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Original investigations

A computed tomography study of Alzheimer's disease

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Summary. Computed tomography (CT) was used to study cerebral atrophy in 18 patients with clinically diagnosed Alzheimer's disease of presenile type and in 14 healthy age-matched subjects as controls. Using the computerized planimetric method, Subarachnoid Space Volume Index and Ventricle Volume Index were calculated as the measure of cortical atrophy and ventricular dilatation respectively. From the results the following conclusions were drawn:

1. The cerebral atrophy in Alzheimer patients could be attributable to the disease processes rather than to physiological aging of the brain.

2. The degree of atrophy increases in parallel with the progress of the clinical stage, and the cortical atrophy is already apparent at an early stage, whereas the ventricular dilatation becomes pronounced at later stages.

3. CT could be one of the most useful clinical tests available for the diagnosis of Alzheimer's disease.

Key words: Cerebral atrophy – Alzheimer's disease – Dementia – Computed tomography (CT) – Measurement method

Zusammenfassung. Die vorliegende Studie beruht auf vergleichende CT-Verlaufsuntersuchungen über die Entwicklung hirnatrophischer Vorgänge bei 18 Patienten mit klinisch diagnostizierter Alzheimerscher Krankheit und einer Kontrollgruppe von 14 altersentsprechenden Gesunden. Mit computerisierter planimetrischer Methode in 3 Ebenen wurden der Subarachnoidal-Volumen-Index (SVI) und der Ventrikel-Volumen-Index (VVI) als Parameter für das Ausmaß der korticalen Atrophien bzw. der ventrikulären Dilatationen errechnet. Aus den Ergebnissen lassen sich folgende Schlüsse ziehen:

1. Die cerebrale Atrophie beim Alzheimer-Patienten könnte eher vom Krankheitsprozeß abhängig sein als von physiologischen Altersvorgängen des Gehirnes.

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2. Der Grad der Atrophien nimmt mit fortschreitenden klinischen Stadien zu. Dabei sind die korticalen Atrophien bereits in frühen Stadien erkennbar, während die Ventrikelerweiterungen erst in späteren erscheinen.

3. CT könnte einer der nützlichsten klinischen Tests für die Diagnostik der Alzheimerschen Krankheit sein.

Although a number of computed tomography (CT) studies in demented patients have been reported, there is no uniformity of opinion on the relationship between dementia and cerebral atrophy as observed on CT. Some researchers have found that cerebral atrophy in the demented was more marked than in the normal aged, and that CT was useful for the assessment of dementia [2, 8, 10]. Others have reported that the atrophy correlated not with dementia, but with physiological aging [3, 9].

The method for the assessment of cerebral atrophy on CT has also not been established. Several methods have been used, including visual assessment, linear measurement, area measurement and volume measurement. This might be one of the reasons for the differing opinions that have been reported.

As far as we know, there have been no CT studies in a number of patients with Alzheimer's disease of presenile type. Therefore, we attempted to answer the following questions in the cases with presenile Alzheimer's disease by means of a volume measurement method:

1. Is the cerebral atrophy attributable to the disease process or to the physiological aging of the brain?
2. How does the atrophy change as the clinical stages progress?
3. Is CT useful for diagnosing Alzheimer's disease in clinical practice?

Materials and methods

CT scans were obtained from 18 patients with clinically diagnosed Alzheimer's disease of presenile type (4 men, 14 women: the Alzheimer group) and from 14 healthy age-matched subjects (5 men, 9 women: the control group). The criteria for inclusion in the Alzheimer group were onset under the age of 65 years, gradual progressive dementia with dysmnesia as the initial feature, no history of cerebrovascular disease, absence of history and evidence suggesting other causes of dementia [4]. The Alzheimer group consisted of in-patients and out-patients of the Tokyo Metropolitan Matsuzawa Hospital, and were grouped in stages I, II or III [14]. In stage I the chief symptoms were impairment of memory and judgement, spatial disorietation and pronounced lack of spontaneity, but the patient could do almost everything required for daily living without assistance. In stage II the progressive intellectual impairment and various cognitive disturbances such as aphasia, apraxia and agnosia became apparent. Certain motor disturbances of a hypertonic-akinetic character were also frequently observed. The patient often required considerable care. In stage III dementia was profound, and the patient became completely mute, inactive, bed-ridden and required total care. All control group subjects were volunteers employed in the hospital and with no previous or current psychiatric and neurological illness. The age at onset and total duration of the disease in the Alzheimer group and the age on examination in both groups are presented in Table 1.

