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# Morphometric Measurements of MRI Findings in Patients with Alzheimer's Disease

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**A** – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

## Abstract

**Background.** Alzheimer's disease (AD) is one of the most common degenerative neurological disorders among elderly people, and is associated with progressive cerebral atrophy. AD is characterized by deterioration of the memory, difficulties with language, alterations in behavior and dysfunction in daily activities.
**Objectives.** The purpose of the present study was to measure the total volumes of different parts of the brain of AD patients and healthy gender-matched controls using Cavalieri's volume estimate method, and to establish some brain ratios. Moreover, the authors wanted to test this method in measuring the volumes of various parts of the brain from MRI scans.
**Material and Methods.** In this study, the MRI scans of 15 right-handed individuals with probable AD and 10 healthy controls were assessed. Cavalieri's volume estimate method was applied to the brain MRI scans to calculate the volumes of various parts of the brain.
**Results.** While the measurements showed a marked increase in the volume of cerebral ventricles and sulci in AD patients in comparison to the gender-matched controls, the volumes of cortical gray matter and cerebral hemispheric brain matter were reduced considerably. However, no significant differences were detected in the volume of the cerebellum + brainstem or intracranium in AD patients. There were also no major variations between male and female values of the two groups.
**Conclusions.** Overall, cerebral hemisphere and cortical gray matter atrophies were the most remarkable findings among AD patients in the present study; consequently, expansions of both the ventricles and subarachnoid space were formed. Cavalieri's volume estimate method was very efficient in calculating the volumes of different parts of brain from the MRI scans of both groups (**Adv Clin Exp Med 2014, 23, 1, 91–96**).

**Key words:** Alzheimer, brain, morphometry, Cavalieri's principle.

Alzheimer's disease (AD) is the most common cause of dementia, with a rate of approximately 10% for people 65 years of age and older. The number of older people at risk is rising as life expectancy increases in most parts of the world [1]. AD is characterized by deterioration of the memory, difficulties with language, alterations in behavior and dysfunction in daily activities. Accurate diagnosis of AD depends on the assessment of brain pathology. Postmortem neuropathological examinations have shown that dementia of the Alzheimer type (DAT) is a progressive neurodegenerative disorder associated with neuron loss and the accumulation of neurofibrillary tangles (dense perikaryal staining) and senile plaques [2–4]. Unfortunately, this is not a practical approach for *premortem* diagnosis, which makes *premortem* diagnoses doubtful. A clinical diagnosis of AD is inaccurate even among experienced investigators in about 10–15% of cases, and it may be that biomarkers could improve the accuracy of diagnoses [5]. Cerebral neuroimaging is one of the best assessment methods for diagnosing AD [6]. In particular, MRI-based volumetry is one of the best established biomarker candidates for Alzheimer's disease (AD) to date [7, 8]. The aim of the current study was to compute the total volumes of different parts of the brain of AD patients and healthy gender-matched controls using Cavalieri's volume estimate method and to establish some brain ratios. In addition, the authors wanted to test this method in measuring the volumes of various parts of brain from MRI scans.

## Material and Methods

A group of probable AD patients, diagnosed by the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association for the clinical diagnosis of probable AD, were included in the present study [9]. A total of 15 AD patients (10 males, 5 females) were evaluated. None of the patients had any diseases other than probable AD. In addition, they had no medical history of significant head injury or psychiatric disorder. The age range was from 62 to 77 for the men and from 50 to 81 for the women. The control group consisted of the same number of males and females as in the study group; the age ranges in the control group were 59–81 for the men and 57–71 for the women. Cavalieri's volume estimate method was applied to brain magnetic resonance imaging (MRI) scans to calculate the volume of various parts of the brain. To accomplish this, a simple point grid with a known area associated with each point *(a/p)* was used for each brain image. Each point on the area under investigation was counted as a *Pi*. The thickness (*T*) of the slice of MRI was also considered in calculating the volume of the brain region being investigated (Fig. 1). The following equation was used for calculating the absolute volume of each part of the brain:

$$V= T.\ a/p.\ \sum Pi \ [10]$$

The average values were determined for each person, and then statistical differences between the MS and control values were determined using the Mann-Whitney rank sum test. IBM SPSS Statistics Software (version 15) was used. $P < 0.05$ was considered significant.

