VENTRICULAR ENLARGEMENT AS AN OUTCOME MEASURE FOR CLINICAL TRIALS EXAMINING ALZHEIMER’S DISEASE

Sabrina Adamo1,2, Joel Ramirez1-3, Melissa F. Holmes1,2, Fuqiang Gao1-3, Mario Masellis1-4, Sandra E. Black1-4

1L.C. Campbell Cognitive Neurology Research Unit, Toronto, Canada; 2Hurvitz Brain Sciences Research Program, Sunnybrook Research Institute, Toronto, Canada; 3Heart & Stroke Foundation Canadian Partnership for Stroke Recovery, Sunnybrook Health Sciences Centre, Toronto, Canada; 4Department of Medicine, Division of Neurology, University of Toronto, Toronto, Canada.

BACKGROUND

• Alzheimer’s disease (AD) is the most common cause of dementia
• In 2016, it was estimated that over 500,000 Canadians are living with dementia [1]
• In addition to neuropsychological tests, MRI-based biomarkers measuring brain atrophy and small vessel disease (SVD) burden may be useful in tracking disease progression in prospective clinical trials of AD [2-3]

OBJECTIVE

Our study aimed at determining the feasibility of using ventricular cerebrospinal fluid (vCSF) growth as an outcome measure for clinical trials in AD.

PARTICIPANTS

• Baseline & follow-up MRI and cognitive test scores from the Sunnybrook Dementia Study were examined
• AD patients (n=133) with varying degrees of SVD, meeting NIA-AA criteria for probable/possible AD dementia [4], and NCs (n=47)

METHODS

• Cognition was measured using the Mini-Mental State Examination (MMSE) at both time points
• Brain Atrophy was assessed using ventricular cerebral spinal fluid (vCSF) volumes
• SVD was assessed using periventricular and deep white matter hyperintensity (p/dWMH) volumes (Fig 1)
• Baseline and follow-up MRI (mean ISI=1.7yrs) was acquired using a 1.5T GE Signa scanner
• Changes in MRI-based biomarkers were assessed using a previously validated method [5]
• ANCOVA was used to compare group dynamic progression
• Partial Pearson r correlations were used to examine relationships between changes in: cognition, atrophy, SVD
• All analyses accounted for baseline age, sex, and education

RESULTS

• Dynamic progression analyses revealed that in just under 2 years, AD patients exhibited significant increases in vCSF volume compared to NCs (p<0.0001; Fig 2)
• Pearson r analyses revealed vCSF volume growth was significantly correlated with pWMH (r=0.4, p<0.001) but not dWMH (p=0.28, n.s.)
• vCSF volume growth exhibited a moderate correlation with change in MMSE score (r=0.37, p<0.0001) over the same period

CONCLUSIONS

• As expected, patients with AD showed greater progression of ventricular atrophy than NCs (Fig 2)
• vCSF expansion in AD patients from their baseline to follow up scans was associated with SVD burden and cognitive decline
• This suggests that ventricular progression may be a viable outcome measure for clinical trials aimed at slowing brain volume loss and cognitive decline
• Novel treatment strategies or drug repurposing such as the use of anti-hypertensives, may employ our MRI-based biomarker for assessment of treatment outcomes (eg. SARTAN-AD ClinicalTrials.gov ID: NCT02085265) [6]

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REFERENCES