Each subject was examined with a General Electric (GE) CT/T 8800 Whole Body Scanner. Slices were scanned parallel to the orbitomeatal line with a thickness of 10 mm. The scans were imaged on a display monitor at a window level of 80 and a mean level of 36. For this study four successive scans through the level of the foramen of Monro and through regions above this level were chosen. The representative scans in each group are shown in Figs. 1, 2, 3 and 4.

Table 1. Mean values of clinical data in each group

		Age (years)	Age at onset	Total duration
Alzheimer's disease	($n = 18$)	60.75 ± 7.25	54.08 ± 6.98	6.67 ± 4.09
Stage I	($n = 6$)	60.83 ± 4.23	57.33 ± 3.08	3.50 ± 1.53
Stage II	($n = 5$)	57.80 ± 6.64	52.70 ± 6.49	5.10 ± 0.86
Stage III	($n = 7$)	62.79 ± 8.84	52.29 ± 8.56	10.50 ± 3.94
Controls	($n = 14$)	55.19 ± 8.00		

(mean ± standard deviation)

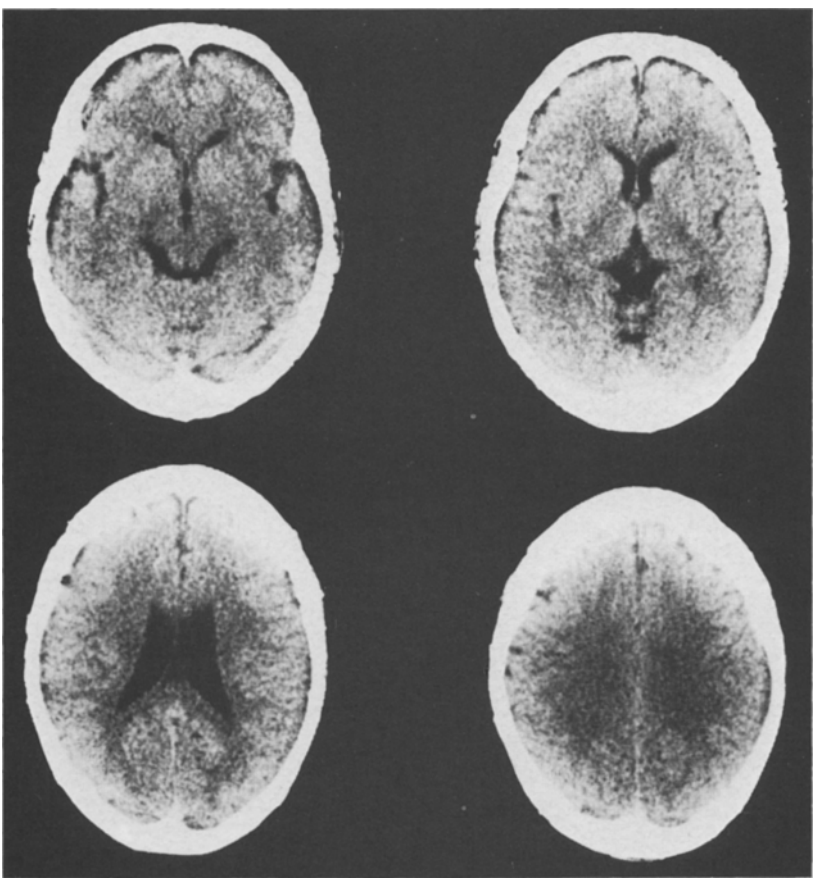

Fig. 1. CT of a control subject

Cerebral atrophy was assessed on the display monitor by applying a programme "Slice Image Analysis", and its two functions were used. The first function was the Region of Interest (ROI) which was used to calculate the area of the traced region with the cursor trace mode on the basis of the number of pixels contained in it. The other function was the Density Contour, which was used to calculate the area of the defined region in a designated range of CT numbers on the basis of the

