DISCUSSION

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 (Davignon et al 1999). An antioxidant role of apoE in promoting the regression of atherosclerosis has also been reported (Tangirala et al 2001). It is possible that a lower plasma apoE level impairs these normal physiological functions (Masliah et al 1995). 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 (Stratman et al 2005).

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 (Breteler et al 1994; Kalaria 2000), and it has been reported that HDL might prevent aggregation and polymerization of amyloid in the human brain (Koudinov et al 1998; Olesen and Dagø 2000). Anti-inflammatory properties of HDL could prevent inflammation from neurodegenerative processes (Cockerill et al 2001).

Recent studies have presented evidence for the involvement of internalized triglyceride-rich lipoprotein (TRL)-derived apoE in the regulation of HDL metabolism (Heeren et al 2003). 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 re-secretion 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. A recent study has shown that HDL-induced recycling of TRL-derived apoE4 is relatively inefficient (Heeren et al 2004). Thus, in the E4+ group, the inefficiency might reduce the recycling of apoE and decrease the protective effect of HDL on cognitive decline.

The present study has limitations. First, we have not quantified the longitudinal data for lipid prior to the baseline evaluation. Second, because we have no autopsies, an accurate pathological background of the cognitive decline among the E4+ carriers has not been determined. However, our longitudinal study is now continuing, and we hope that these limitations will be overcome in the future.

In conclusion, our findings suggest that 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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REFERENCES

Breteler MM, van Swieten JC, Bots ML, Grobbee DE, Claus JJ, van den Hout JH, et al (1994): Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. *Neurology* 44:1246-1252.

Caselli RJ, Reiman EM, Locke DE, Hutton ML, Hentz JG, Hoffman-Snyder C, et al (2007): Cognitive domain decline in healthy apolipoprotein E epsilon4 homozygotes before the diagnosis of mild cognitive impairment. *Arch. Neurol.* 64:1306-1311.

Cockerill GW, Huehns TY, Weerasinghe A, Stocker C, Lerch PG, Miller NE, et al (2001): Elevation of plasma high-density lipoprotein concentration reduces interleukin-1-induced expression of E-selectin in an in vivo model of acute inflammation. *Circulation* 103: 108-112.

Davignon J, Cohn JS, Mabile L, Bernier L (1999): Apolipoprotein E and atherosclerosis: insight from animal and human studies. *Clin. Chim. Acta* 286:115-143.

Grober E, Buschke H, Crystal H, Bang S, Dresner R (1988): Screening for dementia by memory testing. *Neurology* 38:900-903.

Han X (2010): The pathogenic implication of abnormal interaction between apolipoprotein E isoforms, amyloid-beta peptides, and sulfatides in Alzheimer's disease. *Mol. Neurobiol.* 41:97-106.

Heeren J, Grewal T, Laatsch A, Becker N, Rinninger F, Rye K, et al (2004): Impaired recycling of apolipoprotein E4 is associated with intracellular cholesterol accumulation. *J. Biol. Chem.* 279:55483-55492.

Heeren J, Grewal T, Laatsch A, Rottke D, Rinninger F, Enrich C, et al (2003): Recycling of apoprotein E is associated with cholesterol efflux and high density lipoprotein internalization. *J. Biol. Chem.* 278:14370-14378.

Iurescia S, Fioretti D, Mangialasche F, Rinaldi M (2010): The pathological cross talk between apolipoprotein E and amyloid-beta peptide in Alzheimer's disease: emerging gene-based therapeutic approaches. *J. Alzheimers Dis.* 21:35-48.

Kalaria RN (2000): The role of cerebral ischemia in Alzheimer's disease. *Neurobiol. Aging* 21:321-330.

Koudinov AR, Berezov TT, Kumar A, Koudinova NV (1998): Alzheimer's amyloid beta interaction with normal human plasma high density lipoprotein: association with apolipoprotein and lipids. *Clin. Chim. Acta* 270:75-84.

Masliah E, Mallory M, Ge N, Alford M, Veinbergs I, Roses AD (1995): Neurodegeneration in the central nervous system of apoE-deficient mice. *Exp. Neurol.* 136:107-122.

Miyamoto M, Kodama C, Kinoshita T, Yamashita F, Hidaka S, Mizukami K, et al (2009): Dementia and mild cognitive impairment among non-responders to a community survey. *J. Cli. Neurosci.* 16:270-276.

Olesen OF, Dagø L (2000): High density lipoprotein inhibits assembly of amyloid beta-peptides into fibrils. *Biochem. Biophys. Res. Commun.* 270:62-66.

Pfrieger FW (2003): Role of cholesterol in synapse formation and function. *Biochem. Biophys. Acta* 1610:271-280.

Rebeck GW, Reiter JS, Strickland DK, Hyman BT (1993): Apolipoprotein E in sporadic Alzheimer's disease: allelic variation and receptor interactions. *Neuron* 11:575-580.

Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, et al (1993): Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 43:1467-1472.

Small BJ, Rosnick CB, Fratiglioni L, Bäckman L (2004): Apolipoprotein E and cognitive performance: a meta-analysis. *Psychol. Aging* 19:592-600.

Sohlberg M, Mateer CA (1986): Attention process training manual. Washington: Association for neuropsychological research and development.

Solomon PR, Pendlebury WW (1998): Recognition of Alzheimer's disease: the 7 Minute Screen. *Fam. Med.* 30:265-271.

Stratman NC, Castle CK, Taylor BM, Epps DE, Melchior GW, Carter DB (2005): Isoform-specific interactions of human apolipoprotein E to an intermediate conformation of human Alzheimer amyloid-beta peptide. *Chem. Phys. Lipids* 137:52-61.

Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, et al (1993): Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc. Natl. Acad. Sci. U. S. A.* 90:1977-1981.

Tangirala RK, Praticó D, FitzGerald GA, Chun S, Tsukamoto K, Maugeais C, et al (2001): Reduction of isoprostanes and regression of advanced atherosclerosis by apolipoprotein E. *J. Biol. Chem.* 276:261-266.

Wechsler D (1981): WAIS-R : manual : Wechsler adult intelligence scale--revised. New York: Harcourt Brace Jovanovich for Psychological Corp.

Wenham PR, Price WH, Blandell G (1991): Apolipoprotein E genotyping by one-stage PCR. *Lancet* 337:1158-1159.

Yasuno, F., Tanimukai, S., Sasaki, M., Hidaka, S., Ikejima, C., Yamashita, F., Kodama, C., Mizukami, K., Michikawa, M., Asada, T. Association Between Cognitive Function and Plasma Lipids of the Elderly After Controlling for Apolipoprotein E Genotype. *Am. J. Geriatr. Psychiatry* (in press, a). (DOI: 10.1097/JGP.0b013e318211819b).

Yasuno, F., Tanimukai, S., Sasaki, M., Ikejima, C., Yamashita, F., Kodama, C., Hidaka, S., Mizukami, K., Asada, T. Effect of plasma lipids, hypertension and APOE genotype on cognitive decline. (in press, b). (DOI: /10.1016/j.neurobiolaging.2011.12.028).

Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al (1982): Development and validation of a geriatric depression screening scale: a preliminary report. *J. Psychiatr. Res.* 17:37-49.

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