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Alzheimer's Disease: Longitudinal CT Studies of Ventricular Change

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A 3-year longitudinal study was conducted with 50 Alzheimer's disease patients and 45 elderly control subjects. All study participants received an extensive evaluation that included brain CT at baseline and follow-up. Quantitation of ventricular size, using both linear and volume methods, revealed highly significant cross-sectional and longitudinal differences between the Alzheimer patients and control subjects. Specifically, the annual rate of change in ventricular volume was approximately 9% in the Alzheimer patients and approximately 2% in the controls. The presence of age-related white matter lesions had no effect on the clinical course of the patients or on the changes in ventricular size. Among the Alzheimer patients, the rate of clinical decline was strongly related to the rate of change in ventricular size. Baseline ventricular measurements were of no value in predicting the subsequent rate of clinical deterioration or ventricular enlargement.

The results suggest that changes in ventricular size closely reflect the clinical changes in Alzheimer patients.

Cross-sectional CT studies have repeatedly demonstrated statistically significant differences in ventricular size between Alzheimer's disease patients and elderly normal control subjects. However, it is generally acknowledged that a single observation of ventricular size in aged memory-impaired individuals is of limited clinical utility [1, 2]. Very few longitudinal CT studies of either normal aging or Alzheimer's disease have been reported. Furthermore, there are no reported longitudinal studies that include Alzheimer patients and aged normal individuals with white matter lesions. These lesions are commonly found in elderly groups [3]. After excluding patients with infarcts, it appears that the white matter lesions are caused by microvascular hyalinosis and demyelination [3, 4]. However, the possible role of white matter lesions in the course of Alzheimer's disease or normal aging is unknown.

In one longitudinal study, Naguib and Levy [5] followed up 10 Alzheimer patients after 2 years. Their results indicated that the five patients who demonstrated psychometric decline had significantly greater ventricular areas when compared with the five relatively stable Alzheimer patients. These authors also reported that the baseline CT measurements were of no predictive value in the determination of the subsequent course of Alzheimer's disease. Gado et al. [6] studied 21 Alzheimer patients and 24 control subjects on two occasions separated by an interval of 1 year. Using linear measurements to estimate ventricular size (across two different CT scanners), these researchers obtained results that indicated that the Alzheimer group had a greater rate of longitudinal change. In addition, the Alzheimer group had significantly larger ventricles at each of the two cross-sectional time points. Brinkman and Largen [7] did follow-up CT studies on five "significantly" demented patients after 15–35 months. Their results indicated that their patients had rates of linear ventricular change that exceeded those predicted from published cross-sectional normative data. Luxenberg et al. [8] studied 18 Alzheimer patients and 12 aged control subjects with a follow-up interval that ranged from 6 months to 5

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years. Their results indicated significantly increased yearly rates of ventricular enlargement in the Alzheimer group relative to the control group.

The foregoing longitudinal CT studies were carried out with relatively small sample populations. In the study reported here, we followed up a large group of Alzheimer patients and control subjects after a standard 3-year interval. We also report the first longitudinal results on the effect of white matter lesions on ventricular size and clinical outcome. Our CT measurements included both linear and volume studies of ventricular size.

Subjects and Methods

A complete 3-year longitudinal follow-up examination was conducted on 50 Alzheimer patients and 45 control subjects who were comparable in age and follow-up interval (see Table 1). All Alzheimer patients were participants in the New York University Aging and Dementia Research Program, and all met both DSM III [9] and NINCDS-ADRDA diagnostic criteria for Alzheimer's disease [2]. The normal control subjects were volunteers and were mainly derived from the spouses, relatives, and friends of the impaired group. At both baseline and follow-up examinations, all subjects received medical, neurologic, psychiatric, neuropsychological, and CT examinations. Following this standard protocol of assessments, all subjects included in the longitudinal study were diagnosed as normal or as presumed Alzheimer patients at both evaluations. The patients selected for study had no evidence of diseases that could affect brain functioning other than Alzheimer's disease.

