and likely involves interactions of the genome and the environment [2].

The role of apolipoprotein (APOE) in Alzheimer's disease (AD), another age-related neurodegenerative disease, has been elucidated in the past decade. It is generally believed that the ε4 allele is a major susceptibility gene, whereas the ε2 allele is protective for AD and possibly other neurological disorders [see review 3]. A recent systematic review, however,

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demonstrated that it is the ε2 allele, not the ε4 allele, that is positively associated with higher prevalence of sporadic PD.[4] This finding is not the first PD-related "paradox." For example, smoking, a factor known to be associated with cardiovascular diseases and adverse lipid profiles,[5] is consistently associated with decreased incidence of PD. [For example 6;7] In addition, the incidence of myocardial infarction and ischemic stroke is lower in PD patients. [For example 8;9]

Previous epidemiological evidence on dietary fats/cholesterol and PD risk has not been consistent.[10;11] Further, these studies are not directly relevant to the potential role of cholesterol in PD etiology, as non-dietary factors may play more important roles in regulating serum lipid levels. For example, the APOE ε4 allele has been associated with higher low density lipid cholesterol (LDL-C), whereas the ε2 allele has been consistently associated with lower plasma LDL-C.[12;13] Interestingly, there has been one published abstract reporting lower plasma cholesterol concentrations in PD patients than in controls.[14] Further, Musanti et al. [15] reported dramatically lower cholesterol biosynthesis in PD patients than in controls, although there has been no subsequent follow up on this association. The above evidence, coupled with the association between ε2 and PD, led us to test hypothesis that lower serum LDL-C may be associated with PD.

Methods

Participants

We conducted a case-control study to assess the relationship between serum cholesterol concentrations and the prevalence of PD. Consecutive PD patients (124 in total, 69 male and 55 female) who presented at the University of North Carolina (UNC) Movement Disorder Clinic between July 2002 and November 2004 were recruited for the study. Controls (110 in total, 50 male and 60 female) were recruited from the spouses of all patients (both PD cases and non-PD cases) in the Movement Disorder Clinic. All PD patients met the published criteria of idiopathic PD. [16] The unmatched controls were free of PD at the time of enrollment. The study protocol was reviewed and approved by the UNC Institutional Review Board (IRB), and written informed consent provided by all participants.

Data collection

If the participants already had a fasting lipid profile measured within the five years prior to enrollment, those data were obtained from the medical records. From the other participants, a fasting blood sample was obtained and analyzed at the UNC Hospitals Laboratories. Information on gender, age, smoking habits, and use of cholesterol-lowering agents and dopaminergic agents at the time of fasting cholesterol profiles was obtained from all participants. The duration of PD at time of fasting lipid profile testing was estimated from the date of PD diagnosis. Clinical history, interview, and laboratory data were all collected on standardized forms, manually entered into a password-protected database on a secure server, and then validated against source data prior to the final data analysis.

Statistical Analysis

Fasting concentrations of total cholesterol, LDL-C and HDL-C were divided into quartiles based on the distribution of the controls. Odds ratios (OR) and 95% confidence intervals were estimated by unconditional logistic regression, adjusting for age (by 5-year groups from age <45 to >80), gender, smoking (current, past, and never), and use of cholesterol-lowering drugs.

