Dementia-Associated Ventricular Volume Changes In A Large Community Cohort

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Introduction: We investigated the relationship between dementia progression and MR-based measures of lateral ventricle volume in a large cohort.

The relationship between dementia progression and lateral ventricle size was investigated in a set of 389 subjects as part of the Cardiovascular Health Study (CHS). A reliable, fully-automated ventricle segmentation technique provided MR-based measures of lateral ventricle size in MR scans of subjects at the time of study enrollment and at a 4-year follow-up visit. We used linear statistical models to investigate relationships between ventricular size and expansion, presence and progression of dementia, and other clinical variables including age, presence of infarcts, and gender.

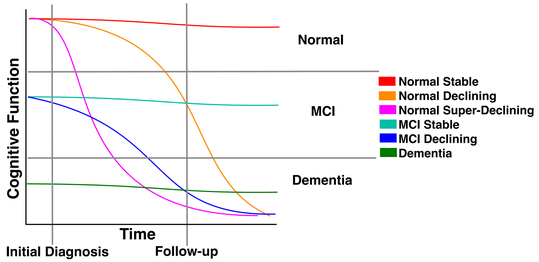
Data: 389 subjects from the Cardiovascular Health Study (CHS) categorized by presence of dementia

389 subjects received 1.5T T1-weighted SPGR MR scans and comprehensive neuropsychological evaluations in 1998-99 as part of the Cardiovascular Health Study (see [1] for evaluation procedure). A subset of 333 subjects received a follow-up clinical evaluation in 2002-03; 142 of these subjects received a follow-up MR scan in 2002-03. Subjects were classified into dementia categories based on the presence of mild cognitive impairment (MCI) or dementia in 1998-99 and 2002-03 (see Table 1 and Figure 1). Dementia diagnoses were sub-typed by NINDS criteria into probable Alzheimer's Disease (AD), possible AD, and non-AD categories. Differences in ventricular size were analyzed between cognitively non-declining, declining, and rapidly declining (or "super-declining") groups.

Table 1. Subjects were categorized by the presence of dementia or MCI at time of study enrollment (Dx1) and at a follow-up visit 4 years later (Dx2). **Followup N** refers to subjects who received a follow-up clinical evaluation but no follow-up MR scan; **Followup scan N** refers to subjects who received both a followup clinical evaluation and a follow-up MR scan.

Group	Follow-up group	Dx 1	Dx 2	Enrollment N	Followup N	Followup scan N
Stable	Normal Stable	Normal	Normal	269	147	56
	MCI Stable	MCI	MCI	81	80	2
Declining	Normal Declining	Normal	MCI		59	32
	MCI Declining	MCI	Dementia (non-AD)		0	0
			Dementia (poss-AD)		19	7
			Dementia (prob-AD)		21	9
Super declining	Super declining	Normal	Dementia (non-AD)		5	0
			Dementia (poss-AD)		21	10
			Dementia (prob-AD)		28	19
Dementia		Dementia (non-AD)		6		
		Dementia (poss-AD)		8		
		Dementia (prob-AD)		25		

Figure 1. Schematic of subject categorization based on dementia diagnosis at time of enrollment and follow-up.



Methods: Fully-automated lateral ventricle segmentation and statistical analysis of ventricle volumes in dementia groups

Lateral ventricular volumes were estimated on all MR scans using a high-accuracy, fully-automated ventricle segmentation technique that was validated on a manually-traced, heterogeneous set of expanded ventricles in non-demented AIDS patients (see Poster #37 M-AM for validation and [2] for algorithm). The lateral ventricles included the frontal (anterior) horn, body, and temporal and posterior horns. The effects of the following factors on ventricle-to-brain ratio (*i,e.*, ventricular volume divided by whole-brain volume) were analyzed in linear statistical models: age, gender, education level, dementia category, and presence of infarcts. The overall significance of each factor was determined by omnibus F tests; focused F tests determined significant differences between pairs of factor levels.

Cross-sectional analysis: Dementia status, age, and gender significantly impact ventricular volume measures

Ventricle-to-brain ratio (VBR) at time of enrollment was the outcome variable in a cross-sectional analysis of all time-of-enrollment data. VBR rose with age ($p<.0001$) and was higher among males ($p=.0279$). VBR was higher in dementia subjects than MCI subjects ($p=.0053$), and VBR was higher in MCI subjects than cognitively normal subjects ($p=.00903$). Within the dementia group, VBR was significantly higher in the possible-AD subgroup than probable-AD subgroup ($p=.0232$), and VBR in possible- and probable-AD subgroups was higher than in the MCI subgroup. However, VBR in the non-AD subgroup was not significantly different from the MCI group. See Figures 2-4.

Figure 2. Box plot of ventricle-to-brain ratio at time of enrollment broken out by dementia diagnosis at time of enrollment.