In defining these two study groups, subjects with any history of stroke or with neurologic or CT evidence of infarction (sharply marginated low-attenuation lesions of gray or white matter), or modified Hachinski [10] scores >3 were excluded. At baseline, subjects with hypertensive (BP > 150/90) and/or clinically significant cardiac disease were excluded. Also excluded were diabetics requiring treatment with insulin or oral medication. Subjects with diabetes under dietary control were not excluded from the study. With these relatively strict subject selection criteria we found no evidence for baseline or follow-up differences between Alzheimer patients and normal subjects on the following medical parameters: hematologic, gastrointestinal, pulmonary, immunologic, cancer, thyroid, or cardiac. Therefore, the two study groups began and remained comparable medically. Over the 3-year interval, less than 4% of all the subjects returning for follow-up showed significant evidence of adverse medical changes. These changes were equally distributed across the two study groups. Within the Alzheimer group, adverse medical changes were not associated with the rate of cognitive decline.

In deriving the study groups we found different attrition rates at the 3-year follow-up for the patient and control groups. Specifically, 87% of the controls contacted returned for follow-up as compared with 48% of the Alzheimer patients. Table 2 summarizes the follow-up attempts for the two study groups. Death was more common in the Alzheimer group, and over 40% of them failed to return due to the severity of the disease and other health-related reasons. However, at least some follow-up information was obtained for approximately 90% of the Alzheimer group. When a visit to the clinic was not possible, information was obtained by phone calls and in some cases by home visits. Lack of clinic follow-up for health-related reasons occurred in less than 8% of the control subjects. Specific study of the separate group of 43 Alzheimer patients who did not return for reexamination, but for whom limited follow-up results were available, revealed that their baseline measurements of age (mean = 72.7 ± 5.7) and severity of impairment based on the Global Deterioration Scale (GDS) (mean = 3.9 ± 0.9) [11] did not differ from those of the 50 Alzheimer patients who were successfully followed up (mean age = 71.2 ± 8.1 years; mean GDS = 3.7 ± 1.2).

TABLE 1: Baseline Ages and Follow-up Intervals for Longitudinal Study Groups

Group	No.	Age (Mean ± SD)	Years of Follow-up (Mean ± SD)
Normal	45	68.9 ± 6.4	3.4 ± 0.7
Alzheimer	50	71.2 ± 8.1	2.9 ± 1.2

TABLE 2: Outcomes for Follow-up Attempts (n = 156)

Outcome	Normal (n = 52)		Alzheimer (n = 104)	
	No.	%	No.	%
Completed follow-up	45	86.5	50	48.0
Limited follow-up				
Deceased	1	1.9	13	12.5
Nursing home	0	0.0	18	17.3
Home contact	3	5.8	12	11.5
No follow-up				
Refused	2	3.8	9	8.6
Lost	1	1.9	2	1.9

Psychiatric and Neuropsychological Evaluations

As part of the comprehensive clinical examination, all patients and control subjects received the GDS at each observation point. Evaluation of the GDS was done by a clinician and was based on subjective complaints of memory deficit, on observation of deficit during careful clinical interview, and (in the case of Alzheimer patients) on discussions with caretakers concerning the patient's ability to perform tasks of daily living. This scale evaluates the general level of an individual's ability to function. The global status of the subject is rated on a 7-point scale that has specific behavioral anchor points. Higher values on the GDS indicate greater cognitive impairment. For the Alzheimer patients, the GDS at baseline was 3.7 ± 1.2 and at follow-up 4.5 ± 1.3. The interrater reliability of the GDS is .90, $p < .01$, as determined by the dual evaluation of 39 patients. This scale is also highly correlated with other dementia scales (e.g., the Mini Mental State [12] $r = -.89$, $n = 170$, $p < .01$).

