Vascular risk factors impact cognition independent of PIB PET and MRI measures of Alzheimer's Disease and vascular brain injury

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Background: Alzheimer's and vascular disease are two common causes of cognitive decline among older individuals. The recent advent of amyloid imaging in combination with MRI markers of vascular brain injury and AD-associated neurodegeneration and detailed medical history allows for in vivo assessment of the combined influence of vascular and Alzheimer' s disease on cognitive decline. Recent work by our group finds evidence that vascular brain injury is significantly associated with cognitive ability independent of amyloid load among individuals selected for high vascular risk (1, 2). We extended this work by examining the impact of vascular risk factors, vascular brain injury, AD-associated neurodegeneration, and amyloid load in a community based cohort more representative of the general population. **Methods:** The study consisted of 65 subjects aged 73.2 + 7.2 years of age, 65% of whom were Caucasian, 17% Hispanic, 14% African American and 4% Asian with mean educational achievement of 15.5 + 3.3 years; 54% were female and 57% cognitively normal, 38% mild cognitively impaired 5% were demented at baseline assessment. Subjects received yearly psychometrically matched measures of memory and executive function over 5.2 + 2.3 years. A history of hypertension, diabetes, elevated cholesterol, coronary artery disease, or cerebrovascular disease was assessed at baseline evaluation and 79% had one or more risk factor, with a median of 2. All subjects underwent PiB PET imaging quantified using a distribution volume ratio with cerebellar reference region. Quantitative MRI (3) measured the volumes of cerebral gray matter, hippocampi, and white matter hyperintensities (WMH) on MRI scans obtained nearest to PiB PET. Mixed effects regression models of individual trajectories of memory and executive functioning were estimated with random effects of baseline level and rate of change. Demographic variables, baseline clinical diagnosis, global amyloid burden defined as the average DVR from cortical regions associated with Alzheimer's amyloid pathology (1), MRI variables, and vascular risk factor burden defined as the simple sum of vascular risk factors present were entered into the model as fixed effects in a stepwise fashion. All fixed effects whose association with memory or executive function passed a p-value threshold of 0.01 were carried forward to subsequent models. **Results:** In the first model, baseline diagnosis was significantly associated with both baseline level and rate of change in memory and executive function. Global amyloid burden, when added to this model, was significantly associated with baseline level and rate of change in one or both cognitive domains. When MRI measures were further added to the model, only hippocampus volume was a significant predictor of baseline level and rate of change in cognitive domains. When total vascular risk factor burden was further added to the model, it significantly predicted baseline level of executive function. When total vascular risk factor burden was replaced with individual risks factors, only hyperlipidemia was significantly associated with baseline level of memory performance. **Conclusions:** In a cohort of community based, predominantly non-demented individuals, greater vascular risk factor exposure was significantly associated with baseline level of executive function in a model that included amyloid burden and MRI measures of vascular and neurodegenerative disease. We conclude that modifiable vascular risk factors are important to cognitive health even after adjusting for the concurrent effects of cerebral amyloid burden.

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