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Aging, Dementia, and Brain Atrophy: A Longitudinal Computed Tomographic Study

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Studies involving linear measurements of ventricular size and a volumetric measurement of the cerebrospinal fluid (CSF) space were performed on elderly subjects with mild dementia of the Alzheimer type and on age-matched controls. Forty-five subjects were studied twice at a 1 year interval; linear ventricular measurements showed not only a greater degree but a more rapid evolution of brain atrophy in individuals with mild dementia as compared with controls. An additional 12 normal subjects were studied twice over a 1 year period with volumetric estimates of the CSF space, which demonstrated development of significant brain atrophy within 1 year, while linear measurements on the same scans showed no significant change. The volumetric method is regarded as a more sensitive indicator of brain volume and is potentially useful in further studies in dementia.

Since the introduction of computed tomography (CT) for the study of intracranial contents, apparent atrophy of the brain in older patients has been obvious. Two questions have been raised by the conflicting data available at this time: (1) Do normal subjects show progressive cerebral atrophy with age? and (2) Do demented subjects show more atrophy than that which relates to aging alone?

The answer to the first question seems clear from a number of cross-sectional studies [1-7] performed over the past 7 years. With increasing age above 55-65 years, the brain apparently undergoes increasing atrophy, although this finding has not been tested or confirmed on longitudinal studies in the same subject population.

The second question has proven more difficult, with some investigators finding evidence for additional atrophy in dementia [1, 2, 6] and others [4, 5] maintaining that this was not the case. Recently Gado et al. [7] found that there was evidence for greater brain atrophy in subjects with dementia than in matched normal controls.

When medical, other neurologic, and clearly vascular causes of dementia have been excluded, most dementia cases in patients over 60 are thought to be due to senile dementia of the Alzheimer type (SDAT) [8]. Without autopsy proof, however, SDAT remains largely a clinical diagnosis, one primarily of exclusion. At Washington University, carefully selected subjects with a clinical diagnosis of mild but definite SDAT have been matched with controls in a longitudinal study of various anatomic, psychologic, and electrophysiologic aspects of this disease. The present study concerns serial CT scans obtained in these subjects in an effort to determine whether or not a change over time would predict the future development of more severe dementia [9].

Subjects and Methods

Study Criteria

Our subjects were enrolled in a longitudinal study of SDAT [9]. Inclusion criteria were sustained deterioration of memory in an alert subject and impairment in at least three of the following five cognitive abilities: orientation; judgment and problem solving; performance in community affairs, home, and hobbies; and personal care. The disorder was required to be progressive, with a gradual onset, and of 6 months' or longer duration. Exclusion criteria included other neurologic disorders, such as brain tumor and multiinfarct dementia. Subjects with a history of psychiatric disorder and those with current depression were also excluded. CT criteria for exclusion included findings suggestive of communicating hydrocephalus, as evidenced by the presence of marked dilatation of the cerebral ventricles with normal or absent cortical sulci [10].

Healthy control subjects were recruited from the community and matched with each SDAT subject for age, gender, race, and social position. SDAT and control subjects ranged in age from 64 to 81 years.

The clinical assessment of these subjects included a structured interview designed to facilitate the diagnosis of SDAT and to rate its severity. Sufficient data were collected to allow the interviewer, a neurologist or psychiatrist involved in this study, to rate the subject in each of the five cognitive and behavioral categories plus memory, and to assign a clinical dementia rating [11]. This yielded a global rating of 0 (no dementia); 0.5 (questionable dementia); or 1, 2, or 3 (mild, moderate, or severe dementia). Repeat assessments were made at 6 months and 12 months after entry.

CT Examination

At the initiation of the study, CT scans were obtained using an EMI 7070 scanner. Slices 6 mm thick oriented to the orbitomeatal line were processed on a 312×312 matrix in a 25.4×25.4 cm field of reconstruction. The scanner was equipped with an interactive console and a software program allowing the computed distance between any two points to be displayed in millimeters.

Before the end of the first year of this study, the EMI 7070 scanner was replaced by a Siemens Somatom 2 unit, which can provide linear measurements like the older EMI 7070 scanner and also permits volumetric measurements.

The Siemens Somatom 2 scans consisted of 8-mm-thick sections processed on a 256×256 matrix in a 25.4×25.4 cm field of reconstruction.

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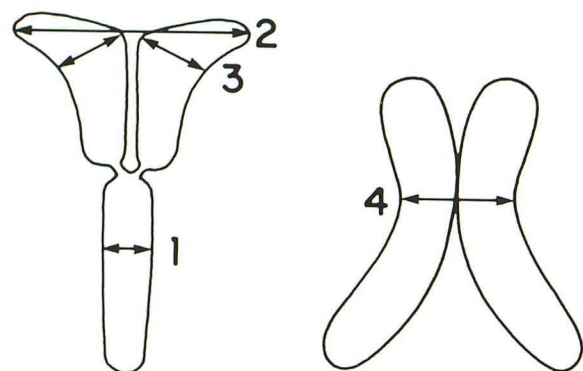


Fig. 1.—Linear measurements of ventricular system on CT. 1 = width of third ventricle. 2 = bifrontal span. 3 = caudate span. 4 = combined width of bodies of both lateral ventricles.