Formal psychometric evaluations were conducted at both time points. In the interest of reducing the number of psychometric variables, we developed a composite Psychometric Deterioration Score (PDS). The PDS represents an equally weighted combination of scores from the Guild Memory Test [13] and the WAIS [14]. The PDS includes five measures from the Guild Memory Test: the immediate and delayed recall of two paragraphs; the immediate and delayed recall of paired associates; and recall of abstract designs. Four subtests of the WAIS were included: vocabulary; digit symbol substitution, and digits forward and backward. To obtain the PDS, the calculated total average percent correct is divided into a quasi 1–7-point scale, with low numbers representing relatively little impairment and high scores representing poor psychometric test performance. For the Alzheimer patients, the PDS at baseline was 4.8 ± 1.6 and at follow-up 5.5 ± 1.9. The test-retest reliability of the PDS is .94, $n = 25$, $p < .001$.

From the GDS and the PDS scores we attempted to define a group of Alzheimer patients who unequivocally demonstrated cognitive decline over the study interval. We defined decliners as those subjects showing changes ≥2 units on either the GDS or PDS, with a minimum of 1 unit of change on the other scale. By this calculation we identified 26 decliners among the 50 Alzheimer patients. The remaining 24 Alzheimer patients, who showed relatively less cognitive deterioration, were termed the nondecliners. In this study, ceiling effects in the evaluation of cognitive change longitudinally were not a problem, since mild to moderately severe patients were selected at baseline (i.e., GDS 3–5).

CT Examination

The longitudinal cohort of patients and controls was developed over a period of time (1978–1986) in which three different CT scanners were used. These included the EMI 5005, the Philips Tomoscan 200, and the GE 8800. Scans from all machines were obtained from the base to the vertex of the brain with contiguous 10-mm-thick slices. Each study was done by using a zero scanning angle relative to the canthomeatal plane. All patients had their follow-up study on the GE 8800 CT scanner. The majority of both Alzheimer patients and control subjects who were followed also had baseline CT evaluations on the GE 8800 CT scanner. With respect to the other machines used at baseline, seven controls and six Alzheimer patients were studied on the EMI 5005, and six controls and 10 Alzheimer patients were studied on the Philips machine.

In the interest of utilizing as much of this valuable data as possible, several studies were conducted to determine the potential errors in making comparisons across machines. Water phantom studies revealed that for relatively large volumes, which include the ventricular anatomy, accurate and reproducible volume estimates were possible across machines. However, for water volumes that were relatively small, i.e., in the range of the cortical sulci, the recovery errors combined with partial volume errors were large. Therefore, in the present study only ventricular size was quantitatively determined. We also examined among the normal subjects and the Alzheimer patients the effect of a particular CT machine on the baseline ventricle/brain ratio for both the linear and the volume measures. Our results failed to show significant machine-related effects for these two measures ($F = 1.97$ and 1.84, $p > .05$, respectively). We also found no evidence for a diagnosis by machine interaction ($p > .05$) for the two ventricle measures. Therefore, data for the three machines were combined in the analyses reported below.

Linear ventricular assessments. For each CT study ventricular size was estimated by using the arithmetic sum of five ratios of linear measurements. Each measurement was corrected for brain size by dividing by a corresponding measurement of the brain width (inner table to inner table) and thereby forming a linear ventricle/brain ratio (VBR-L). These measurements were taken from the one or two CT slices that best depicted the basal ganglia, foramen of Monro, and third ventricle. The measurements included the maximum widths across the frontal horns, the bicaudate diameter, the width of the third ventricle, and the oblique widths of the left and right frontal horns. This procedure is well documented as being a useful index for describing Alzheimer-related changes [15] and is highly reliable across observers. ($r = .91$, $p < .001$, $n = 109$).