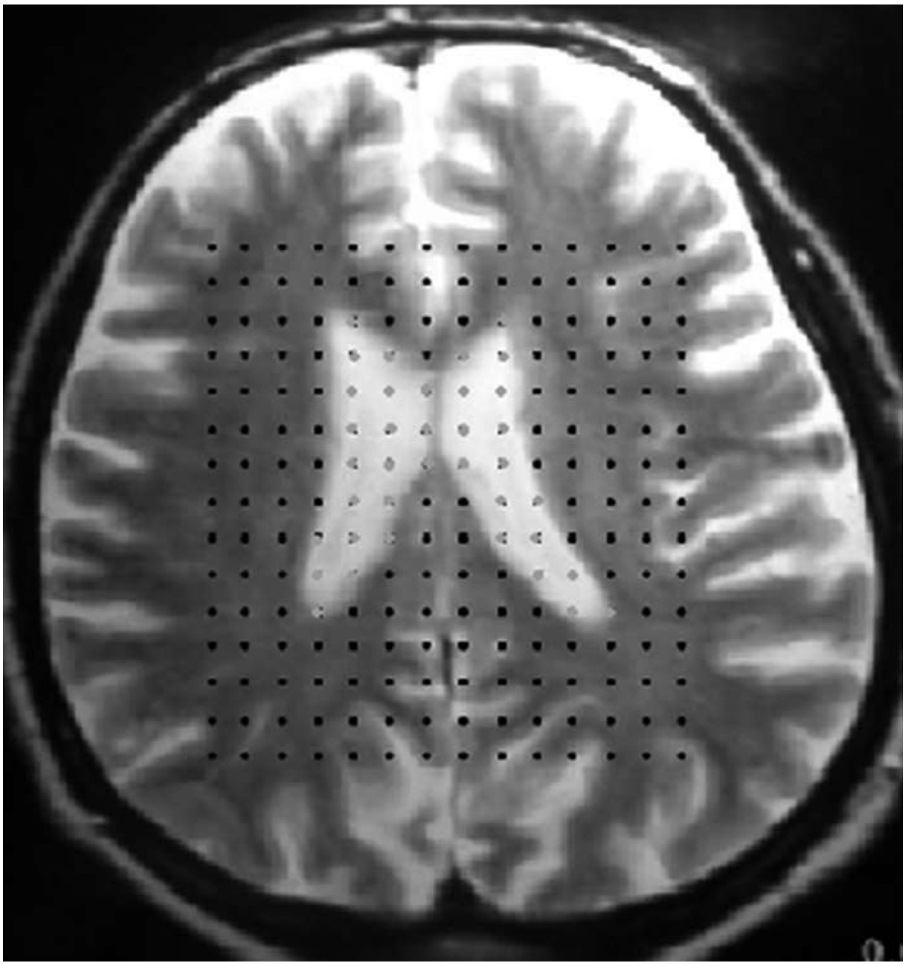

**Fig. 1.** Axial MRI scan of a human brain with a transparent test system superimposed. For the Cavalieri estimate of total ventricular volume every point that hit the ventricle was counted as a Pi. Here, 37 points (grey) hit the ventricle

## Results

While *cerebral ventricle* and *sulci cerebri* volumes were significantly higher in AD patients compared to the gender-matched controls, cerebral hemisphere brain matter and cortical gray matter volumes were significantly reduced. But no significant difference was detected in the cerebellum + brainstem and intracranial volumes in AD patients. There was also no significant difference between the male and female values of the 2 groups (Table 1).

## Discussion

In the present study, cerebral ventricular volume was 125% higher in the male AD patients compared to the male controls and 99% higher in the female AD patients compared to the female controls. While the overall cerebral ventricular volume was 66.96 $cm^3$ in male AD patients and 61.48 $cm^3$ in female AD patients, in the control group it was 29.71 $cm^3$ in males and 30.94 $cm^3$ in females, suggesting that ventricular volume might be a useful marker for diagnosing AD. Similar results have been reported by many other researches [11–13]. For example, a 118% increase in AD patients was shown in the Barber's study [13]. According to Ridha et al., there is a strong correlation between brain atrophy and ventricular enlargement, and (as those authors wrote) "cognitive scales probably reflect the correspondence between these measures of overall cerebral loss and global cognitive measures in the moderate stages of AD" [14].

