Comparison of Hippocampal Volume Measured Using Magnetic Resonance Imaging in Alzheimer’s Disease, Vascular Dementia, Mild Cognitive Impairment and Pseudodementia

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OBJECTIVE: To examine the relationship between different types of dementia and hippocampal volume. METHODS: Hippocampal volume was measured by magnetic resonance imaging in patients with Alzheimer’s disease (n = 22), vascular dementia (n = 14), mild cognitive impairment (n = 12) or pseudodementia (n = 16), and in healthy control subjects (n = 11). The Mini Mental State Examination was used to stratify subjects according to cognitive function. RESULTS: Hippocampal volume was reduced by 42% in Alzheimer’s disease, 21% in vascular dementia, 15% in mild cognitive impairment and 13% in pseudodementia compared with controls. The severity of dementia increased in line with decreasing hippocampal volume. CONCLUSIONS: Measurement of hippocampal volume may facilitate differentiation between dementia subtypes. There was a relationship between reduced hippocampal volume and the degree of cognitive impairment.

KEY WORDS: DEMENTIA; HIPPOCAMPUS; ATROPHY; COGNITIVE IMPAIRMENT; MAGNETIC RESONANCE IMAGING

Introduction

Dementia is a progressive decline in mental function, memory and acquired intellectual skills. It has multiple causes, including degenerative, vascular, traumatic, neoplastic, infectious or inflammatory processes, hydrocephaly, systemic or toxic diseases, and demyelination. Dementia is not a result of ageing, but indicates an underlying pathology.¹ Alzheimer’s disease is the most common and well-known type of cortical dementia, and is the fourth leading cause of death among the elderly.² Neuronal loss in Alzheimer’s disease is most prominent in the entorhinal cortex, hippocampus and subcortical nucleus.¹,³ Vascular dementia, the second most common type of dementia, is characterized by the acquired loss of cognitive function due to brain damage resulting from cerebrovascular disease.⁴ Mild
cognitive impairment is characterized by subjective and objective memory impairment, with other cognitive functions remaining intact. Depression and dementia commonly occur together in the elderly and may be confused with one another. In the depressed elderly, cognitive deficit is known as pseudodementia secondary to depression.

Magnetic resonance imaging (MRI) is a reliable supportive tool for the diagnosis of dementia and can reveal cortical atrophy, sulcal and ventricular dilatation, decreased parenchymal and hippocampal volume and changes in parenchymal intensity. Most imaging studies concerning measurements of regional atrophy have focused on the hippocampus. The present study examined hippocampus size in Alzheimer’s disease, vascular dementia, mild cognitive impairment and pseudodementia in order to determine the relationship between cognitive impairment and the degree of hippocampal atrophy.

Patients and methods

STUDY POPULATION

Patients with memory loss presenting at the Behavioural Neurology Department, Department of Neurology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey, between July 2003 and February 2004 were sequentially included in the study. A complete blood count, thyroid function test, quantification of serum vitamin B₁₂ and folate, and a syphilis test were performed in order to exclude other causes of dementia. Patients with abnormal laboratory results, intracranial mass lesions, history of brain trauma or other neurological disorders (including Parkinson’s disease), acute stroke within the past 6 months, or who were dependent on alcohol or psychoactive substances were excluded from the study. Healthy age-matched volunteers with no neurological, psychiatric or systemic disease were recruited to the control group from the local population of Eskisehir, Turkey. Age, handedness and education level were recorded for all study participants.

The study was approved by the Ethics Committee of the Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey. All study participants provided written informed consent.

DIAGNOSIS OF DEMENTIA

All study participants were evaluated according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Alzheimer’s disease was diagnosed according to the methods described by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS–ADRDA). The National Institute of Neurological and Communicative Disorders and Stroke and Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS–AIREN) criteria were used for diagnosis of vascular dementia. Pseudodementia was diagnosed by psychiatric evaluation and assessment on the Montgomery–Asberg Depression Rating Scale. Amnesic mild cognitive impairment was diagnosed according to the Petersen criteria.