Volume ventricular assessment. We estimated ventricular volume by outlining the anatomy of the ventricles and the skull inner table on a transparent plastic overlay. The overlay was digitized by using a video camera connected to a Data General-Grinnell imaging computer station. With this system we are able to precisely determine the number of picture elements in each enclosed component, i.e., the subvolumes of the ventricular anatomy and the whole-slice brain volume minus the ventricular subvolumes. The volume ventricle/brain ratio (VBR-V) measurement was constructed slice by slice as the ratio of the ventricular area divided by the brain plus ventricular area. Across all machine and subject studies it was determined that the most reliable data would be obtained by using the three contiguous slices that depicted the greatest VBR-V. This procedure avoids measurement of the small ventricular subvolumes in the inferior temporal horns and in the most superior aspects of the bodies of the lateral ventricles. Direct comparison of this procedure with our earlier published ventricular volume method [16] was excellent ($r = .85$, $p < .01$, $n = 61$). The earlier procedure relies on interactive use of the GE 8800 CT computers and the definition of pixel ranges that separately defines CSF and brain (white and gray), and uses seven slices to estimate ventricle volume and three contiguous slices to estimate brain volume.

White matter lesions. All evaluations of white matter lesions were done on the follow-up study by using hard-copy X-ray film from the GE 8800 CT scanner obtained under standard conditions, which included X-ray tube power and window and level settings for the hard-copy imaging. Each CT study was evaluated separately for the presence or absence of white matter lesions. The white matter lesions were defined as areas of reduced CT white matter attenuation, typically in the periventricular white matter. With MR scanning that employed long TR images, these white matter areas show increased signal [17]. At neuropathology these white matter lesions are associated with demyelination and arteriolar hyalinization, and in severe cases there is axonal loss [3]. Using procedures that we have reported elsewhere [3], we categorized each study according to the severity and location of the CT lesions. In the longitudinal analysis, we identified 10 Alzheimer patients and 14 control subjects as having white matter lesions. All subjects with white matter lesions at follow-up had demonstrated white matter lesions at baseline. We did not observe any cases in which white matter lesions either developed or resolved during the 3-year course of the study. In several cases the apparent area of involvement of the white matter lesions increased in size.

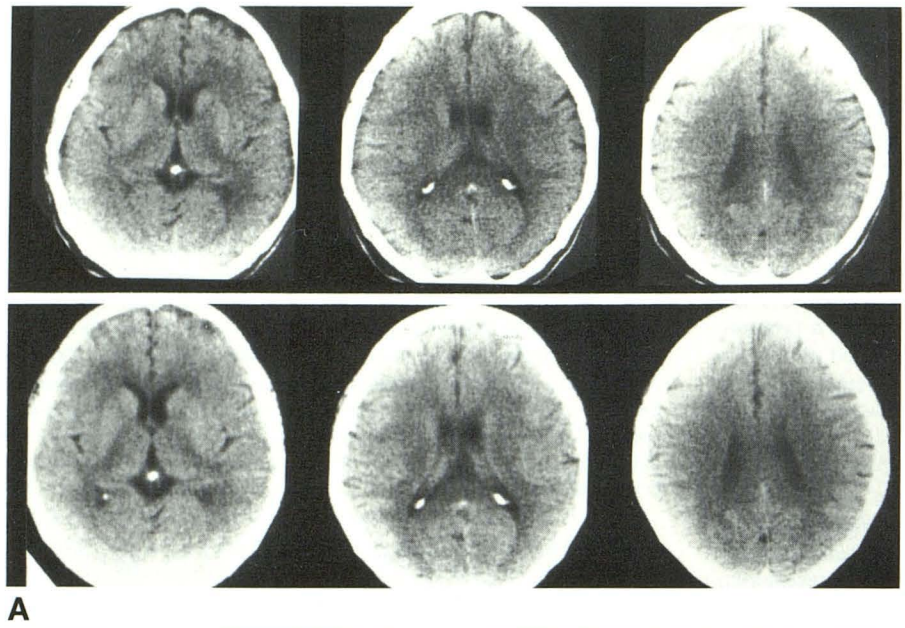
Results

As summarized in Table 3, the results for the linear and volume measurements were remarkably consistent. For both linear and volume VBR measurements two-way Analyses of Variance (ANOVA) (i.e., two diagnostic groups and presence or absence of white matter disease), indicated significant

