Cerebrovascular and Alzheimer's disease are associated with different subcortical white matter microstructural damage mechanisms

Omar Al-Janabi, MD [1] • Christopher Brown, PhD [2] • Gregory Jicha, MD, PhD [3]

[1]Behavioral Science and SBCoA, University of Kentucky • [2]University of Kentucky • [3]Neurology and SBCoA, University of Kentucky

Background: Alzheimer's disease (AD) and vascular dementia (VaD) often co-exist and may share common risk factors such as hypertension (HTN). Debate is ongoing as to whether these disease states are additive or whether they act synergistically in the development of subcortical white matter injury and eventually dementia. Recent reports suggest that AD may be responsible for subcortical white matter hyper intensities (WMH), previously thought due solely to cerebrovascular risks, further confounding this issue. The present study was undertaken to explore potential additive and/or synergistic actions of AD and VaD on the development of subcortical white matter injury.
Methods: A Cross-sectional analysis of spinal fluid amyloid levels (CSF Aβ 1-42), HTN status, and quantitative MRI WMH volumes on 72 subjects was performed. Partial correlation of WMH volumes, CSF Aβ 1-42 levels, HTN and global FA measures were performed to examine the association between these variables and WMH volumes. Two mediation analysis models, adjusted for age, gender, and education, were constructed to examine the interdependence of WMH volumes on HTN vs. CSF Aβ 1-42 levels. Additional two mediation analysis models were conducted to explore if the white matter injury (measured as global FA) that is due to AD or HTN is mediated by WMH volume.
Results: Results from the partial correlation model for CVD risks showed that all three measures were correlated with WMH volume (HTN p= 0.025, CSF Aβ 1-42 p= 0.007 and global FA p= 0.002) in this sample. The first mediation analysis model showed that CSF Aβ 1-42 did not alter the relationship between HTN and WMH volume (Indirect effect = 0.05 [- 0.001 – 0.15], direct effect = 0.23 [p= 0.026]). Furthermore, HTN did not mediate the relation between CSF Aβ 1-42 and WMH volume in the second model, suggesting independent contributions to the development of WMH in aging and MCI. The third mediation analysis model showed that HTN is not associated with the decrease in global FA measures directly. However, this relationship is found to be mediated by WMH volume (Indirect effect = - 0.002 [0.006 – 0.000], direct effect = - 0.005 [p= 0.06]). Finally, the last mediation model showed that the relationship between CSF Aβ 1-42 and global FA measures is both a direct relationship and an indirect one via CSF Aβ 1-42 relation with WMH volume (Indirect effect = 0.002 [0.000 – 0.006], direct effect = - 0.006 [p= 0.04]). The latter model is suggesting a different mechanism of subcortical white matter microstructural damage between AD and VaD.
Conclusion: Results from this study suggest that the relationship between VaD and AD may be additive rather than synergistic. These results suggest that therapeutic interventions designed to prevent or treat these common brain pathologies may require combination therapy targeting VaD as well as AD to show beneficial effect in the vast majority of MCI and dementia patients that have evidence for comorbid disease.