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ALZHEIMER DISEASE

Sex-specific inflammatory link to early Alzheimer pathology

Blood concentrations of the inflammatory protein α2-macroglobulin (α2M) are associated with tau pathology and the risk of Alzheimer disease (AD) in men, according to recent research. The molecular basis of the association could offer new therapeutic opportunities.

Inflammation has been linked to AD pathogenesis, but the relationship between systemic inflammation and early AD is poorly understood. Several lines of evidence suggest that α2M, an acute-phase protein of the innate immune system, is central to this relationship, and in their new work, Madhav Thambisetty and colleagues aimed to gain further insight into its role.

"Our goals were to first ask whether systemic inflammation, as measured by serum α2M concentration, was related to the risk of incident AD in individuals who were initially cognitively normal," explains Thambisetty. "Second, we wanted to identify plausible molecular mechanisms underlying the role of α2M in AD pathogenesis."

The researchers initially analysed data from 274 participants in the Predictors of Cognitive Decline Among Normal Individuals (BIOCARD) study. They used a Cox proportional hazards model to determine whether serum concentrations of α2M were associated with the risk of AD, and a linear mixed effects regression model to determine whether serum α2M levels were related to cerebrospinal fluid (CSF) levels of amyloid-β_{42}, total tau and phosphorylated tau — all established markers of AD.

Serum concentrations of α2M correlated with CSF levels of total tau across the cohort, and high serum levels of α2M were associated with a threefold increase in the risk of AD in men. The findings were validated in a cohort of 353 participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI).

"In the context of previous studies suggesting differential vulnerability to AD between males and females, our results indicate that one plausible mechanism underlying this observation is a sex-specific systemic inflammatory response in early AD," explains Thambisetty.

The team then examined the molecular basis of the link between serum α2M and AD. They identified a network of nine genes, the expression of which was associated with that of α2M. This network included *RCAN1*, which regulates the tau phosphatase calcineurin, suggesting a direct link between α2M levels and AD pathology. Protein levels of α2M in the brain were also associated with those of calcineurin. "To our knowledge, this is the first study to suggest that peripheral α2M levels reflect or respond to tau phosphorylation states," says Thambisetty.

The researchers say that their findings warrant further studies on the molecular basis of sex differences in the risk of AD, and that their mechanistic insights could have therapeutic implications. "We are exploring α2M–tau interactions in human CSF samples and cell culture models," says Thambisetty. "Evidence for such interactions may open the door to therapeutic approaches in AD that target tau pathology by modulating α2M levels."

Ian Fyfe

> "high serum levels of α2M were associated with a threefold increase in the risk of AD in men"

ORIGINAL ARTICLE Varma, V. R. *et al.* Alpha-2 macroglobulin in Alzheimer's disease: a marker of neuronal injury through the RCAN1 pathway. *Mol. Psychiatry* http://dx.doi.org/10.1038/mp.2016.206 (2016)