TABLE 3: Comparison of Cross-Sectional and Longitudinal Measures of Ventricular Size in Normal Aging and Alzheimer's Disease

CT Variable	Normal ($n = 45$) Mean ± SD	Alzheimer ($n = 50$) Mean ± SD	Percent Change in Alzheimer Group
Linear ventricle/brain ratio × 100			
Time I	63 ± 12	72 ± 15*	+14
Time II	65 ± 11	80 ± 19*	+23
% change per year	0.7 ± 1.2	3.4 ± 4.4*	+385
Volume ventricle/brain ratio × 100			
Time I	90 ± 29	119 ± 44*	+32
Time II	98 ± 30	141 ± 49*	+44
% change per year	2.3 ± 3.7	9.3 ± 12.1*	+304

* Different from normal control $p < .05$.



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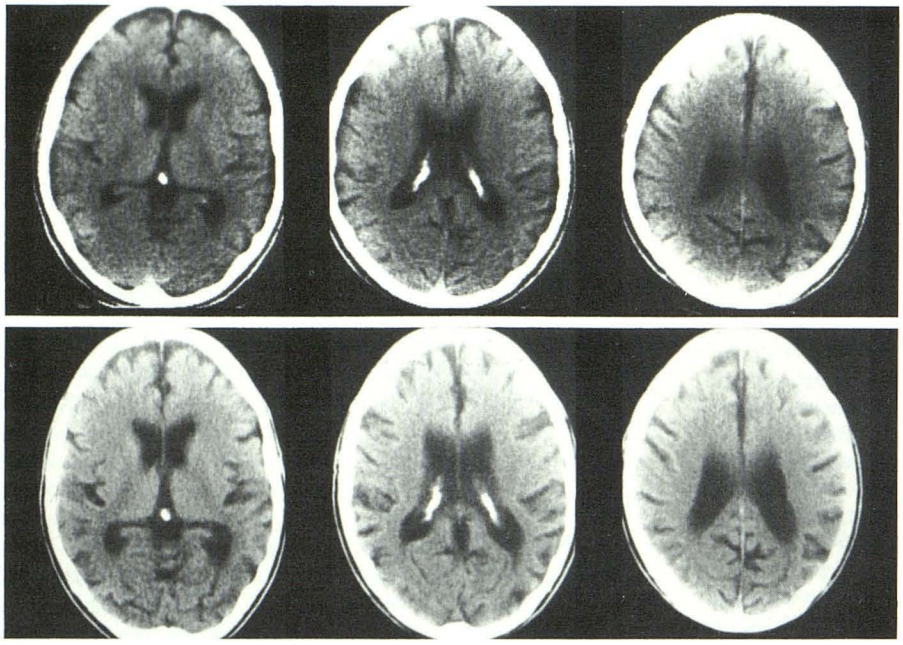

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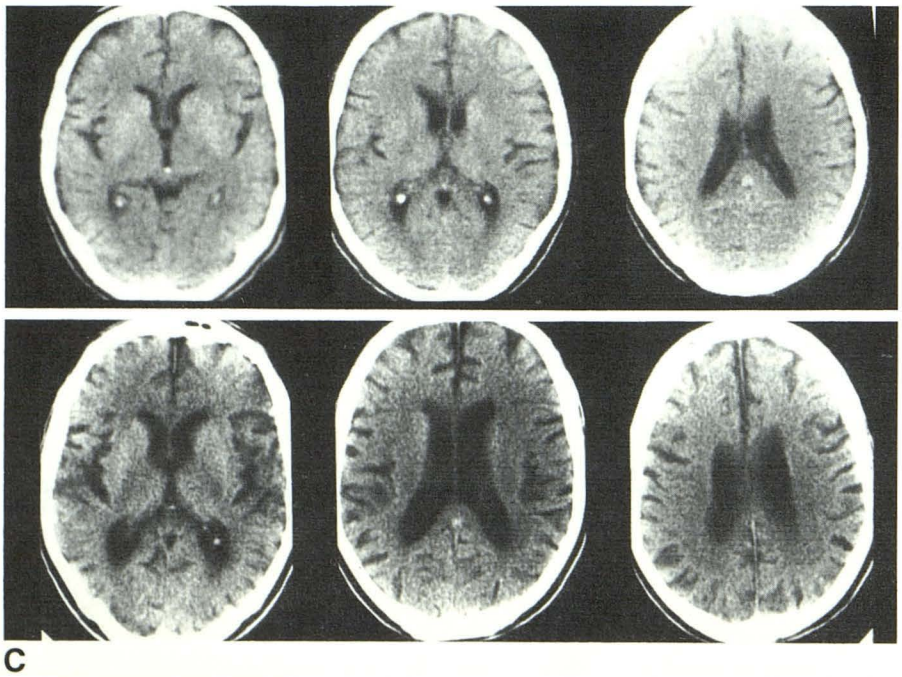

