Apolipoprotein E Levels and Alzheimer Risk

Rasmussen et al[1] report, in this issue of *Annals of Neurology*, a large population-based study in which plasma levels of ApoE protein are linked to differential risk for Alzheimer disease (AD). The *APOE* gene has been linked to risk of AD for >2 decades, with individuals homozygous for the E4 allele having a >10 fold increased risk, and those with the protective allele, E2, about half the age-adjusted risk, compared to the most common allele, E3. Additionally, various polymorphisms in the promoter region appear to impact risk to a generally much smaller extent, leading to the possibility that both type and amount of apoE protein might be important in conferring risk. This idea was further supported by the observations that, in mouse models, apoE null mice are strongly resistant to developing amyloid β (Aβ)-related parenchymal and vascular AD-related pathological changes.[2,3]

The current study takes advantage of a longitudinal population-based study of >75,000 participants. In addition to demonstrating the expected robust effect of *APOE* genotype on risk for developing AD and all dementia, the data show a statistically significant $\sim$1.5$\times$ increased risk for AD associated with decreased plasma levels of apoE protein. This increased risk persisted after adjusting for genotype, age, and other potential confounds, including an effect for a common promoter polymorphism. Major strengths of the approach of this study were the large numbers of participants, no loss to follow-up, and a 4-year median follow-up interval after enrollment. Interestingly, the measures of plasma protein were performed well before diagnostic evaluation, so that the result implies a true biological risk factor rather than a consequence of disease state (although note the caveats mentioned below). The result agrees with a recent meta-analysis of 8 smaller studies, that (together) reanalyzed 2,250 controls and 1,498 AD cases, and similarly found a decrease in plasma apoE in AD cases.[4] Although it is unlikely that the effect will be of use in a clinical setting, the result is potentially important for several reasons. First, it further builds the case that apoE protein is an important mediator in the pathobiology of AD, and hence that therapeutics that manipulate apoE protein, or apoE protein clearance, may be of use. Second, large case–control studies have been employed in recent years for their power to explore genetic underpinnings of disease; the current study reinforces the power of large population-based studies to uncover effects in terms of biomarkers and natural history as well.

However, there are several concerns. Although the increased risk was still present after adjusting for the potential confounds, these confounds, *APOE* genotype and age, both strongly affect plasma apoE levels. The age range of participants included in this study (20s–80s) with median follow-up of 4 years is both a strength and a weakness, and conversion to dementia may be difficult to assess in large populations over a (relatively) short median follow-up. It is important to keep in mind several other caveats. ApoE is synthesized peripherally primarily in the liver, and in the central nervous system (CNS) primarily by glia including astrocytes. The compartments are believed to be distinct, with little or no crosstalk across the blood–brain barrier.[5,6] Even the type of lipoprotein particles found in the cerebrospinal fluid (CSF) are different than the type of particles found in the blood. It is unknown whether or how the lower plasma apoE levels observed to be associated with increased risk of dementia relate to CNS levels. Smaller studies suggest that CNS levels are not different between AD and control patients,[7,8] and the Alzheimer's Disease Neuroimaging Initiative data set shows the opposite effect—a relationship between elevated CSF apoE and cognitive decline.[9] Second, the *APOE4* genotype is associated with lower plasma levels of apoE protein,[10] probably due to different kinetics of peripheral turnover.[11] In the current study, lower plasma levels are associated with increased risk, even after accounting for genotype, but the size of the effect is much larger for genotype than protein level. Third, from a technical perspective, there may be concerns about enzyme-linked immunosorbent assay (ELISA) measurements in individuals of different genotypes, because Rasmussen et al show that their ELISA may not detect ApoE2, 3, and 4 protein levels equally well.[1] Finally, the results are surprising in the context of the animal literature, because in animal models lower ApoE levels are associated with decreased Aβ-related pathological changes in the CNS.[2,3] Although dissociations between human data and animal models of disease are certainly not uncommon, this potentially dichotomous result demands further exploration.

These concerns aside, taken at face value, the results from Rasmussen et al[1] open a new set of fascinating questions about how peripheral ApoE levels are related to dementia. Plasma ApoE levels reflect both synthesis

(peripherally, primarily in the liver) and clearance (again, peripherally, primarily in the liver). Is decreased synthesis or increased clearance reflective of underlying physiological properties that impact the CNS? Could peripheral apoE be part of the complex CNS–peripheral equilibrium of Aβ, with lower plasma apoE levels impacting to some extent CNS levels of Aβ or other molecules of importance in CNS function? Or might peripheral apoE levels reflect broader issues related to inflammation, or to cholesterol metabolism, either of which may be relevant in mediating a biological process that impacts likelihood of dementia? Rasmussen et al[1] provide an intriguing data set that motivates further exploration of these questions.

Potential Conflicts of Interest

Nothing to report.

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