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EDITORIAL

Cholesterol Trafficking in the Brain

Are We Overlooking an Important Risk Factor for Parkinson Disease?

AU1 Giovanni Mario Pes, Yong-Moon Park, and Gian Pietro Sechi

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Association of High-Density Lipoprotein Cholesterol Variability and the Risk of Developing Parkinson's Disease
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Elevated plasma high-density lipoprotein (HDL) cholesterol levels have been regarded for decades as an important protective factor against cardiovascular disease.[1] Besides their popularly known antiatherogenic effect, via modulation of blood cholesterol trafficking, HDL cholesterol levels are directly involved in the proper functioning of many organs and tissues through activation of multiple antioxidant pathways and blunting of the inflammatory response.[2] In the field of neurology, elevated plasma HDL cholesterol levels have recently been associated with a decreased risk for developing neurodegenerative diseases, including Parkinson disease (PD), although results are controversial.[3]

A few early studies have reported an inverse association between plasma HDL cholesterol level and the risk of PD,[2,4] while other studies reported direct or null association.[5,6] In particular, a recent meta-analysis, recruiting 8 cohort studies and 3 case-control studies, did not find any significant association between HDL cholesterol and PD, although subjects with higher low-density lipoprotein cholesterol levels seemed less likely to develop PD compared with subjects with lower levels.[6] These inconsistent results may be explained in part by different recruitment strategies and intercohort heterogeneity, and these issues deserve more in-depth investigations across ethnically different populations. In addition, the potential confounding effect of age, sex, use of cholesterol-lowering agents, and variability of HDL cholesterol levels over time is unclear.[5,6]

In this issue of *Neurology*®, Park et al.[7] provide a longitudinal nationwide, population-based study using data from the National Health Insurance Service data and the National Health Check-Up hospitals considering the nearly entire South Korean population ≥65 years of age, aiming to investigate whether baseline plasma HDL cholesterol levels and their temporal variability were significantly associated with the onset of PD. In the study, the diagnosis of PD was very accurate, being based on the ICD-10-CM diagnostic code for PD and the national registration code for PD. The authors found that individuals in the lower quartile of HDL cholesterol levels at baseline were more likely to develop PD, confirming previous results of an inverse association between baseline HDL cholesterol levels and future disease risk. They also showed for the first time that an increased temporal variability of serum HDL was an independent predictor of PD development after adjusting for relevant potential confounders. These findings may have important implications for a better understanding of PD pathophysiology and considerable clinical relevance because a pharmacologic therapy with niacin or fibrates to raise HDL cholesterol levels[8] may potentially contribute to reducing the PD risk beyond the protective effect of this drug treatment on cardiovascular risk in general. Notably, diverse extrapyramidal symptoms, including parkinsonism, have been reported in alcoholic pellagra encephalopathy due to chronic niacin deficiency.[9]

The exact mechanisms by which an excess, long-term, visit-to-visit variability in some lipid parameters may portend an adverse outcome remain to be elucidated but may account for some of the discordant results observed in prior studies. In addition to the above-mentioned antioxidative and anti-inflammatory properties of HDL cholesterol that might contribute to preventing neurodegeneration in PD, a direct interaction between α-synuclein and cholesterol may be hypothesized, which may influence α-synuclein aggregation and accumulation.[3] In addition,

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the possibility of an as-yet unidentified confounding factor linked to both HDL cholesterol levels and PD might explain the proposed association found in this report and deserves to be mentioned.

Potential limitations are discussed in the study. Although in most populations PD has a male-biased incidence and low HDL cholesterol levels are more frequent in the male sex, the authors of this study did not find substantial differences between men and women with regard to the predictability of PD by HDL plasma levels. The absence of a sex difference in the studied cohort may be attributed, at least in part, to the unique female preponderance in PD reported in Asian populations, as well as to the lower mean HDL cholesterol levels in Korean women after 70 years of age.[10] Furthermore, elevated plasma HDL cholesterol levels may be associated with genetic variants such as mutations in the cholesterol ester transfer protein (CETP), which are very frequent in Asian populations. It is therefore possible that the top quartile of HDL cholesterol levels may be enriched in subjects carrying CETP gene variants associated with outliers in HDL cholesterol levels who may subsequently experience a lower risk of developing PD. Last, although patients with prior diagnosis of PD during the 4 years before recruitment were not included in the study, a concern remains about the possibility of reverse causality owing to the long prodromal phase of PD. The question may arise of whether the altered HDL cholesterol profile is a mere epiphenomenon of PD, a disorder with evident features of systemic involvement.

Despite these limitations, the study by Park et al. represents the only longitudinal report that has explored the effect of plasma HDL cholesterol variability on the appearance of clinical features of PD, providing new and important clues about the role of HDL cholesterol trafficking in this neurodegenerative disorder. A deeper understanding of the role of specific lipid classes and lipoproteins in the pathophysiology of PD may foster the identification of new disease-modifying treatments for this devastating disease.

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Disclosure

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