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

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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 was 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)

Table 1: Demographics and Volumetrics

	AD n=133	NC n=47	P-value	Cohen's *d*
Demographics				
Age				
Baseline	71.6 (8.6)	70.4 (7.3)	0.43	0.14
Follow-up	73.2 (8.7)	72.2 (7.1)	0.46	0.13
Sex, M/F	57/76	22/25	0.22†	
Education	13.3 (3.5)	15.9 (2.8)	0.00*	0.80
ISI	1.7 (0.9)	1.7 (0.8)	0.67	0.07
Volumetrics				
Ventricles				
Growth	10.59 (8.02)	5.63 (3.89)	0.00*	0.79
Shrinkage	3.18 (4.81)	3.36 (3.48)	0.82	0.04
Stable	44.9 (23.37)	32.2 (17.15)	0.00*	0.62

Data are presented as Mean (SD) unless otherwise indicated. All volumes are reported in cubic centimeters (cc).
†chi square test
*p<0.001

METHODS

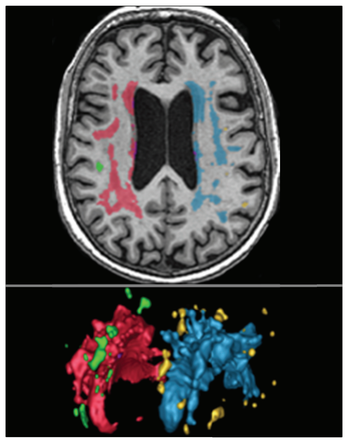


Figure 1: *(Top)* Axial T1-weighted MRI. *(Bottom)* 3-D rendering of WMH segmentation. Deep WMH shown in green & yellow, periventricular WMH shown in red & blue.

- **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

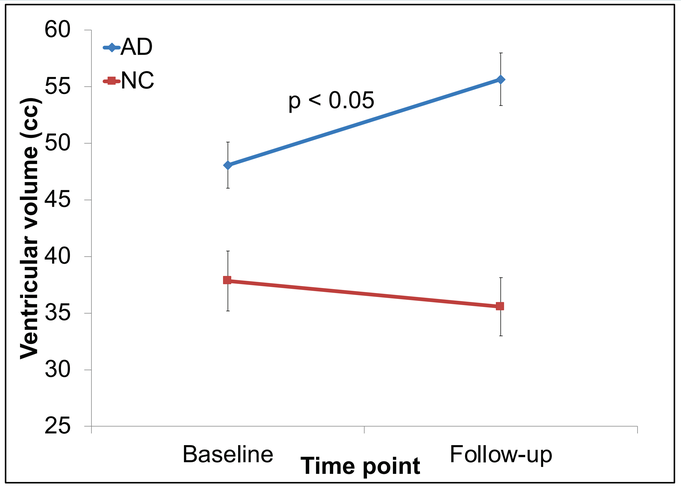
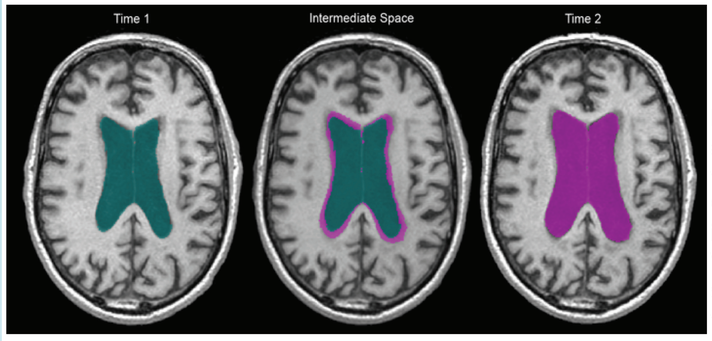


Figure 2: Mean (± SEM) ventricular change in Alzheimer's disease (AD; n=133) and normal controls (NC; n=47) after ~1.7 years.



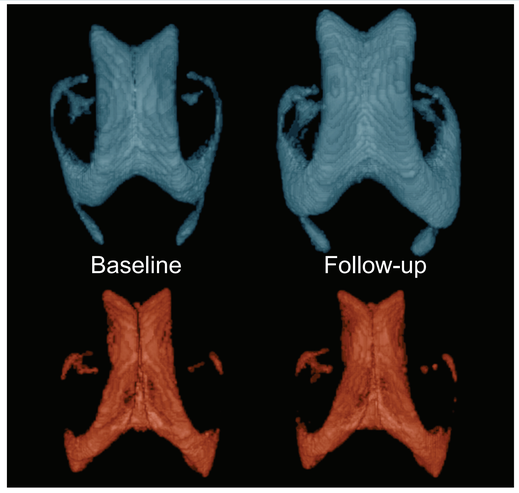


Figure 3: Shows top view of 3D volume surface renders of ventricles from an Alzheimer's disease patient (blue) and a normal elderly control (red). Left images show ventricles at baseline scanning and right images show after 1 year follow-up.

Figure 4: Two year ventricular expansion in a 60 year old man living with AD. Baseline vCSF = 83.6 cc, follow-up vCSF = 119.0 cc. Green indicates baseline vCSF voxels, pink indicates follow-up (right) and growth (middle). WMH within vCSF growth regions were subsequently removed to account for ventricular expansion.

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RESULTS (CONT)

- 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<0001) 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 time 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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