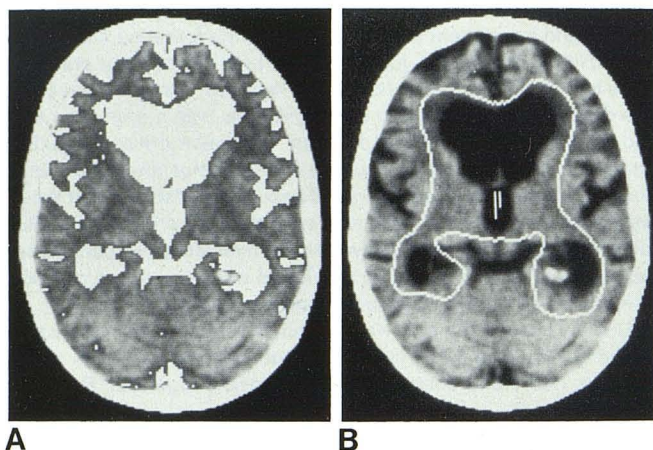


Fig. 2.—A, Highlighting pixels of ventricles and subarachnoid spaces. B, Region of interest is determined to exclude cerebral sulci and limit highlighting to ventricular system.

Linear Measurements

The linear measurements used in this study are (fig. 1): (1) the width of the third ventricle; (2) the bifrontal span between the furthest points at the lateral margins of both frontal horns; (3) the caudate span, measured as the sum of the shortest distance on each side between the medial border of the caudate nucleus and the anterior end of the septum pellucidum; and (4) the combined width of the bodies of the lateral ventricles in their midportion (the narrowest part of the body). The distance between the inner table of the skull at the same plane of measurements 1, 2, and 4 was obtained. The width of the inner table at the frontal horn was used as the denominator to obtain the ratio of the caudate span to the cranium.

The following ratios were computed from the linear measurements of the ventricle and the cranium as described above: frontal horn ratio, the caudate span ratio, ventricular body ratio, and ratio of the width of the third ventricle. A ventricular index was computed by adding the linear measurements of the ventricles and dividing the sum by the width of the cranium at the level of the body [5].

Volumetric Measurements

Volumetric measurements were obtained only from Somatom 2 images after filtering to reduce the noise level to 1–2 Hounsfield

TABLE 1: Age and Gender of Control and Dementia Subjects

Gender	Demented		Controls		Totals
	No. Subjects	Mean Age ($\pm$ SD)	No. Subjects	Mean Age ($\pm$ SD)	
Men	10	70 (6.3)	10	69 (3.7)	20
Women	11	72 (4.7)	14	72 (4.4)	25
Totals	21	71 (5.5)	24	71 (4.3)	45

units (H). To obtain a volumetric index of the cerebrospinal fluid (CSF) spaces, three sections above the roof of the lateral ventricle and four below it were selected, and the following procedure was followed [7]:

1. Interacting with the console, the operator highlighted and recorded the pixels constituting the ventricles (V) and/or subarachnoid spaces (S) within each section (fig. 2).

2. On sections containing both ventricles and the subarachnoid spaces, the process was repeated after determining a region of interest encompassing the ventricles but excluding the subarachnoid space (fig. 2).

3. The pixel count for the cranial cavity (C) in each section, defined as all pixels with a density below 100 H, was obtained.

4. Total values of V; S; V + S; and C for all seven sections were computed and used to formulate the volumetric indices, defined as: volumetric index of ventricular size = $V\% = \frac{V_{Total}}{C_{Total}} \times 100$; volumetric index of sulcal size = $S\% = \frac{S_{Total}}{C_{Total}} \times 100$; and volumetric index of the ventricles and subarachnoid space = $(V + S)\%$.

Subjects

The subjects comprised two groups. The first consisted of 21 demented subjects with a mean age of 71.1 years and 24 normal controls with mean age of 71.0 years at the time of entry in the study. There were 20 men and 25 women (table 1). While the demented subjects were all mildly affected at entry, some were moderately or severely demented on reexamination 1 year later; none were improved. All of the control subjects remained healthy on assessment 1 year later. Each subject had a CT scan on the EMI 7070 scanner at entry and a follow-up scan by the Somatom 2 unit 1 year later. A smaller group of 12 normal subjects (nine men and three women) was examined both at entry and 1 year later on the same scanner (Somatom 2).

The scans of both groups were analyzed for the size of the CSF spaces. The EMI scans were analyzed with linear measurements of ventricular size while the Somatom 2 scans were subjected both to linear and volumetric measurements of the ventricles and subarachnoid spaces. Statistical methods consisted of multiple analyses of variance, paired *t* tests, and an analysis of covariance.

Results

In the first phase of this study, 45 subjects were evaluated, each of whom had CT initially on the EMI unit and 1 year later on the Siemens scanner. The actual interval between the CT scans was 12.9 ± 2.9 months. Table 2 shows the correlation of these measurements with dementia at both points. Both at entry and 1 year later, there were highly significant differences in all of the linear measurements between the control and demented groups as indicated by the results of the *t* tests.