NEUROPSYCHOLOGICAL ASSESSMENT

Cognitive function was evaluated in all participants using the Mini Mental State Examination (MMSE). Subjects were stratified according to MMSE score: severe dementia (< 18); moderate dementia (19 – 23); mild dementia (24 – 27); and normal cognitive function (> 28).
MRI
All participants underwent MRI after assessment for any contraindications. Scanning was performed in the supine position with a 1.5 T imaging system (Vision Plus®; Siemens, Munich, Germany). The imaging protocol comprised a coronal T1-weighted FLASH (Fast Low Angle Shot) MRI 3D sequence with slice thickness 2 mm, repetition time 28 ms, echo time 5 ms, flip angle 45° and matrix 160 × 256. The head coil was used for signal acquisition and a scout image was obtained before scanning. A slab was placed perpendicular to the temporal horns and the long axis of the hippocampus on the baseline sagittal image, and coronal images were obtained. The boundaries of the hippocampus were outlined manually on each slice according to previously described criteria by a radiologist who was blind to the diagnosis. The hippocampal borders were defined by the temporal horn of the lateral ventricle both laterally and superiorly, and by the white matter that joins the parahippocampal gyrus inferiorly. Because of the difficulty of distinguishing the hippocampus from the subiculum, the subiculum was included in the border of the hippocampus by using the cerebrospinal fluid in the cisterna ambiens as the medial border. The amygdala is anterior to the hippocampus. Anteriorly, drawing began just posterior to the alveus, the white matter separating the amygdala from the hippocampus. When the alveus was not discernible, the coronal slice where the third ventricle was split from the cistern by the hypothalamus was used as the most anterior slice of the hippocampus. Posteriorly, drawing continued to the slice in which the full length of the fornices or crura of the fornices were still visible. Representative MRI images of hippocampal
measurements in the control group and Alzheimer's patients are shown in Figs 1 and 2, respectively. The hippocampus was visible in approximately 20 consecutive slices. Hippocampal volume was calculated by multiplying the total area of the hippocampus visible in the slices by the total thickness of all the slices.

STATISTICAL ANALYSES
All data were presented as mean ± SD. The nonparametric Kruskal–Wallis test was used for between-group comparisons of MMSE scores, and one-way analysis of variance was used for comparisons of hippocampal volume. All statistical analyses were performed using SPSS® version 11.5 (SPSS Inc., Chicago, IL, USA) for Windows®. A P-value < 0.05 was considered statistically significant.

Results
The study population comprised 64 patients (22 with Alzheimer’s disease, 14 with vascular dementia, 12 with mild cognitive impairment and 16 with pseudodementia) and 11 control subjects. There were no significant between-group differences in age, education or dominant hand. Mean MMSE scores were significantly lower in patients with Alzheimer’s disease or vascular dementia compared with all other groups (P < 0.001). Demographic, hippocampal volume and MMSE score data are shown in Table 1.

Hippocampal volume was reduced by 42% in patients with Alzheimer’s disease, 21% in those with vascular dementia, 15% in those with mild cognitive impairment and 13% in patients with pseudodementia, compared with control subjects (Table 1). Hippocampal volume was significantly smaller than controls in patients in all groups except pseudodementia (P < 0.001 for
Due to the small number of patients with each type of dementia it was not possible to analyse the relationship between the severity of dementia and hippocampal volume for each dementia subtype; instead the entire study population was stratified according to MMSE score. The relationship between MMSE score and hippocampal volume is shown in Fig. 3. Hippocampal volume was reduced by 4% in subjects with mild dementia \((n = 9)\), 15% in those with moderate dementia \((n = 16)\) and 38% in those with severe dementia \((n = 20)\) compared with subjects with normal cognitive function \((n = 30)\). The severity of dementia increased in line with decreasing hippocampal volume.

**Discussion**

This study examined the relationship between hippocampal volume and cognitive impairment in patients with Alzheimer's disease, vascular dementia, mild cognitive impairment or pseudodementia and control subjects, using an MRI-based volumetric method. MRI-based hippocampal volume analysis has been used extensively for *in vivo* diagnosis of different types of dementia. Although the neuropathological changes of Alzheimer's disease begin in the entorhinal cortex and hippocampus, hippocampal atrophy is present in Alzheimer's disease and other types of dementia, as well as in depression, schizophrenia, epilepsy and amnesia.\(^{16,17}\)
Measurements of the hippocampus revealed a progressive decrease in volume from control subjects through (in order) pseudodementia, mild cognitive impairment and vascular dementia to patients with Alzheimer's disease in the present study. Patients with Alzheimer's disease had significantly smaller hippocampal volumes than all other groups. This finding is consistent with studies in which hippocampal atrophy was more prominent in patients with Alzheimer's disease than in patients with other dementia subtypes or in controls.\textsuperscript{3,16 – 18} Measurement of hippocampal volume may be used to differentiate patients with Alzheimer's disease from those with vascular dementia, mild cognitive impairment or pseudodementia, and from healthy subjects. Other studies have found no significant difference in hippocampal volume between Alzheimer's disease and vascular dementia, but the lateral portion of the left hippocampus (intersecting the CA1 subregion and including the dentate gyrus, hilar region and subiculum) has been shown to be more severely affected in Alzheimer's disease.\textsuperscript{19} Routine imaging does not allow for subregional volume analysis, but the diagnosis of vascular dementia can be facilitated by the ability to detect cerebral ischaemic features such as lacunae, cortical and subcortical infarcts and white matter abnormalities. Hippocampal atrophy in vascular dementia is independent of the number of lacunae and white matter abnormalities.\textsuperscript{20 – 22}

