**SERUM SPHINGOMYELINS AND CERAMIDES AS BIOMARKERS OF ALZHEIMER DISEASE PROGRESSION**
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Background: There is an inherent need to identify biomarkers in the early stages of Alzheimer's disease (AD) that can predict the transition from normal aging to mild cognitive impairment (MCI) and AD. Ceramides, sphingomyelin (SM) metabolites, play an important role in regulating physiological processes including cellular differentiation, proliferation and apoptosis by activating a variety of signaling cascades and promoting the generation of free radical species. Given the direct connection between these lipids and apoptosis, it is likely they could be indicators of neurodegeneration and AD progression. Limited research has examined the role of ceramides in AD pathogenesis in humans. We previously reported that high serum ceramide levels predicted memory impairment, but that low levels were cross-sectional associated with impairment. However, no studies have examined the utility of these blood lipids in AD or MCI patients. Identifying a blood-based biomarker would be superior to other mediums (i.e. neuroimaging and CSF) in terms of costs, invasiveness, and feasibility. Blood based biomarkers for AD have been questionable because it is difficult to ascertain the relationship and mechanisms between peripheral markers and brain functioning.

Objective: To examine plasma levels of ceramides and SM in well-characterized cognitive normal controls (NC), MCI, and AD cases and to assess the validity of these lipids as potential biomarkers by correlating them to brain white matter integrity, as assessed by fractional anisotrophy (FA), using diffusion tensor imaging (DTI).

Methods: Participants were cognitively and physically well-characterized and included 25 NC, 17 amnestic MCI, and 21 early probable AD. All participants were consensus diagnosed via the Johns Hopkins Alzheimer Disease Research Center and received a detailed clinical evaluation, a neuropsychological battery, neuroimaging and a blood draw. Ceramides and SM were assayed from plasma using ionization mass spectrometry. DTI data were analyzed with DTIStudio using a standardized protocol with established reliability. FA was assessed in the following regions of interest (ROI): 1) fornix, 2) splenium, 3) cingulum, and 4) cerebral peduncles (control region). Group differences in ceramides and SM levels were examined with ANOVA, and pairwise associations with T-tests. Partial correlation coefficients were used to examine the correlation between the ROIs and blood lipids. Age, sex, vascular conditions, Apoe E4, and statin use were examined as possible confounders.

Results: MCI cases had lower mean levels of all ceramide species compared to NC and AD cases. Adjusting for age, sex, vascular conditions, Apoe E4, and statin use had little effect on the results. There were no group differences in levels of plasma SM. There was a significant correlation between the plasma ceramides and FA in the fornix and splenium. This association was strongest in the MCI group.

Conclusion: Plasma ceramide levels are specifically altered early in the AD pathological process such that MCI cases have lower mean levels compared to both NC and AD cases. Importantly, there was a strong correlation between the blood ceramides and FA, particularly among MCI, further validating the utility of these blood markers. Together, these findings suggest that blood ceramides may be representative of AD pathology, vary by AD severity, and, therefore, be incorporated as early biomarkers of AD progression.