Abstract

Parkinson's disease (PD) has many paradoxes. For example, although smoking is highly associated with cancer and cardiovascular disease, smoking is associated with a much lower risk of PD (which itself is associated with a lower occurrence of cardiovascular disease). Whereas the apolipoprotein E ε4 allele is associated with higher risk of Alzheimer's disease, the ε2 allele, rather than ε4, is associated with greater risk of PD (1). Because the ε2 allele also is associated with lower low density lipoprotein-cholesterol (LDL-C), we recently tested the *hypothesis that lower LDL-C concentration was positively associated with PD, first in a clinic based case-control study* (2; 3) *and then in the prospective Honolulu-Asia Aging Study* (4). The results from both studies supported this hypothesis. Concurrently, two independent prospective studies reported a similar association, one in the Rotterdam cohort (5) and the other in the Nurses' Health Study and the Health Professionals Follow-up Study (6). A third report whose case identification was based on national insurance data, however, offered a contradictory finding (7). There is yet no study examining the relationship between serum cholesterol and PD progression, although hyperlipidemia was found to be a significant prognostic factor for survival of patients with ALS (8). Cholesterol has a host of critical biological functions that range from roles in affecting cellular repair or degeneration (9-14) to being a neurosteroid precursor (15-18). Thus, it is possible that lower LDL-C is etiologically linked to PD and influences PD progression, and this hypothesis may have critical clinical and public health impact. We propose to test ***the hypothesis that lower plasma cholesterol may be associated with faster progression of PD.*** For this purpose, we plan to study the relationship between serum cholesterol values obtained at baseline visit and outcome data from the DATATOP and PRECEPT studies. Our aims are to:

Aim 1: Explore the association prospectively of baseline serum cholesterol and the time to require levodopa therapy of PD subjects in both the DATATOP and PRECEPT studies.

Aim 2: Explore the association prospectively between baseline serum cholesterol and other important clinical landmark(s) of PD progression [i.e. time to freezing of gait, time to death] in the DATATOP Study.

Aim 3: Explore the association between baseline serum cholesterol and both clinical (reflected as UPDRS scores) and radiographic progression [reflected as striatal uptake of [^{123}I]-2-β-carbomethoxy-3-β-(4-iodophenyl)tropanes] in PD in the PRECEPT study.

1. Huang X, Chen PC, and Poole C (2004) APOE-[varepsilon]2 allele associated with higher prevalence of sporadic Parkinson disease. *Neurology* **62**:2198-2202.
2. Huang, X., Miller, W.C., Mailman, R. B., Woodard, J. L. Chen P. C., Xiang, D., Murrow, R. W., and Wang, Y.-Z. Cardiovascularly "desirable" cholesterol levels associated with Parkinson's disease. Ann.Neurol. 58(Suppl. 9), S24. 2005.
3. Huang X, Chen H, Miller WC, Mailman R, Woodard JL, Chen P, Xiang D, Murrow RW, Wang YZ, and Poole C (2007) Lower LDL cholesterol levels are associated with Parkinson's disease: a case control study. *Mov.Disord.* **22**:377-381.
4. Huang X, Abbott RD, Petrovitch H, Mailman RB, and Ross GW (2008) Low LDL cholesterol and increased risk of Parkinson's disease: prospective results from Honolulu-Asia Aging Study. *Mov Disord.* **23**:1013-1018.
5. de Lau LM, Koudstaal PJ, Hofman A, and Breteler MM (2006) Serum Cholesterol Levels and the Risk of Parkinson's Disease. *Am.J.Epidemiol.* **164**:998-1002.
6. Simon KC, Chen H, Schwarzschild M, and Ascherio A (2007) Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. *Neurology* **69**:1688-1695.
7. Hu G, Antikainen R, Jousilahti P, Kivipelto M, and Tuomilehto J (2008) Total cholesterol and the risk of Parkinson disease. *Neurology*.
8. Dupuis L, Corcia P, Fergani A, Gonzalez De Aguilar JL, Bonnefont-Rousselot D, Bittar R, Seilhean D, Hauw JJ, Lacomblez L, Loeffler JP, and Meininger V (2008) Dyslipidemia is a protective factor in amyotrophic lateral sclerosis. *Neurology* **70**:1004-1009.
9. Vasan RS (1992) Lowering cholesterol and death due to accidents, suicides: unresolved issues. *Arch.Intern.Med.* **152**:414, 417.
10. Maes M, Delanghe J, Meltzer HY, Scharpe S, D'Hondt P, and Cosyns P (1994) Lower degree of esterification of serum cholesterol in depression: relevance for depression and suicide research. *Acta Psychiatr.Scand.* **90**:252-258.
11. Barres BA and Smith SJ (2001) Neurobiology. Cholesterol--making or breaking the synapse. *Science* **294**:1296-1297.

12. Thiele C, Hannah MJ, Fahrenholz F, and Huttner WB (2000) Cholesterol binds to synaptophysin and is required for biogenesis of synaptic vesicles. *Nat.Cell Biol.* **2**:42-49.
13. Lang T, Bruns D, Wenzel D, Riedel D, Holroyd P, Thiele C, and Jahn R (2001) SNAREs are concentrated in cholesterol-dependent clusters that define docking and fusion sites for exocytosis. *EMBO J.* **20**:2202-2213.
14. Bruses JL, Chauvet N, and Rutishauser U (2001) Membrane lipid rafts are necessary for the maintenance of the (alpha)7 nicotinic acetylcholine receptor in somatic spines of ciliary neurons. *J.Neurosci.* **21**:504-512.
15. Stoffel-Wagner B (2001) Neurosteroid metabolism in the human brain. *Eur.J.Endocrinol.* **145**:669-679.
16. Rouge-Pont F, Mayo W, Marinelli M, Gingras M, Le Moal M, and Piazza PV (2002) The neurosteroid allopregnanolone increases dopamine release and dopaminergic response to morphine in the rat nucleus accumbens. *Eur.J.Neurosci.* **16**:169-173.
17. Barrot M, Vallee M, Gingras MA, Le Moal M, Mayo W, and Piazza PV (1999) The neurosteroid pregnenolone sulphate increases dopamine release and the dopaminergic response to morphine in the rat nucleus accumbens. *Eur.J.Neurosci.* **11**:3757-3760.
18. Frank C and Sagratella S (2000) Neuroprotective effects of allopregnenolone on hippocampal irreversible neurotoxicity in vitro. *Prog.Neuropsychopharmacol.Biol.Psychiatry* **24**:1117-1126.