Results

The characteristics of cases and controls are presented in the Table 1. The mean age of diagnosis for cases are 63.7 (SD = 11.4). Among cases, the fasting cholesterol concentrations were determined on average 4.2 (6.1) years after diagnosis; and the concentrations were not related to either disease duration or the use of dopaminergic drugs. At the time of cholesterol measurement, 17% of the cases and 34% of controls used cholesterol lowering drugs, primarily statins (94.9%). Use of cholesterol-lowering drugs in this population was associated with a lower occurrence of PD, the multivariate OR was 0.36 (95% CI: 0.19–0.68) after adjusting for age, gender and smoking status. This association was found in both men and women and persisted after further adjusting for LDL-C concentration [OR=0.32 (95% CI: 0.17–0.63)]. Similar results were also obtained when we examined statin use separately: the ORs with and without further adjusting for LDL-C concentrations were 0.37 (95% CI: 0.19–0.72) and 0.41 (95% CI: 0.22–0.79) respectively. Lower concentrations of LDL-C were associated with higher occurrence of PD (Table 2). Although the sample size is too small for a detailed gender-specific analysis, an explorative analysis suggested similar results for both men and women. Similar results were obtained when participants using cholesterol-lowering drugs were excluded: the corresponding ORs were 2.4, 3.8 and 2.8 respectively. One possibility is that high LDL-C is associated with higher mortality, thus making competing risk of death an explanation for our findings. Therefore, we conducted a further post-hoc analysis by only including cases diagnosed before age 65 and appropriate controls, as the overall mortality among this group was presumably low. The association remained, and actually appeared stronger: comparing with the reference, the ORs for higher LDL categories were 2.7 (95% CI: 0.8–9.8), 3.0 (95% CI: 0.9–9.8), and 5.9 (95% CI: 1.6–22.4) respectively.

The results for total cholesterol were overall similar to those for LDL-C, but the associations tended to be weaker (Table 2). HDL-C concentration was not related to occurrence of PD.

Comment

In this case-control study, we found an association between lower LDL-C and higher occurrence of PD. As with any other epidemiologic study, the results are subject to potential biases. The incidence of PD in general population is low, making it difficult to conduct prospective studies on cholesterol levels and the risk of PD. As the first step to test our hypothesis, we conducted this preliminary case-control study. The study was retrospective in nature, and we could not make a causal inference between LDL-C, and/or statin use and risk of PD. Further, the study had a relatively small sample size, and thus limited statistical power. Nevertheless, these are clinically-relevant observations that deserve to be confirmed in larger prospective studies, and in other populations. Although cholesterol concentrations were not determined uniformly, and may result in some misclassifications, this misclassification should be random and might have underestimated the association between cholesterol and PD risk. We chose to recruit controls from the spouse population of our movement disorder clinics as the most practical way of accounting for unmeasured social, economic, and lifestyle issues, and this might also have contributed to an underestimation of potential association with disease.

Lower cholesterol (including total, LDL and HDL cholesterol) is sometimes associated with clinical and subclinical conditions, [17–19] especially inflammatory diseases [17;20] and malignancy. [18] This association, however, is not usually a strong one in chronic CNS neurodegenerative disorders like AD [21–23] Indeed, in spinal cord injury [24;25] there is higher total and LDL-cholesterol. Coupled with our finding of no relationship between LDL-C concentration and either disease duration or use of dopaminergic agents in our population, it seems unlikely that this association between LDL-C and PD was purely a consequence of the disease process or its treatment.

Another interesting finding is the much higher percentage of use of cholesterol-lowering agents (primarily statins) in the control versus PD subjects (PD men 20.3% vs. Control men 38.0%; PD women 12.7% vs. control women 30.6%). Some statins have been hypothesized to be protective against neurodegenerative diseases, [see reviews 26;27] although recent clinical trial data on Alzheimer's disease are less supportive.[28–30] Examining the protective effects of statins was not the primary aim of our study, but testing this hypothesis as it relates to PD (and elucidation of potential mechanisms) is of clinical importance. This would require much larger sample size, and stratification of subjects by the type of statin they were taking (e.g., according to blood-brain barrier penetration). On the other hand, if the association of lower LDL-C with PD is itself the critical mechanism, then the higher use of statins in the controls vs. cases reflects the different biology of the two groups rather than a protective effect on PD of the cholesterol-lowering agents.

In summary, study shows an association between lower LDL-C and PD occurrence. Either lower LDL-C levels are etiologically linked to PD risk, or cholesterol-lowering agents have a neuroprotective effect re. PD. We favor the former hypothesis, but these data make it critical to replicate our results in other populations, and to elucidate the underlying mechanism(s) that may be of profound importance in understanding the etiology of PD and its public health implications.

