Normal cognition in patient without apolipoprotein E, risk factor for Alzheimer's

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A 40-year-old California man exhibits normal cognitive function although he has no apolipoprotein E (apoE), which is believed to be important for brain function but a mutation of which is also a known risk factor for Alzheimer disease (AD). Researchers suggest this could mean that therapies to reduce apoE in the central nervous system may one day help treat neurodegenerative disorders such as AD.

The study was authored by Angel C. Y. Mak, Ph.D., of the University of California, San Francisco, and colleagues.

The patient was referred to UCSF with severe high cholesterol that was relatively unresponsive to treatment. He has a rare form of severe dysbetalipoproteinemia (abnormally high levels of cholesterol and triglycerides in the blood) and the authors identified a mutation leading to his apoE deficiency.

Extensive studies of the patient's retinal (eye) and neurocognitive function were performed because apoE is found in the central nervous system and the retinal pigment epithelium of the eye.

Despite lacking apoE, the patient had normal vision and exhibited normal cognitive, neurological and eye function. The patient also had normal brain imaging findings and normal cerebrospinal fluid levels of other proteins.

"Failure of detailed neurocognitive and retinal studies to demonstrate defects in our patient suggests either that the functions of apoE in the brain and eye are not critical or that they can be fulfilled by a surrogate protein. Surprisingly, with respect to central nervous system function, it appears that having no apoE is better than having the apoE4 protein. Thus, projected therapies aimed at reducing apoE4 in the brain could be of benefit in neurodegenerative disorders such as Alzheimer disease."

In a related editorial, Courtney Lane-Donovan, S.B., and Joachim Herz, M.D., of the University of Texas Southwestern Medical Center, Dallas, write: "More than 20 years ago, a polymorphism in the apolipoprotein E (apoE) gene was identified as the primary risk factor for late-onset Alzheimer disease (AD). Individuals carrying the ?4 isoform of apoE (apoE4) are at significantly greater risk for AD compared with apoE3 carriers, whereas the apoE2 allele is associated with reduced AD risk."

"Despite two decades of research into the mechanisms by which apoE4 contributes to disease pathogenesis, a seemingly simple question remains unresolved: is apoE good or bad for brain health? The answer to this question is essential for the future development of apoE-directed therapeutics. … In light of apoE as the primary risk factor for AD, the lack of neurological findings in this patient would appear to answer the question of whether apoE is necessary for brain function with a resounding no," they continue.

"Overall, the patient's normal cognitive function together with the earlier mouse work suggest that interventions that reduce cerebral apoE levels may hold promise as a potential therapeutic approach to AD," they conclude.

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