Ceramides predict vascular brain injury and dementia

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Novel blood-based biomarkers for dementia could identify disease at an early preclinical stage, serve as surrogate outcomes for clinical trials of investigational therapies and even identify future potential therapeutic targets. Unlike cerebrospinal fluid biomarkers that require a spinal tap, plasma biomarkers can be extracted from the blood, making their collection much less invasive and much more appealing for patients. In a study published in *Annals of Clinical and Translational Neurology*, a team led by investigators from Brigham and Women's Hospital describes the role of plasma ceramides in dementia and Alzheimer's disease (AD) and their potential as a blood-based biomarker.

"Our findings indicate that circulating ceramide ratios may be useful predictors of future dementia risk and may have a role in predicting dementia at an early, preclinical stage, when the greatest opportunity for disease modification exists," said Emer McGrath, MD, Ph.D., associate neurologist in the Department of Neurology at the Brigham. "However, these results will require replication in other cohorts."

Altered lipid metabolism is believed to play an important role in the development of dementia and Alzheimer's disease. Ceramides are a type of lipid belonging to the sphingolipid family and are thought to play an important role in lipid aggregation, inflammation, endothelial dysfunction and neuronal cell death. Recently, attention has focused on the possibility that the adverse effects of ceramides may be related to the relative proportions of circulating very-long-chain to long-chain fatty acyl chains, rather than simply due to elevated total ceramide levels. Very-long-chain fatty acyl ceramides are important for myelin function and may have a protective effect against dementia, while long-chain ceramide species are linked with deleterious pro-inflammatory and apoptotic effects.

In their study, McGrath and colleagues compared levels of very-long chain and long-chain ceramides in blood samples from approximately 1,900 participants in the Framingham Heart Study Offspring cohort. They analyzed the risk of dementia, MRI structural measures of vascular brain injury and ?-amyloid burden on brain PET, AD's gold-standard imaging marker. The team found that an elevated ratio of very-long-chain to long-chain ceramides was associated with a 27 percent reduction in the risk of dementia and AD dementia as well as a lower burden of white matter injury on MRI of the brain.

In an exploratory analysis of 48 individuals with available amyloid-PET data, an elevated ratio of ceramide 24:0 (very-long chain ceramide) to ceramide 16:0 (long-chain ceramide) was associated with a reduced burden of ß-amyloid. Ceramides have previously been shown to stimulate ß-amyloid formation and inhibition of ceramide synthesis results in reduced production of ß-amyloid. It is possible that pharmacological inhibition of long-chain ceramide synthesis could slow down or even prevent the progression of AD dementia through prevention of ß-amyloid accumulation. Modification of ceramides could represent an attractive therapeutic option for prevention of vascular contributions to dementia, although this remains to be tested.

More information: Emer R. McGrath et al, Circulating ceramide ratios and risk of vascular brain aging and dementia, *Annals of Clinical and Translational Neurology* (2020). DOI: 10.1002/acn3.50973

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