C

Fig. 1.—Typical 3-year changes in ventricular size in three women 59–65 years old at baseline.

A, Normal control subject.

B, Nondeclining Alzheimer patient (level 4 on Global Deterioration Scale).

C, Declining Alzheimer patient (from level 3 to level 5 on Global Deterioration Scale).

diagnostic group differences at baseline, at follow-up, and for the yearly rate of ventricular enlargement, [F's (1,90) > 13.5, ($p < .01$)]. The yearly rate of change was computed by using the following equation:

$$\text{yearly rate} = \frac{[\text{ventricle size follow-up} - \text{ventricle size baseline}]}{\text{Follow-up interval (years)}}$$

The yearly rate of change of ventricle size (either linear or volume) was observed to be three to four times greater in Alzheimer patients than in normal subjects. Figure 1 depicts the average 3-year ventricular changes in Alzheimer patients and in normal subjects.

In the ANOVA, the presence of white matter lesions in both the cross-sectional and longitudinal analyses had no significant effects on ventricular size, and there were no interaction effects on ventricle size between clinical diagnosis and white matter lesions [F's (1,90) < .8, $p > .05$]. Figure 2 shows that the average yearly rates of ventricular change differ between the Alzheimer and normal groups, but within each group the rates are unchanged by the presence or absence of white matter lesions.

In further analyses, we examined the hypotheses that (1) patients showing clinical deterioration over the study interval would show larger ventricles at baseline than would the relatively stable patients and thereby demonstrate the predictive value of the ventricle measure, (2) that the deteriorating patients would show correlated changes in the rate of ventricular size, and (3) that the deteriorating patient group would comprise a disproportionate number of patients with white matter disease. Results from one-way analyses of variance showed that on both the linear and volume measures there were no baseline differences between decliners and nondecliners ($p > .05$). Only at follow-up was there significantly increased ventricular enlargement ($p < .05$) in the decliner group over the nondecliner Alzheimer group (see Fig. 3). Additionally, the Alzheimer group that did not return for follow-up ($n = 43$) was no different at baseline than the Alzheimer group that was followed ($p > .05$). In summary, at baseline there were no age, GDS, or ventricular differences between the Alzheimer groups ($p > .05$).

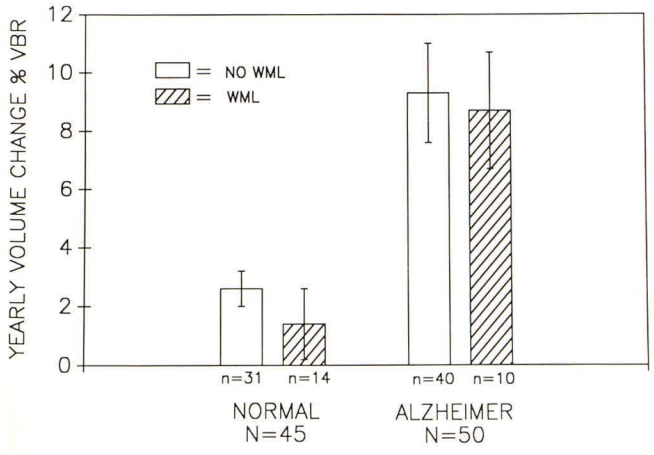

Fig. 2.—Annual rate of change of ventricular volume in Alzheimer patients and control subjects: the effects of white matter lesions (WML).