In addition to the increase in ventricular volume, *sulci cerebri* volume was also higher in AD patients. This increase was 11% and 13% in male and female patients, respectively. Moreover, cortical gray matter volume was reduced by 31% and 24% in male and female AD patients, respectively, in comparison with their gender-matched controls. In the AD patients, there was an additional decrease in cerebral hemisphere brain matter volume, which was 11% and 19% in males and females, respectively. Comparable results were found by Matsumae et al. as well [15]. On the other hand, the brain atrophy and ventricular expansion rates were shown to be higher in patients with mild cognitive impairment (MCI) that progressed into AD within 12 months of follow-up when compared with MCI subjects who remained stable [16]

The results of the present study demonstrated that AD-associated atrophy was greater in cerebral white matter than in cortical gray matter, as indicated by the presence of markedly increased ventricular volume compared to *cerebral sulci* volume. In addition, cerebral hemisphere brain matter volume in AD patients changed only 11% and 19%. An earlier study on the impact of AD on the volume of the *cortical nuclei* revealed that the volume of the *subcortical nuclei* was not significantly different between AD patients and controls [17]. Likewise, similar recent studies reported significant volumetric reduction in the *corpus callosum* of AD patients [18–21]. These results suggest that the axons of the neurons are more vulnerable than the perikaryon in AD patients. Moreover, a study by Duan et al. demonstrated that the white matter of the patients with Alzheimer's disease was selectively impaired, that the extent of the damage showed a strong correlation with cognitive function, and that selective impairment reflected cortico-cortical and cortico-subcortical disconnections in the pathomechanism of Alzheimer's disease [22].

**Table 1.** The mean absolute volumes ($cm^3$) of various parts of the brains of healthy controls and AD patients

| Structure | Control | | AD | % Difference |
|---|---|---|---|---|
| Cerebral ventricles (V) | Male (n = 10)<br>Female (n = 5) | 29.71 ± 3.38<br>30.94 ± 4.13 | 66.96 ± 3.01<br>61.48 ± 4.47 | +125***<br>+99** |
| Cerebral hemisphere (H) | Male (n = 10)<br>Female (n = 5) | 1009.31 ± 33.40<br>999.64 ± 14.60 | 898.71 ± 39.00<br>810.43 ± 38.90 | –11*<br>–19** |
| Sulci cerebri (S) | Male (n = 10)<br>Female (n = 5) | 405.27 ± 18.68<br>375.74 ± 13.00 | 451.30 ± 16.00<br>424.41 ± 20.30 | +11**<br>+13 ns. |
| Cortical gray matter (C) | Male (n = 10)<br>Female (n = 5) | 561.48 ± 10.10<br>541.59 ± 29.90 | 388.09 ± 32.90<br>408.79±36.90 | –31***<br>–24* |
| Cerebellum + Brainstem (CE+BS) | Male (n = 10)<br>Female (n = 5) | 141.61 ± 8.65<br>154.32 ± 8.22 | 164.63 ± 7.120<br>156.57 ± 12.70 | +16 ns.<br>+2 ns. |
| Total intracranial volume (TIV) | Male (n = 10)<br>Female (n = 5) | 1585.89 ± 31.40<br>1501.05 ± 52.80 | 1537.63 ± 42.20<br>1472.93 ± 62.50 | –3 ns.<br>–2 ns. |

N – number of subjects, $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, ns. – not significant.

As expected, there was no significant difference in total intracranial volume in the AD patients as compared with the controls. This is in agreement with the results of a recent study [23]. Because AD causes some disorders in brain structures such as ventricle enlargement and increases in *sulci cerebri* volume, the volume of white and gray cortical matter diminish.