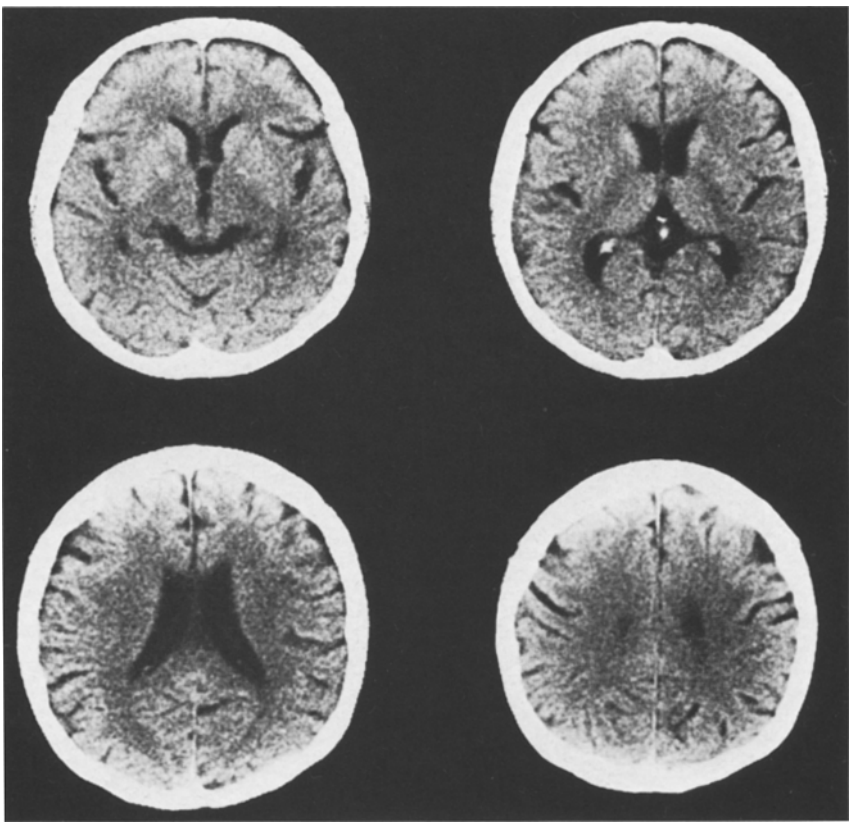

Fig. 2. CT of a stage I patient

number of pixels contained within that range. The following operations were done in each slice: (1) tracing the outline of the ventricle and measuring its area (area A in Fig. 5); (2) tracing the outline of the brain and measuring the area of both the brain and the ventricle (area B in Fig. 5); (3) measuring the area of the intracranial space by entering the range of CT numbers (min. −10, max. 200: area C in Fig. 5). These determinations were repeated three times and the average taken. All these operations were done by the same researcher.

The Subarachnoid Space Volume Index (SVI) and Ventricle Volume Index (VVI) were then calculated using the following formulae:

$$\text{SVI} = \left\{ \sum_{i=1}^{4} (\text{Ci} - \text{Bi})/\text{Ci} \right\} \times 100$$

$$\text{VVI} = \left(\sum_{i=1}^{4} \text{Ai}/\text{Ci} \right) \times 100$$

(i = slice no.)

