Effect of plasma lipids and APOE genotype on cognitive decline
Fumihiko Yasuno, MD, PhD; Takashi Asada, MD, PhD

Introduction

The presence of an apolipoprotein E4 allele (APOE4) increases the risk of, and reduces the age at onset of, Alzheimer’s disease (AD) in a dose-dependent manner. Additionally, APOE4 carriers have been reported to have higher rates of cognitive decline than noncarriers before the diagnosis of mild cognitive impairment.

Apolipoprotein E (apoE) plays a significant role in cholesterol delivery to neurons and AD pathogenesis associated with amyloid beta (Aβ). The plasma level of apoE has been shown to depend upon the APOE genotype. In elderly individuals without dementia, the interactive effect of apoE and other plasma lipids on cognitive function has also been reported to vary, depending upon the APOE genotype.

A complex synergism of APOE4 and cerebrovascular pathology in cognitive function of the elderly has been reported. The detrimental effect of APOE4 may be exacerbated by synergistic preventable risk factors such as plasma apoE/lipids. With stratification by APOE allele status, we examined the effect of plasma apoE/lipids on...
longitudinal change in the cognitive function of community-dwelling elderly using the data from a 3-year follow-up study.

Three-year follow-up examinations of the effect of plasma apoE/lipids on cognitive function in the elderly

Participants were recruited in the present study from the “Tone Project” in Tone town, Ibaraki, Japan. A total of 1395 volunteers participated in the first baseline study between December 2001 and April 2002. Three years later, 622 of them who had no history of stroke during follow-up were able to be evaluated again between December 2004 and April 2005, and we used the results from those subjects tested twice. At the initial examination, all of the eligible subjects provided written informed consent for their participation in the study. This study was approved by the ethics committee of Tsukuba University.

All participants underwent the same cognitive assessment at the baseline and 3-year examinations using a set of four tests to measure the following cognitive domains: attention, memory, language, and reasoning. We evaluated attention by using the Japanese version of a Set-dependent activity,11 memory ability using the Category Cued Recall test,10 and language ability with a category fluency test.13 Abstract reasoning ability was evaluated with the Similarities subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R).14 The assessment for all of the cognitive domains used was described elsewhere.15 A composite cognitive score was computed from the four scores using the first component of the scores of principal component analysis.

Blood samples were collected from the subjects at fasting visits at the initial examination. Plasma levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC) were measured using standard enzymatic methods on routine automated chemistry systems. Plasma apoE levels were determined by turbidimetric immunoassay. Genomic DNA was used for APOE typing. Subjects were divided into two APOE groups by E4 status with E4+ (n=113) (genotypes ε2/ε3 [n=52], ε3/ε3 [n=457]) and E4- (n=109) (genotypes ε2/ε4 [n=56], ε3/ε4 [n=49] and ε4/ε4 [n=8]) to test for the influence of genotype on the association between lipids and cognitive function. The subjects in each category were divided into three strata according to the plasma concentrations of lipids. To examine the influence of plasma lipids on cognitive function, composite cognitive scores of the three strata of plasma concentrations were compared in E4- and E4+ groups separately by ANCOVA, with age, sex, years of education, Geriatric Depression Scale score, cigarette smoking, and medical history of diseases as covariates.

Cognitive scores were associated with plasma apoE level in both E4- and E4+, and the HDL level in E4-

The demographic data for the E4- and E4+ groups in the analysis of the effect of lipids/apoE on cognitive function are shown in Table I. There were no group differences in demographic characteristics, except for the cognitive score. Our finding of a higher cognitive score at 2002 and 2005 in the E4+ group is consistent with previous studies.15 Figures 1 and 2 show the median plasma concentrations of lipids for the three strata according to the tertiles of plasma levels of lipids/apoE, and the mean cognitive scores of the E4- and E4+ groups at 2002 and 2005 according to the three strata of plasma concentrations of lipids/apoE.

ANCOVA analysis evaluating the influence of lipids level on cognitive function showed a significant influence of the HDL level on composite cognitive scores at both 2002 and 2005 in the E4+ group (F2, 498=9.3, P<0.001 for 2002, F2, 498=9.3, P<0.001 for 2005). Subjects with higher HDL concentrations had higher cognitive scores. The effect size of the influence of the plasma HDL level on cognitive score was more than 0.01 (η2=0.04 for 2002, η2=0.04 for 2005). No such significant association was observed in the E4+ group (Figure 2).