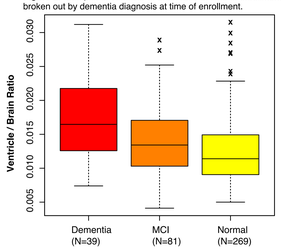


Figure 3. Scatter plot of ventricle-to-brain ratio at time of enrollment as a function of age at time of enrollment. The least-squares best-fit line is shown.

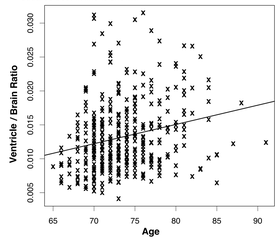
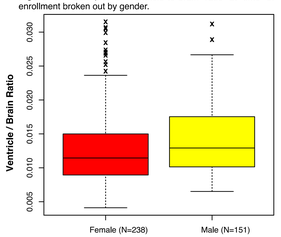


Figure 4. Box plot of ventricle-to-brain ratio at time of enrollment broken out by gender.



Retrospective analysis: Advanced and rapid decliners had significantly larger ventricles prior to dementia

VBR at time of enrollment was the outcome variable in a retrospective analysis of the 333 subjects who had a follow-up clinical exam. VBR at time of enrollment was significantly lower in the normal stable and normal decliner groups compared to all other dementia progression groups (maximum $p=.05$), but differences between the normal stable and normal decliner groups were not statistically significant ($p=.454$). VBR was significantly lower in the normal stable group compared to the possible-AD and probable-AD super-decliner groups($p=.01$, $p=.0047$), but not the non-AD super-decliner group ($p=.53$). See Figures 5 and 6.

Figure 5. Box plot of ventricle-to-brain ratio at time of enrollment broken out by dementia progression between enrollment and follow-up.

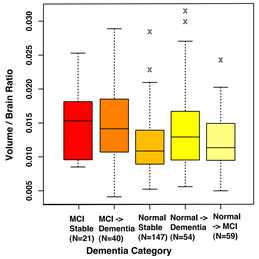
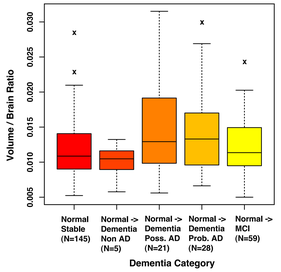


Figure 6. Ventricle-to-brain ratio at time of enrollment among initially-normal subjects, broken out by dementia progression sub-groups between enrollment and follow-up.



Longitudinal analysis: Faster ventricular expansion among advanced decliners

The rate of VBR change over time between time-of-enrollment and follow-up MR scans was the outcome variable in a longitudinal analysis of 142 subjects with two scans. No overall factors significantly modulated the rate of VBR change although age trended toward significance ($p=.055$). Rate of VBR change was not significantly different between normal stable, normal decliner, and any normal super-decliner subgroups (minimum $p=.278$). However, rate of VBR change among MCI decliners was significantly higher compared to normal stable and normal decliner subjects ($p=.03$, $p=.04$), and trended toward being significantly higher compared to possible-AD super-decliners ($p=.06$). See Figures 7 and 8.

Figure 7. Rate of VBR change between enrollment time and follow-up, broken out by dementia progression.

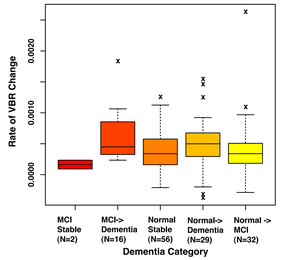
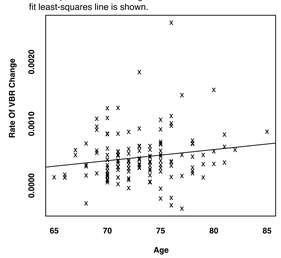


Figure 8. Rate of VBR change between enrollment time and follow-up, as a function of age at time of enrollment. The best-fit least-squares line is shown.



Conclusion: Lateral ventricle size may represent a susceptibility factor for rapid dementia progression

We believe this is the largest study to date to demonstrate detailed ventricular differences between dementia groups. Larger pre-dementia ventricles among normal subjects rapidly declining to dementia of the AD type suggests the possible role of ventricular size as a susceptibility factor for rapid AD progression. Future work should investigate the apparent acceleration of ventricular expansion with age and advanced progression from MCI to AD.

References

[1] Lopez OL, Kuller LH, Fitzpatrick A, Ives D, Becker JT, Beauchamp N. Evaluations of dementia in the cardiovascular health cognition study. Neuroepidemiology 2003;22(1):1-12.
[2] Carmichael OT, Aizenstein HA, Davis SW, Becker JT, Thompson PM, et al. Atlas-based hippocampus segmentation in Alzheimer's disease and mild cognitive impairment. To appear, NeuroImage, 2005.

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