Results

Intercorrelations between the volume indexes and the clinical data (Table 2)

In the Alzheimer group, there were significant correlations of both SVI and VVI to the total duration of disease ($P < 0.001$; Table 2), while correlations with age on

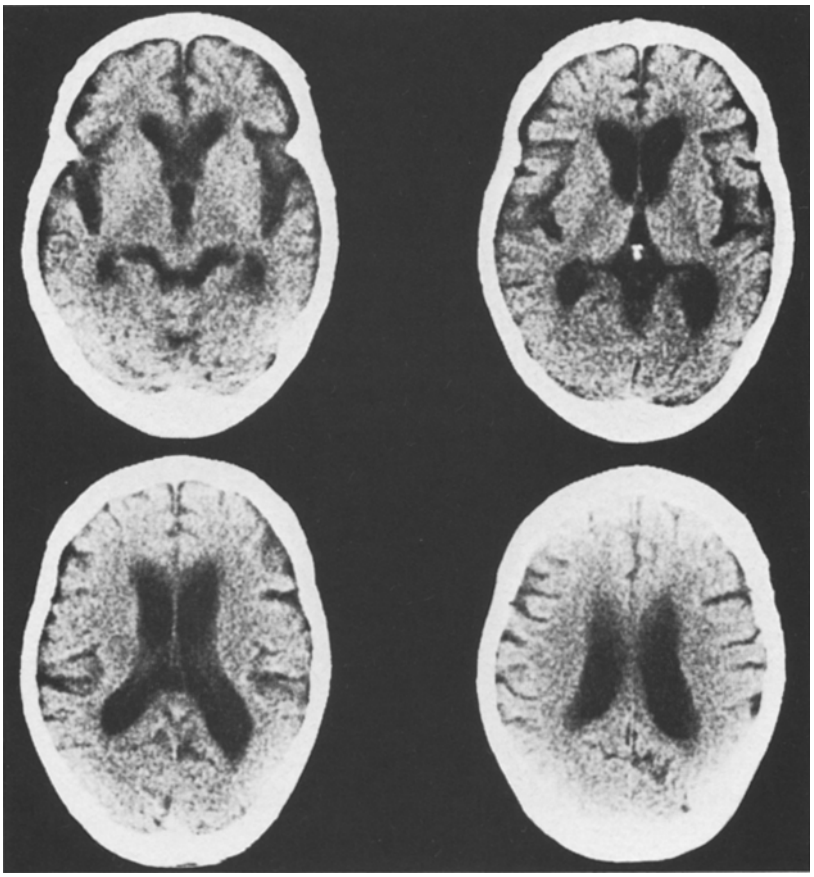

Fig. 3. CT of a stage II patient

examination, as well as age at onset, were not found. In the control group, there was a significant correlation only between SVI and age ($P < 0.001$; Table 2).

Mean scores of volume indexes in each group

The mean values of both SVI and VVI in each group are presented in Fig. 6. One-way analysis of variances disclosed that both indexes significantly increased inproportion to the progress of the clinical stage ($P < 0.001$). Particularly in the stage I group, the SVI was significantly different from that of the controls at the level of 0.1% (Student's *t*-test), while VVI in stage I was significantly different only at the level of 1% (Fig. 6). VVI in stage II group indicated a significant difference from that of the controls at the level of 0.1%.

No overlapping was noted between the Alzheimer and the control groups in the values of SVI.