A significant main effect of the apoE level was found by ANCOVA on composite cognitive scores at 2002 and 2005 in both of the E4- and E4+ group (F2, 498=11.3, P<0.001 for 2002, F2, 498=7.3, P=0.001 for 2005 in the E4-, and F2, 102=7.0, P=0.001 for 2002, F2, 102=4.0, P=0.02 for 2005 in the E4+). Subjects with higher plasma apoE concentration had higher cognitive scores in both groups. The effect size of the association of the plasma apoE level on these cognitive scores was more than 0.01 (η2=0.04 for 2002, η2=0.03 for 2005 in the E4-, and η2=0.12 for 2002, η2=0.07 for 2005 in the E4+).
Figure 1. Mean cognitive test score of each tertile groups of lipid levels in the ApoE4- group. a, data are mean after adjustment for age, sex, years of education, Geriatric Depression Scale score, cigarette smoking, and medical history of cardiovascular disease, diabetes mellitus, and hypertension; b, indicates significance at $P<.05$ after Bonferroni adjustment for multiple comparisons. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; TC, total cholesterol; apoE, apolipoprotein E.

| Cognitive score (Light 2002, Dark 2005) | Plasma lipid/apoE level (mg/dL) [median(min-max)] |
|----------------------------------------|-----------------------------------------------|
|                                       | HDL                                           |
|                                       | 41(25.0-47.0) b                               |
|                                       | 52(48.0-60.0) b                               |
|                                       | 69(61.0-138.0) b                              |
|                                       | ApoE                                          |
|                                       | 1.2(0.5-1.7) b                               |
|                                       | 2.2(1.8-3.0) b                               |
|                                       | 3.8(3.1-10.5) b                              |
|                                       | LDL                                           |
|                                       | 73(25.6-87.0)                                 |
|                                       | 99(88.0-116.0)                                |
|                                       | 134.0(117.0-350.0)                            |
|                                       | TG                                            |
|                                       | 85(32.0-119.0)                                |
|                                       | 148.0(120.0-183.0)                            |
|                                       | 258(184.0-921.0)                              |
|                                       | TC                                            |
|                                       | 169(95-190)                                  |
|                                       | 205(191-220)                                 |
|                                       | 240(221-360)                                 |
Figure 2. Mean cognitive test score of each tertile groups of lipid levels in ApoE4+ group. * data are mean after adjustment for age, sex, years of education; Geriatric Depression Scale score, cigarette smoking, and medical history of cardiovascular disease, diabetes mellitus, and hypertension; b indicates significance at P<.05 after Bonferroni adjustment for multiple comparisons. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; TC, total cholesterol; apoE, apolipoprotein E.
Why are cognitive scores associated with plasma apoE and HDL levels?

Each of the analyses using the data from the baseline and 3-year follow-up examinations revealed that cognitive scores were associated with the plasma apoE level in both E4- and E4+, and the HDL level in E4-. We will discuss these findings.

ApoE plays a significant role in response to neuronal injury by reducing inflammation, endothelial dysfunction, and lipid oxidation. An antioxidant role of apoE in promoting the regression of atherosclerosis has also been reported. It is possible that a lower plasma apoE level impairs these normal physiological functions. If this is the case, a lower plasma apoE level may lead to cognitive decline and the exacerbation of cerebral degenerative changes. On the other hand, apoE is thought to bind Aβ and promote its clearance and degradation, such that a lower apoE level may reduce the efficiency of Aβ clearance, and contribute to AD pathogenesis.

The expression of apoE is transcriptionally regulated by the ligand-activated nuclear receptors, peroxisome proliferator-activated receptor gamma (PPARγ) and liver X receptors (LXRs), which form obligate heterodimers with retinoid X receptors (RXRs). Expression of the ApoE gene is increased by agonist of these receptors. Recently, Cramer et al tested whether the RXR agonist bexarotene, which activates both the PPAR-RXR and LXR-RXR receptors, would rapidly alter the amount of Aβ, and diminish behavioral abnormalities , in mice genetically engineered to express a mutant form of the APP gene. They observed rapid clearance of soluble Aβ from the brain, reduction in neuritic plaque burden, and reversal of behavioral deficits. The effects of bexarotene were not observed when the drug was administered to mice lacking the APOE gene. These observations support our finding of the significant protective effect of apoE on cognitive decline in later life, and that the strategies increasing apoE expression might prevent cognitive decline in old age.

Higher plasma levels of HDL were associated with better cognitive function in the E4- group. Low-level HDL is thought to be a risk factor for atherosclerotic diseases, and it has been reported that HDL might prevent aggregation and polymerization of amyloid in the human brain. Anti-inflammatory properties of HDL could prevent inflammation from neurodegenerative processes. Recent studies have presented evidence for the involvement of internalized triglyceride-rich lipoprotein (TRL)-derived apoE in the regulation of HDL metabolism. The greater portion of TRL-derived apoE remains in peripheral recycling endosomes. This pool of apoE is then mobilized by HDL to be recycled back to the plasma membrane, followed by apoE resecretion and the subsequent formation of apoE-containing HDL. This recycling of apoE may prevent cognitive decline. We found no significant association between HDL and cognitive function in the E4+ group.
shown that HDL-induced recycling of TRL-derived apoE4 is relatively inefficient. Thus, in the E4+ group, the inefficiency might reduce the recycling of apoE and decrease the protective effect of HDL on cognitive decline.

**Conclusion**

Our findings showed positive effect of plasma apoE and HDL on better cognitive function of elderly. They suggest a possible interaction between apoE and HDL may be linked to a protective effect on cognitive decline and that the interaction is affected by APOE4 allele in later life. It is known that neuropathological cascades leading to cognitive impairment and AD start to develop before the manifestation of cognitive impairment. Therefore, ensuring higher plasma apoE and HDL from an earlier stage of life may be useful for the maintenance of cognitive function in later life, and especially for APOE4 carriers.

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