Men with Alzheimer's gene at risk of brain bleeding, study finds

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A common genetic variation, ApoE4, linked to Alzheimer's disease greatly raises the likelihood of tiny brain bleeds in some men, scientists have found.

Such hemorrhages in brain tissue - microbleeds - leave small points of damage throughout the brain and contribute to memory loss.

The study led by USC Davis School of Gerontology scientists reveals that the gene variant, ApoE4, has different effects on men and women diagnosed with mild cognitive impairment or Alzheimer's disease.

The research further underscores the significance of ApoE4 (apolipoprotein E 4) in Alzheimer's, and it builds upon prior studies that indicate the disease has sex-based differences that may affect treatment approaches.

"It's important to study sex-based differences in Alzheimer's because women live longer than men, and, as this study shows, the disease can affect them differently," said corresponding author Caleb Finch, University Professor in the USC Davis School of Gerontology and Dornsife College of Letters, Arts, and Sciences.

The finding is especially striking since prior research indicated that Alzheimer's disease was more troublesome for women. Women with ApoE4 are almost twice more likely than men to be diagnosed with the disease. Also, women suffer worse memory loss than men for a given load of plaques and tangles of proteins - the classic Alzheimer's disease markers.

USC studies have found ApoE4 can be an aggravating factor even for non-Alzheimer's patients; ApoE4 is well known for worsening the effects of traumatic brain injury.

The latest study, which involved research on mice and on humans, also provides new evidence that Alzheimer's disease is unique to humans.

"Most diseases can be studied in lab animals without introducing human genes," Finch said. "That is not the case for Alzheimer's."

Even mice and apes that have some factors associated with the disease do not suffer the same cognitive impairments and neuron losses that Alzheimer's patients do, the scientists noted. The likely difference that spares animals from this brain-wasting disease is that animals do not have multiple genetic variants of ApoE - lipid-carrying proteins produced by the liver and by the brain.

Humans have three variants, including ApoE4, the most common Alzheimer's risk gene, while chimpanzees, their closest relative, have only one type of ApoE. The ApoE proteins transport cholesterol and other fats through the bloodstream.

Clinical scientists on Finch's team examined brain scans of 658 subjects, aged 48 to 91 years old, in the United States and Canada, who are part of the Alzheimer's Disease Neuroimaging Initiative. Of those subjects, 402 had mild cognitive impairment, 90 had early-stage Alzheimer's disease, and 166 were cognitively normal.

The ongoing study in the Karolinska Institute Dementia Study in Sweden also analyzed the scans of 448 other subjects, aged 36 to 88 years old. Of those, 152 had mild cognitive impairment, 152 had Alzheimer's, and 144 were cognitively normal.

The researchers found that ApoE4-carrying men with mild cognitive impairment or Alzheimer's disease suffered twice as many microbleeds in their brains as women with similar diagnoses.

Microbleeds differ from stroke in size and impact, Finch said. Stroke is a macro event that usually

occurs on one side of the brain and its effect is usually immediate. Microbleeds occur anywhere in the brain over time, with cumulative effect.

Based on the findings, Finch said researchers must now see if they can reduce the microbleeds using sex steroids. They may consider other changes in treatment, too.

"We may need different therapeutic strategies for ApoE4-carrying men who are Alzheimer's patients than for women," he said.

The study was published online on Oct. 19 by the journal *Neurobiology of Aging*.

More information: The APOE4 allele shows opposite sex bias in microbleeds and Alzheimer's Disease of humans and mice, dx.doi.org/10.1016/j.neurobiolaging.2015.10.010

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