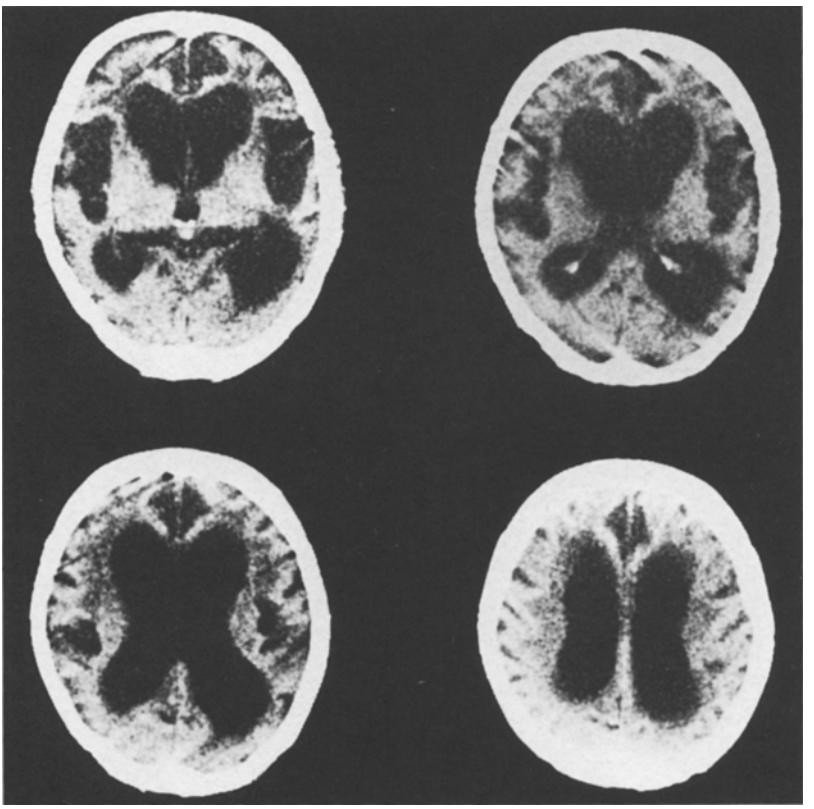

Fig. 4. CT of a stage III patient

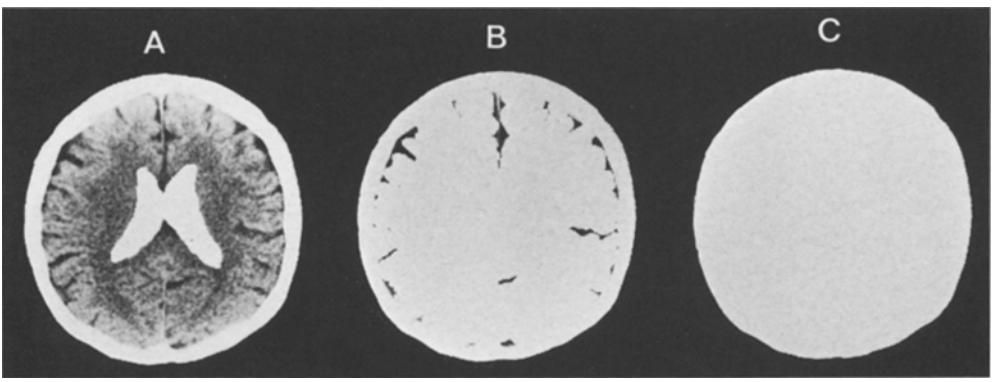

Fig. 5A–C. Measurement method. **A** Measurement of area A; **B** measurement of area B; **C** measurement of area C

Discriminative ability of CT

In order to appraise the discriminative ability of CT, a discriminant analysis was carried out. With these discriminant functions, differentiations of the control and the stage I group, of the stage I and II, and of the stage II and III group were possible at the error rate of 5%, 27% and 8% respectively (Fig. 7).

Table 2. Intercorrelation between volume indexes and clinical data

		Correlation coefficient	
		SVI	VVI
Alzheimer's disease	Age	0.32	0.20
	Age at onset	−0.12	−0.31
	Total duration	0.77***	0.88***
Controls	Age	0.88***	0.36

*** $P < 0.001$
SVI = Subarachnoid Space Volume Index; VVI = Ventricle Volume Index

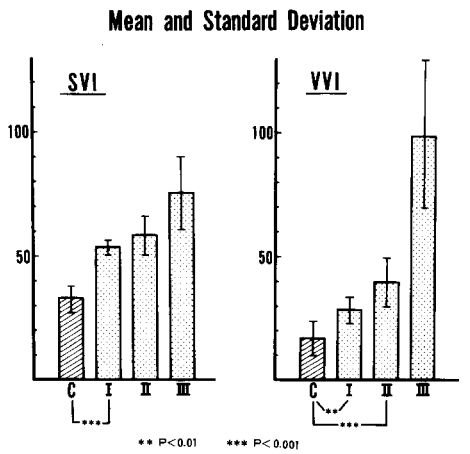

Fig. 6. Mean values of volume indexes in each group. *C* = control group; *I, II* and *III* = stage I, II and III groups, respectively

