The Corpus Callosum Area and Brain Volume in Alzheimer’s Disease, Mild Cognitive Impairment and Healthy Controls1

Hee Seok Choi, M.D.1,2, Hyung Suk Seo, M.D.3, Kwang Ki Kim, M.D.4, Yup Yoon, M.D.1

Purpose: To compare the corpus callosum (CC) area and brain volume among individuals with Alzheimer’s disease (AD), mild cognitive impairment (MCI) and healthy controls (HC).

Materials and Methods: To evaluate the relationship of CC area and brain volume in 111 subjects (M:F = 48:63; mean age, 56.9 years) without memory disturbance and 28 subjects (11:17; 66.7 years) with memory disturbance. The 11 AD (3:8; 75.7 years), 17 MCI (8:9; 60.9 years) and 28 selected HC (11:17; 66.4 years) patients were investigated for comparison of their CC area and brain volume.

Results: A good positive linear correlation was found between CC area and brain volume in subjects without and with memory disturbance (r = 0.64 and 0.66, respectively, p < 0.01). The CC area and brain volume in AD patients (498.7 ± 72 mm², 715.4 ± 107 cm³) were significantly smaller than in MCI patients (595.9 ± 108, 844.1 ± 85) and the HCs (563.2 ± 75, 818.9 ± 109) (p < 0.05). The CC area and brain volume were not significantly different between MCI patients and the HCs.

Conclusion: The CC area was significantly correlated with brain volume. Both CC area and brain volume were significantly smaller in the AD patients.

Index words: Alzheimer’s disease
Cognition disorders
Corpus callosum
Magnetic resonance (MR)
Brain
Alzheimer’s disease (AD) is a progressive, neurodegenerative disorder associated with cognitive impairment and memory dysfunction, which is severe enough to interfere with the activities of daily living (1, 2). Moreover, Alzheimer’s disease is the most common cause of dementia in all age groups (3). With increasing life expectancy worldwide, the number of elderly people at risk for developing dementia and AD is growing rapidly. Accordingly, the worldwide cost of caring for patients with dementia in 2005 was estimated to be $315.4 billion USD on the basis of a population 29.3 million persons with dementia (4). The early detection and intervention in persons with mild memory symptoms who are at risk for progressing to AD is becoming more important (3).

Mild cognitive impairment (MCI) is a disorder that includes mild memory impairment. Patients with MCI do not meet the criteria for dementia and have otherwise normal cognition and the ability to function independently in their daily activities (5, 6). MCI is thought to be a transitional stage between normal aging and dementia. The early diagnosis of patients with MCI is important because treatment of MCI may be effective in delaying the progression to AD (7).

MR imaging is now recognized as an important tool for the diagnosis of AD and the monitoring of the progression of AD (8). The accumulation of β-amyloid plaques and neurofibrillary tangles in the neocortex of the AD brain produces diffuse brain atrophy, gross widening of the sulci, and enlarged ventricles. These symptoms represent the major MR findings of AD (9). However, it is hard to differentiate the brain atrophy in AD from normal aging because all contiguous sections of the brain MR images must be considered.

Fig. 1. The measurement of the brain volume. The MR scans were analyzed using the ANAYZE software package (Mayo Clinic, Rochester, MN, U.S.A.). The CSF spaces, including the ventricles, were automatically subtracted (A). With volume rendering, the cerebellum and pons were subtracted (B).
Disproportionate atrophy of the amygdale [10], hippocampus [10], entorhinal cortex [11], and substantia innominata [12] has been proposed as hallmarks of AD. However, tracing these brain structures is difficult in a clinical setting. In addition, inter-observer variation in the assessment of these brain structures on MR images makes the interpretation of the findings subjective.

The corpus callosum (CC) is a major inter-hemispheric commissure connecting the right and left cerebral hemispheres [13, 14]. Several reports have shown a positive relationship between the CC and brain volume in healthy and young populations [15-17]. The measurement of the CC area is relatively easy and reproducible. There have been several studies reporting on the atrophy of the CC in patients with AD [18, 19]. However, there is little knowledge on the change of the CC in patients with MCI.

The purpose of this study was to investigate the relationship between the CC area and brain volume in patients with memory impairment as well as in a large healthy population with a wide age range and to compare the CC area and brain volume among patients with AD and MCI, as well as in healthy controls (HC).

**Materials and Methods**

**Study population**

From March 2006 to October 2007, 183 consecutive patients presented at our hospital with memory disturbance. All patients were evaluated by the MMSE (mini-mental status examination) and CDR (clinical dementia rating). The MMSE is a brief 30-point questionnaire test that is used to assess cognition. The CDR is a numeric scale used to quantify the severity of symptoms of dementia with scores ranging from 0 through 3.5. A MMSE score below 25 and a CDR score of 1 or 2 were considered to indicate AD. A MMSE score of 25 to 30 and a CDR score of 0.5 of CDR were considered to indicate MCI. Patients with structural abnormalities on MR imaging that could have affected the brain volume were excluded from the study. In addition, patients with cerebral lesions associated with previous trauma, surgery, an ischemic infarction larger than the lacunar size, or hemorrhage, were excluded from the study.

