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 irreversible cause of dementia.
- In 2016, it has been estimated that over half a million Canadians are living with dementia [1].
- In addition to neuropsychological tests, recent studies on AD and aging suggest that MRI-based biomarkers measuring brain atrophy and small vessel disease burden may be useful indicators to track disease progression in prospective clinical trials of AD [2-3].

OBJECTIVE

Using established MRI-based biomarkers and a global measure of cognition, our study examined changes in brain atrophy, small vessel disease burden, and cognition, in AD patients and healthy elderly.

PARTICIPANTS

- Baseline & follow-up MRI and cognitive test scores were obtained from participants enrolled in the Sunnybrook Dementia Study.
- AD patients (n=133) with varying degrees of small vessel disease, who met NINCDS-ADRDA criteria for probable/possible AD dementia [4], and cognitively normal elderly controls (n=47) were examined.

Table 1: Demographics and Volumetrics

	AD n=133	NC n=47	P-value	Cohen's *d*
Demographics				
Age				
Baseline	71.56 (8.61)	70.45 (7.27)	0.43	0.14
Follow-up	73.24 (8.66)	72.2 (7.13)	0.46	0.13
Sex, M/F	57/76	22/25	*0.22	
Education	13.3 (3.54)	15.85 (2.78)	0.00	0.80
MMSE				
Baseline	23.63 (3.84)	28.77 (1.34)	0.00	1.79
Follow-up	19.92 (12.94)	28.64 (1.17)	0.00	0.95
ISI	1.69 (0.87)	1.75 (0.78)	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).
Abbreviations: AD, Alzheimer's disease; NC normal control; MMSE, mini-mental state examination; ISI, interscan interval.
*chi square test

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.
- **Small Vessel Disease** was assessed using periventricular (pWMH) and deep white matter hyperintensity (dWMH) volumes (See Fig 4).
- Baseline and follow up MRI (mean ISI=1.7yrs) was acquired using a 1.5T GE Signa scanner
- Changes in MRI-based biomarkers measured at both time points were assessed using a previously validated dynamic volumetric progression method [5].
- An analysis of covariance (ANCOVA) was used for group comparisons of the dynamic progression metrics and partial Pearson r correlations were used to examine the relationship between changes in atrophy, small vessel disease, and cognition.
- All analyses accounted for age at baseline, sex, and years of education.

RESULTS

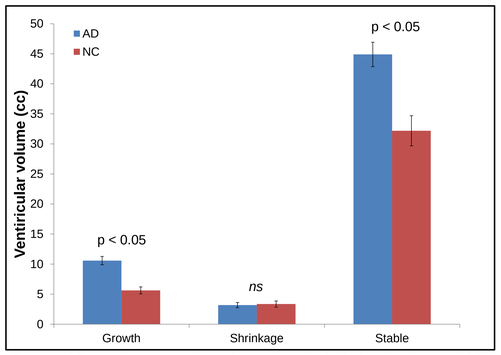

Figure 1: Dynamic progression of ventricles in Alzheimer's disease (AD; n=133) and normal controls (NC; n=47) after 1.7 years. Data are presented as mean ± SEM.

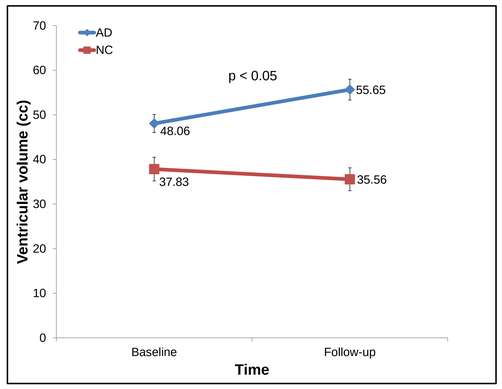

Figure 2: Mean (± SEM) ventricular change in Alzheimer's disease (AD; n=133) and normal controls (NC; n=47) after ~1.7 years.

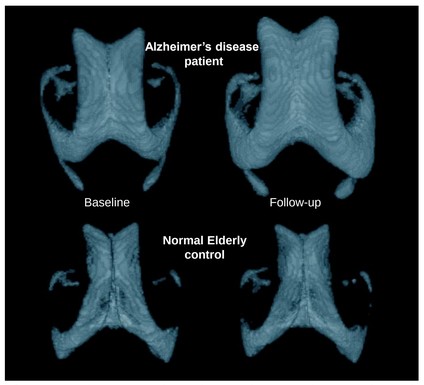

Figure 3: Shows top view of 3D volume surface renders of ventricles from an Alzheimer's disease patient (top) and a normal elderly control (bottom). Left images show ventricles at baseline scanning and right images show after 1 year follow-up.

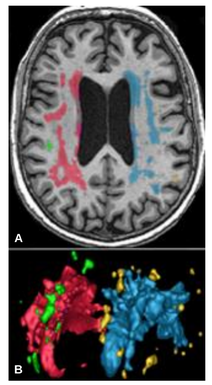

Figure 4: dWMH in green & yellow and pWMH in red & blue. (A) Axial T1 (B) 3-D volume rendering of WMH segmentation.

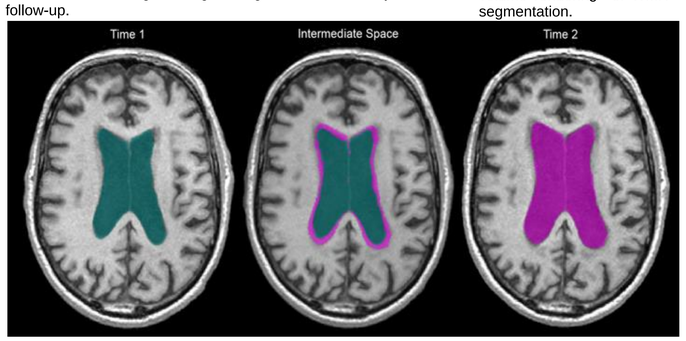

Figure 5: Two year ventricular expansion in a 60 year old man living with AD. Baseline vCSF = 83.6 cc, follow-up vCSF = 119.0 cc. Green indicates baseline vCSF voxels, pink indicates follow-up (right) and growth (middle). WMH within vCSF growth regions were subsequently removed to account for ventricular expansion.

- Dynamic progression analyses revealed that in just under 2 years, AD patients exhibited significant increases in vCSF volume compared to normal elderly (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 (n.s.).
- Additionally, vCSF volume growth exhibited a moderate correlation with change in MMSE score (r=0.372, p<0.0001) over the same time period.

CONCLUSIONS

- As expected, patients with AD showed a greater progression of ventricular atrophy compared to cognitively normal elderly (Fig 1) [2].
- Additionally, vCSF expansion in AD patients from their baseline to follow up scans was consistent with their small vessel disease burden and decline in cognition (Fig 2).
- The findings from our study suggest that changes in ventricular expansion is a promising biomarker that may be used as viable outcome measure for clinical trials exploring novel treatments aimed at halting progression and improving cognitive outcome.
- In addition to standard cognitive testing, novel treatment strategies such as the use of anti-hypertensives, may use our MRI-based progression results as a useful tool to assess treatment outcomes [6].

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