The accurate and efficient diagnosis of mild cognitive impairment is important because this condition may progress to Alzheimer's disease.\textsuperscript{23} Hippocampal volume
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was significantly smaller in patients with mild cognitive impairment than in controls in the present study, a finding consistent with other reports.\textsuperscript{3,17,24} This finding is important in terms of predictive accuracy. Hippocampal atrophy may be a marker of hippocampal pathology in patients with mild cognitive impairment and predict more rapid deterioration to clinical Alzheimer’s disease.\textsuperscript{25} The correct diagnosis of pseudodementia (depression presenting as dementia) is also important. Hippocampal volume and MMSE scores in patients with pseudodementia were not significantly different from those in control subjects in the present study but were considerably higher than in patients with Alzheimer’s disease. The use of these variables may facilitate differentiation between pseudodementia and Alzheimer’s disease. It has been shown that patients with a history of depression have smaller hippocampal volumes than patients without a history of depression, and that the duration of depression is correlated with hippocampal volume loss.\textsuperscript{26,27}

There were differences in hippocampal volume between patients with moderate or severe dementia and subjects with normal cognitive function in the present study. Analysis of the pooled study population revealed a relationship between the degree of cognitive impairment and hippocampal atrophy, such that subjects with greater cognitive impairment (low MMSE score) had smaller hippocampal volumes. Hippocampal atrophy is expected in those with memory impairment because the hippocampus is believed to play a central role in declarative memory.\textsuperscript{28}

This study had several limitations. First, patients were not examined throughout their disease course. There are likely to be differences between the early and late stages of dementia in the same patient, and

### Table 1: Demographic data, hippocampal volume and Mini Mental State Examination (MMSE)\textsuperscript{13} scores of the patients with Alzheimer’s disease, vascular dementia, pseudodementia or mild cognitive impairment, and healthy control subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls</th>
<th>Alzheimer’s disease</th>
<th>Vascular dementia</th>
<th>Pseudodementia</th>
<th>Mild cognitive impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>22</td>
<td>14</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Age, years</td>
<td>63.90 ± 7.62</td>
<td>70.78 ± 7.56</td>
<td>70.27 ± 5.85</td>
<td>70.78 ± 7.56</td>
<td>72.55 ± 7.95</td>
</tr>
<tr>
<td>Males/females</td>
<td>6/5</td>
<td>6/16</td>
<td>6/8</td>
<td>6/8</td>
<td>8/16</td>
</tr>
<tr>
<td>Hippocampal volume, cm\textsuperscript{3}</td>
<td>3.57 ± 0.53</td>
<td>2.07 ± 0.15</td>
<td>2.81 ± 0.53\textsuperscript{c}</td>
<td>3.12 ± 0.39\textsuperscript{d}</td>
<td>2.01 ± 0.67\textsuperscript{c}</td>
</tr>
<tr>
<td>MMSE score\textsuperscript{a}</td>
<td>29.36 ± 0.67</td>
<td>20.34 ± 1.33\textsuperscript{b}</td>
<td>26.36 ± 0.67\textsuperscript{b}</td>
<td>18.68 ± 2.83\textsuperscript{b}</td>
<td>28.83 ± 0.83\textsuperscript{b}</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD, or number (n) of patients. \textsuperscript{a}Score < 18 indicates severe dementia; 19 – 23, moderate dementia; 24 – 27, mild dementia; > 28, normal cognitive function. \textsuperscript{b}P < 0.001 compared with controls; \textsuperscript{c}P < 0.001 compared with Alzheimer’s disease; \textsuperscript{d}P < 0.001 compared with vascular dementia; \textsuperscript{e}P < 0.001 compared with pseudodementia; one-way analysis of variance (hippocampal volume) or Kruskal–Wallis test (MMSE score).
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Hippocampal atrophy in the late stage of one dementia subtype may be indistinguishable from that in the early stage of another dementia subtype. The diagnosis of dementia subtype may be difficult with a single measurement, and repeated volumetric analyses may have higher discriminatory value. Secondly, the volumetric index was not calculated. This index is calculated by dividing hippocampal volume by total intracranial volume and results in individual hippocampal volumes being normalized for intersubject variation in head size. Thirdly, the diagnosis of dementia subtypes was based on clinical rather than pathological features. Fourthly, measurement of hippocampal volume was performed manually and by only one radiologist. Finally, the small size of the study cohort meant that it was not possible to analyse the relationship between severity of dementia and hippocampal volume for each dementia subtype. Further investigation with a larger cohort is needed to examine this relationship.

In conclusion, measurement of hippocampal volume may assist in differentiating between dementia subtypes. Hippocampal atrophy was most severe in patients with Alzheimer's disease, followed by vascular dementia, mild cognitive impairment and pseudodementia. There was a relationship between hippocampal volume and the degree of cognitive impairment.

Conflicts of interest
The authors had no conflicts of interest to declare in relation to this article.

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FIGURE 3: Hippocampal volume assessed by magnetic resonance imaging in subjects with mild (n = 9), moderate (n = 16) or severe dementia (n = 20) or normal cognitive function (control; n = 30). Mini Mental State Examination score < 18 indicated severe dementia; 19 – 23, moderate dementia; 24 – 27, mild dementia; and > 28, normal cognitive function.
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References