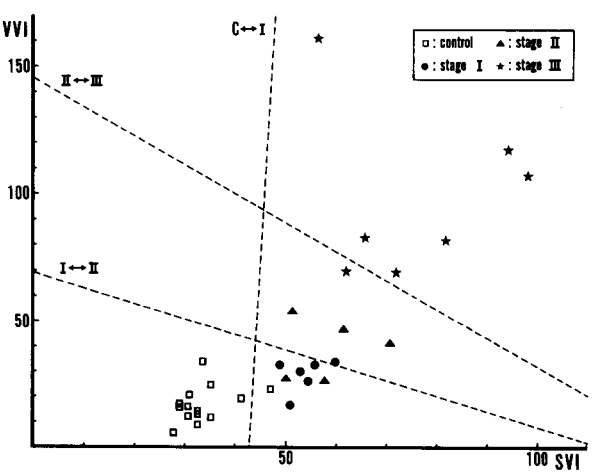

Fig. 7. Relationship between SVI and VVI. The *dotted lines* are the discriminative functions

Discussion

The Density Contour function, which has been reported to be suitable for measuring the ventricular volume [13], was used only for the measurement of the intracranial spaces in this study, since it is liable to produce errors owing to the problems of partial volume artefact and threshold CT numbers [11], of noise in CT [12] and of calcified organs, especially in the measurement of the subarachnoid spaces and the ventricles with calcified choroid plexus. The ROI function, the use of which has not been reported in the literature, was found to be better than the Density Contour function, since it was much less effected with these problems.

Most of the previous CT studies in normal aged subjects have indicated a close correlation between age and cerebral atrophy [1, 5–7, 11], but no significant correlation in the demented [10]. Our study supports these reports. Moreover, it discloses a significant correlation between the volume indexes and the total duration of the disease. This suggests that the cerebral atrophy shown on CT in Alzheimer patients is attributable to the disease processes themselves rather than to physiological aging of the brain.

We studied SVI and VVI in all three stages of the Alzheimer group and the control group. As far as we know, there are no reports in which quantitative CT indexes were studied in each clinical stage of presenile or senile dementia. SVI is regarded as an index for cortical atrophy and VVI for ventricular dilatation. Therefore, our results indicate that the degree of cerebral atrophy increases in parallel with the progress of the clinical stage, and that the cortical atrophy is already apparent at stage I, whereas the ventricular dilatation becomes pronounced at later stages. These findings are of importance, since they support neuropathological observations that the primary lesion of Alzheimer's disease consists of a cortical degeneration, while degeneration of white matter and ventricular dilatation are secondary changes.

There are only a few reports indicating that cortical atrophy in the demented was significantly more advanced than in normal aged subjects [8, 10]. However, even in these reports there were considerable overlaps between the CT indexes in the demented and the normal aged. The difference between the results of previous studies and ours might be accounted for by the difference in the measurement method for cortical atrophy, in the subjects examined and in the kind of CT apparatus used.

The finding that the stage I group could be differentiated on CT from the control group at the error rate of 5% on discriminant analysis suggests the usefulness of CT for the clinical diagnosis of the early stage of Alzheimer's disease. In this study there was only one case in the controls which was misclassified as a stage I subject (Fig. 7). This control subject was the oldest and scored the largest SVI in the control group. In order to avoid such errors, a discriminant analysis with three factors (SVI, VVI and age) was carried out with good results.

Further follow-up studies of the same patients and more extensive inquiries in larger groups of patients with Alzheimer's disease and other demented disorders will be performed.

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