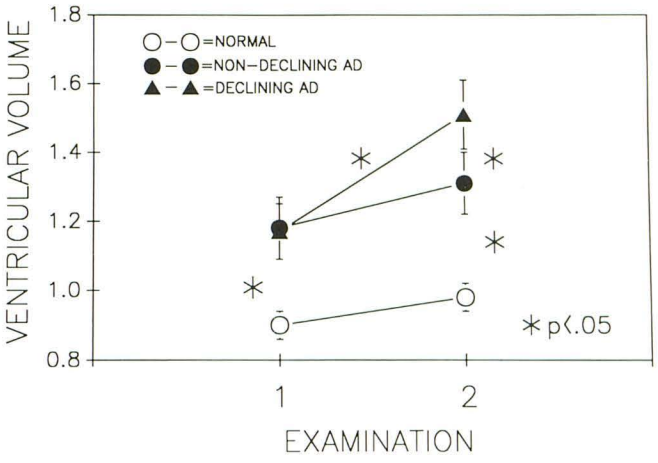

Fig. 3.—Ventricular volume changes in declining ($n = 26$) and nondeclining ($n = 24$) Alzheimer disease (AD) patients and control subjects ($n = 45$).

With respect to the second hypothesis, one-way analyses of variance with Tukey follow-up procedures showed that the rate of ventricular enlargement was significantly greater ($p < .05$) in the decliner group than in either the nondeclining Alzheimer group or the control group. The control subjects and the nondeclining Alzheimer patients did not differ significantly with respect to rate of ventricular enlargement. However, these two groups did differ significantly in the amount of ventricular enlargement at each of the two time points. The nondeclining Alzheimer group always showed significantly more ventricular enlargement (see Fig. 3).

The third hypothesis that patients with white matter lesions would be more represented in the declining group was not supported. Specifically, six patients with white matter lesions were in the declining group and four patients with white matter lesions were in the nondeclining group ($\chi^2 = .41$, $p > .05$).

Discussion

The results of this longitudinal CT study show that Alzheimer patients have more rapid ventricular enlargement than do control subjects. The effects of the accelerated atrophic process in Alzheimer's disease are clearly seen at each of the two cross-sectional time points studied. This result is in agreement with earlier studies [6–8]. Our results also show a strong relationship over the study interval between the magnitude of ventricular enlargement and the presence or absence of significant clinical decline. Also in agreement with the earlier studies, our results show no predictive value for baseline ventricular size in determining the further rate of clinical deterioration or the further rate of ventricular enlargement. As such, these data suggest that changes in ventricular size either follow changes in clinical condition or are more closely associated in time to observed clinical deterioration

than our study could have detected after a 3-year time interval.

Surprisingly, the results suggest that coincident white matter lesions have no effect on either (1) the severity of clinical deterioration in Alzheimer patients or (2) the magnitude of ventricular enlargement in the Alzheimer or control groups. These results suggest that in the absence of infarction, the presence of CT white matter disease (microvascular hyalinosis, edematous changes, and demyelination [3, 4, 17]), does not have a measurable impact on the Alzheimer process affecting the patient. Although our previous studies have identified clinical neurologic correlates of white matter lesions (e.g., gait and other motoric dysfunctions) [3, 18], the present longitudinal study was not designed to assess progressive motor changes. However, the results do indicate that white matter lesions had no significant longitudinal effect on cognition, memory, general medical health, or the project's attrition rate. Nevertheless, the relatively small sample size in the present study needs to be substantially expanded before these conclusions can be considered definitive.

Over all analyses, the linear and volumetric ventricular measurements gave the same results. Therefore, our findings suggest that the easily determined linear measures can be substituted for the more laborious area and volume measurements.

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