In order to determine whether the demented group showed a greater change over time than the controls, an analysis of covari-

TABLE 2: Ventricular Size (Linear Measurement Ratios) in Demented and Control Subjects over Time

Linear Measurement	Mean Ratio (±SD)						Variance Ratio
	At Entry			1 Year Later			
	Controls	Demented	t Test	Controls	Demented	t Test	
Third ventricle	5.3 (1.5)	7.6 (2.3)	3.98*	4.9 (1.0)	7.6 (2.3)	5.19*	8.01†
Frontal horn	33.0 (4.8)	36.7 (4.3)	2.67‡	34.5 (4.2)	38.4 (4.5)	3.01†	1.68
Caudate nucleus	18.5 (5.0)	22.7 (4.5)	2.94†	23.0 (5.8)	29.4 (9.1)	2.80†	1.07
Body of lateral ventricle	22.7 (4.7)	27.1 (3.8)	3.39†	21.3 (4.5)	28.3 (4.5)	5.17*	12.03†
Ventricular index	74.2 (12.8)	87.6 (11.4)	3.70*	77.0 (11.6)	95.5 (15.5)	4.57*	5.38‡

* $p < 0.001$.† $p < 0.01$.‡ $p < 0.05$.

TABLE 3: Changes in Size of Cerebrospinal Fluid Spaces over Time in Normal Subjects

Measurement	Mean ($\pm$ SD)		
	At Entry	1 Year Later	t Test
Volumetric indices (%):			
Ventricles	5.45 (1.84)	5.65 (1.99)	2.99*
Sulci	5.95 (2.39)	6.74 (2.80)	3.45†
Ventricles + sulci	11.30 (3.28)	12.39 (3.59)	4.77†
Linear measures (ratio):			
Third ventricle	4.23 (1.85)	4.15 (1.36)	-0.25
Frontal horn	32.63 (4.31)	33.14 (4.26)	0.91
Caudate nucleus	16.79 (3.75)	17.99 (3.98)	1.24
Body of lateral ventricle	21.37 (3.17)	20.92 (3.67)	-0.52
Ventricular index	69.23 (10.43)	70.71 (10.92)	1.10

* $p < 0.05$.† $p < 0.01$.

ance was performed on the 1 year data for each linear measurement ratio using the appropriate scores at entry as the covariates. The columns on the right in table 2 indicate that for the three linear measurement ratios there was a significantly greater change with time in the demented group. The ratios involving the third ventricle and the width of the bodies of the lateral ventricles as well as the ventricular index showed significant differences between groups in the degree of change over time.

The second phase of this study involved 12 normal control subjects who had both the initial scan and the later scan obtained on the Siemens scanner permitting volumetric as well as linear comparisons. The actual interval between the CT scans was 12.7 ± 1.9 months. Table 3 shows the values for ventricular and sulcal size at entry and 1 year later for the subjects as well as the linear measurement ratios obtained from the same group of scans. All of the volumetric measurements showed a small but significant change over a 1 year period.

Discussion

The two goals of our studies were to evaluate brain volume changes longitudinally in a group of patients with SDAT and to compare the accuracy of linear and volumetric analyses for this purpose. We confirmed by linear measurements of ventricular size performed serially on CT scans in the same subjects taken 1 year apart that more pronounced brain atrophy is found in subjects with clinically diagnosed SDAT than in normal controls. Previous cross-sectional studies [1, 2, 6] had repeatedly suggested this but were subject to the usual criticisms of such methods.

With the use of the Siemens scanner, improved separation of brain and CSF densities and low noise permitted the volumetric analysis used in this study. We previously compared these volumetric methods with linear methods performed on the same scans [7] and demonstrated that volumetric measures provided a much greater separation between demented and control subjects. In this study, a smaller group of control subjects were studied serially on the same (Siemens) scanner. Volumetric measurements revealed a small but highly significant (particularly for sulcal volume) increase in CSF space within 1 year's time. Linear measurements performed on the same scans showed no significant differences.

We therefore conclude that the volumetric measurements listed above are more sensitive indicators of CSF space and more capable of documenting subtle changes than the linear measurements of ventricular space. The chief reason for this conclusion lies in the value of measuring the volume of a complex space by a method which, while essentially planimetric, allows for the inclusion of small and hard-to-see spaces. The partial-volume effect, with many pixels having density values intermediate between CSF and brain parenchyma, remains a theoretical problem; however, trial studies at this institution (unpublished data) have shown these volumetric measurements to be highly reproducible both on the same day and 1 week apart. Further support for the utility of this method comes from this and previous work in which the volumetric method showed greater separation between demented and control subjects [7], but also a significant decline in brain volume over 1 year in normal controls when linear measures suggested no change.

The implications of these results for future studies in aging and dementia are substantial. Not only has this volumetric method been shown to be sensitive and reliable, but changes in brain volume have been demonstrated over a short period of time in normal controls. It is conceivable that subjects with rapidly progressive dementia might show changes over even shorter intervals. This method might also permit a closer regional correlation with electrophysiologic, psychometric, and dynamic (positron emission tomography) studies in subjects with progressive dementia.

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