Similarly, cerebellum + brainstem volume did not differ between the AD patients and the controls. The results of the present study are consistent with the findings of Murphy et al. [12]; in contrast, Wegiel et al. [24] found that the cerebellar volume was significantly reduced in AD patients. Moreover, the cortical thickness of the temporal lobe, parahippocampal gyrus, and enthorhinal cortex in both hemispheres of AD patients have been reported to show some decrease in addition to cortical thinning in the isthmus of cingulate gyrus and middle temporal gyrus in the right hemisphere [25].

Along with the significant volume changes in some of brain regions of AD patients, marked changes were also observed in the volume ratios of these patients. In particular, the changes in the ratios of H/S, H/V, C/V, CE + BS/V and TIH/V appear to be especially useful for interpreting the atrophies correlating with the severity of AD.

In their study, Matsumae et al. compared the extraventricular volume (subarachnoid space)/ /ventricular volume ratio for AD patients with that of normal-pressure hydrocephalus (NPH) patients and found that this ratio was 3 times greater than in NPH patients [15].

In conclusion, Cavalieri's volume estimate method can be applied to MRI scans to calculate the volumes of different parts of the brain in AD patients. The present results indicated that the occurrence of atrophies in the cerebral hemispheres and cortical gray matter are the most remarkable findings in AD patients. In addition, enlargements of both the ventricles and the subarachnoid spaces were present in the brain matter of AD patients. A comprehensive assessment of brain atrophy rates might help to explain the loss of cognitive function in AD patients.

The H/V, H/S, C/V, CE + BS/V, and C/TIH ratios were decreased in AD patients of both sexes. H/CE + BS, C/S, C/CE + BS, CE + BS/TIH ratios were decreased only in male patients. On the other hand, V/TIH and S/TIH ratios were increased in AD patients of both sexes. However, the S/CE + + BS ratio did not differ from the control values (Table 2).

**Table 2.** The volume ratios of various parts of the brains of healthy controls and AD patients

| Ratios | Control | | AD | % Difference |
|---|---|---|---|---|
| H/S | Male (n = 10)<br>Female (n = 5) | 2.73 + 0.16<br>2.67 + 8.97 | 2.02 + 0.12<br>1.92 + 0.11 | −26**<br>−28*** |
| H/V | Male (n = 10)<br>Female (n = 5) | 36.63 ± 3.03<br>34.95 ± 5.20 | 13.85 ± 1.15<br>13.49 ± 1.32 | −62***<br>−61** |
| H/CE+BS | Male (n = 10)<br>Female (n = 5) | 7.30 ± 0.41<br>6.55 ± 0.33 | 5.62 ± 0.48<br>5.31 ± 0.50 | −23*<br>−19 ns. |
| S/CE+BS | Male (n = 10)<br>Female (n = 5) | 2.74 ± 0.18<br>2.47 ± 0.20 | 2.78 ± 0.13<br>2.79 ± 0.28 | +1 ns.<br>+13 ns. |
| C/V | Male (n = 10)<br>Female (n = 5) | 20.19 ± 1.32<br>19.34 ± 3.66 | 5.72 ± 0.34<br>6.78 ± 0.82 | −72***<br>−65* |
| C/CE+BS | Male (n = 10)<br>Female (n = 5) | 4.06 ± 0.19<br>3.58 ± 0.36 | 2.40 ± 0.24<br>2.65 ± 0.28 | −41***<br>−26 ns. |
| CE+BS/V | Male (n = 10)<br>Female (n=5) | 5.01 ± 0.36<br>5.26 ± 0.55 | 2.50 ± 0.15<br>2.63 ± 0.34 | −50***<br>−50** |
| TIH/V | Male (n =10)<br>Female (n = 5) | 57.06 ± 3.93<br>52.69 ± 8.36 | 34.5 ± 1.40<br>44.3 ± 2.01 | −40***<br>−16* |
| TIH/CE+BS | Male (n = 10)<br>Female (n = 5) | 11.47 ± 0.15<br>9.86 ± 0.71 | 9.48 ± 0.43<br>9.63 ± 0.81 | −17*<br>−2 ns. |

N – number of subjects, *p < 0.05, **p < 0.01, ***p < 0.001, ns. – not significant.

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