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ALZHEIMER DISEASE

Iron—the missing link between ApoE and Alzheimer disease?

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High levels of iron in the brain may predict cognitive decline and progression from mild cognitive impairment (MCI) to Alzheimer disease (AD), according to new research published in *Nature Communications*. Moreover, the apolipoprotein E ε4 (*APOE*ε4*) allele—the main genetic risk factor for AD—is associated with increased concentrations of the iron storage protein ferritin in the cerebrospinal fluid (CSF), indicating a possible link between ApoE function and brain iron homeostasis.

"It has been known since the 1950s that iron elevation is exaggerated in affected brain regions of people with AD, but there has not previously been a study to investigate what impact iron elevation has on the progression of the disease," explains study leader Ashley Bush. "We set out to determine whether measures of brain iron in the CSF could predict longitudinal AD outcomes, and might explain the role of ApoE."

The study population included 302 older individuals (average age ~75 years) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort: 91 with normal cognition, 144 with MCI, and 67 with AD. CSF ferritin levels—thought to be a robust indicator of brain iron content—were measured at baseline, and the participants were monitored by means of structural MRI and neuropsychiatric assessments for 7 years.

Mean CSF ferritin levels did not differ significantly between the three groups of participants. Within each group, however, high baseline levels of CSF ferritin were associated with increased cognitive decline and hippocampal atrophy over the 7-year follow-up period. In participants with MCI, high CSF ferritin levels at baseline heralded accelerated conversion to AD, with the time to diagnosis of AD being reduced by 3 months for each 1 ng/ml increase in ferritin concentration.

The researchers also found an intriguing relationship between ApoE and CSF ferritin. In both *APOE*ε4* carriers and non-carriers, levels of ApoE in the CSF correlated positively with ferritin levels. In addition, mean levels of CSF ferritin were increased by more than 20% in the *APOE*ε4* carriers compared with the non-carriers.

These findings raise the possibility that the *APOE*ε4* allele confers susceptibility to AD via brain iron accumulation. Bush and colleagues suggest that lipoprotein trafficking could be a key factor: previous studies have implicated HDL recycling in the regulation of intracellular iron levels, and ApoE4 has a lower affinity for HDL than do the other ApoE isoforms. Therefore, iron retention in the brains of *APOE*ε4* carriers could be related to impaired ApoE-mediated trafficking of HDL.

"This study has implications for predicting who will develop AD, and is also a strong foundation for future clinical trials into drugs that aim to lower brain iron content," says Bush. "A phase II study in 1991 showed beneficial effects of the iron chelator deferoxamine in patients with AD, but this study was never followed up—our new study supports the future trialling of iron chelator drugs for AD."

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