Acknowledgements

The authors thank Mr. Kirk James and Mr. Chad Kloekornc for help with data collection. The authors appreciate the thoughtful input of Dr. Frank Longo, and acknowledge the invaluable guidance and inspiration offered by Professor Pierre Morell before his untimely death.

Dr. Huang's effort was supported in part by NIH grant K23-AG21491. The General Clinical Research Center of the University of North Carolina School of Medicine (NIH grant RR000046) provided support for aspects of the clinical studies of these subjects. Dr. Chen's effort was supported by the Intramural Research Program of the NIH, the National Institute of Environmental Health Sciences.

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Table 1

Summary characteristics of cases and controls*

	All Participants	
	Cases	**Controls**
Number of Participants	124	112
Age (years)†	67.9 (10.4)	65.7 (10.9)
Women (%)	55 (44.4)	62 (55.4)
Disease duration	4.2 (6.1)	-
Use of Cholesterol Lowering Agents	21 (16.9)	38 (33.9)
Use on DA Agents	85 (68.6)	-
Smoking status	71 (57.3)	55 (49.1)
Never smokers	45 (36.3)	42 (37.5)
Past smokers	8 (6.5)	15 (13.4)
Current smoked		
Total Cholesterol (ml/dL)	191.6 (38.4)	200.7 (43.8)
LDL Cholesterol (ml/dL)	110.7 (31.0)	116.5 (37.1)
HDL Cholesterol (ml/dL)	54.6 (17.3)	54.4 (17.0)

* Means (standard deviations) are provided for continuous variables and numbers (proportions) are provided for categorical variables.

† Age of cases and controls were based at time of fasting lipid profile testing

*** The disease duration were calculated based at time of fasting lipid profile testing from the date of PD diagnosis.

Table 2

Odds Ratios of Parkinson's disease according to quartiles of serum cholesterol concentrations

	All Participants		Men		Women	
	Case/Control*	OR (95%CI)†	Case/Control	OR (95%CI)*	Case/Control	OR (95%CI)*
Total Cholesterol (ml/dL)						
224–335	25/28	1	7/10	1	18/18	1
199–233	14/28	0.6 (0.2–1.5)	6/14	0.6 (0.1–2.7)	8/14	0.7 (0.2–2.7)
170–198	48/28	2.2 (1.0–4.7)	28/9	6.3 (1.6–24.9)	20/19	1.5 (0.5–4.5)
94–168	37/27	1.7 (0.7–3.8)	28/16	3.5 (1.0–12.6)	9/11	1.3 (0.3–5.5)
LDL Cholesterol (ml/DL)						
138–224	16/28	1	5/12	1	11/16	1
115–137	30/28	2.2 (0.9–5.1)	17/13	4.0 (1.0–16.0)	13/15	2.0 (0.5–7.7)
93–114	44/26	3.5 (1.6–8.1)	25/8	7.7 (1.9–31.2)	19/18	2.9 (0.8–10.2)
36–92	33/27	2.6 (1.1–6.0)	21/16	3.6 (1.0–13.5)	12/11	3.4 (0.9–13.8)
HDL Cholesterol (ml/dL)						
20–41	27/27	1	25/19	1	2/8	1
42–51	35/28	1.5 (0.7–3.4)	22/14	1.0 (0.4–3.1)	13/14	3.4 (0.5–25.2)
52–66	37/28	1.5 (0.7–3.5)	17/8	2.0 (0.6–6.6)	20/20	1.6 (0.2–11.5)
67–107	25/27	1.0 (0.4–2.5)	5/7	0.4 (0.1–1.7)	20/20	1.6 (0.2–11.6)

*Numbers may not add up to total due to missing values

†Adjusted for age, gender (for overall only), smoking, and cholesterol lower agent use