From March, 2007 to September, 2007, 111 consecutive subjects (48 men and 63 women; mean age, 56.9 years; age range, 34–81 years) without memory disturbance and who visited the neurology department at our hospital were examined via a brain MRI, were included in this retrospective study to evaluate the relationship of the CC area with brain volume. Their chief complaints included headache (n = 60), dizziness (n = 20), facial palsy (n = 12), peripheral neuropathy (n = 10), syncope (n = 6), and essential tremor (n = 1). To compare the CC area and brain volume among the patients with AD and MCI, age and sex matched HCs without memory disturbance were selected from the 111 HCs.

**MRI Acquisition**

The MR imaging of the brain was performed with a 1.5T MR scanner (Avanto; Siemens Medical, Erlangen, Germany). Sagittal T1-weighted spoiled gradient-recalled acquisition (SPGR) in the steady state MR imaging (TR/TE = 1100/4 msec; matrix size = 320 × 320; FOV = 240 × 240 or 220 × 220 mm; slice thickness = 1.0 mm with no gap between slices), was performed. In addition, axial T1-weighted images (TR/TE, 476/10; field of view, 167 × 220 mm; matrix size, 256 × 224; slice thickness, 5 mm), axial FLAIR images (9,000/121; FOV, 167 × 220 mm; matrix size, 320 × 196; slice thickness, 5 mm), and axial T2-weighted images (4,270/97; FOV, 167 × 220 mm; matrix size 512 × 269; slice thickness, 5 mm) were obtained.

**MRI Analysis**

The MR scans were transferred to an independent Windows workstation and analyzed using the ANAYZE software package (Mayo Clinic, Rochester, MN, U.S.A.). An experienced neuroradiologist, blinded to the clinical data, retrospectively reviewed all of the MR images. Conventional MR images were used to detect structural...
abnormalities that would exclude a patient from the study. The brain volume was obtained by automated subtraction of the CSF spaces (Fig. 1, 2). The ventricular CSF spaces were also subtracted. With volume rendering, the cerebellum and brainstem were removed. The CC area was measured manually at the midsagittal slice using the regions of interest (ROI) (Fig. 3). The midsagittal slice was defined as the slice where the cerebral aqueduct was the most prominent and only the vermis of the cerebellum [no hemispheres] was in view.

**Statistical Analysis**

The statistical analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL, U.S.A.). A linear regression analysis was carried out to evaluate the relationship between the CC area and brain volume. The statistical relationship between the CC area and brain volume was evaluated in 111 subjects without memory disturbance and 28 patients with memory disturbance (total n = 139 subjects). The CC area and brain volume among patients with AD and MCI, as well as the HCs were compared using a one-way analysis of variance (ANOVA). P-values less than 0.05 were considered to be statistically significant.

**Results**

**Clinical characteristics and Demographics**

Among the 183 patients with memory disturbance, 11 (3 men and 8 women; mean age 75.7 years; age range 67–80 years) were diagnosed with AD and 17 (8 men and 9 women; mean age 60.9 years; age range 44–79 years) were diagnosed with MCI. Twenty eight age- and sex-matched HCs (11 men and 17 women; mean age 66.4 years; age range 44–81 years) were selected among the 111 subjects without memory disturbance.

Fig. 3. The correlation between the corpus callosum area and brain volume. The scatterplots.
A. The distribution of the CC and brain volume in subjects without memory disturbance (n = 111). Regression analysis; r² = 0.41 and p < 0.01.  
B. Patients with memory impairment (n = 28). Regression analysis; r² = 0.43 and p < 0.01.  
C. Subjects without memory disturbance and patients with memory impairment (n = 139). Regression analysis; r² = 0.44 and p < 0.01. There is a good positive linear correlation between the corpus callosal area and brain volume. VOL, brain volume; CC, corpus callosal area.
The general patient information is shown in Table 1. The mean scores of the MMSE were 17.5 ± 5.5 and 27.8 ± 1.4 in patients with AD and MCI, respectively. The mean scores of the CDR were 1.5 ± 1.5 and 0.5 in the patients with AD and MCI, respectively. The MMSE and CDR were not evaluated in the 111 subjects without memory disturbance (M/F = 48/63; mean age 56.9 ± 12.3 years) and the 28 selected HC (M/F = 11/17; mean age 66.4 ± 11.6 years).

**The relationship between the CC area and brain volume**

The regression analysis of the CC area and brain volume showed a good positive linear correlation for the 111 subjects without memory disturbance (r = 0.64, p < 0.01). The same is true for the 28 patients with memory disturbance (r = 0.66, p < 0.01). Hence, the CC area and brain volume were positively correlated in all of the 139 subjects (r = 0.66, p < 0.01). This correlation could be statistically expressed as follows: CC area [mm³] = 0.49 × Brain volume [cm³] + 169.6 (Fig. 3).

**The comparison of the CC area and brain volume among AD, MCI and the HC**

The brain volume of patients with AD (715.4 ± 107 cm³) was significantly smaller than in MCI patients (844.1 ± 85 cm³, p < 0.05) and the HC (818.9 ± 109 cm³, p < 0.05). There was no significant difference between MCI patients and the HC (Table 2) (Fig. 4).

![Fig. 4. The comparison of the brain volumes using a box plot. The brain volume in patients with Alzheimer’s disease is significantly smaller than in patients with mild cognitive impairment and healthy controls. The comparison of the brain volume between patients with mild cognitive impairment and healthy controls is not statistically significant. VOL, brain volume; AD, Alzheimer disease; MCI, mild cognitive impairment; HC, healthy control.](image)

![Fig. 5. The comparison of the corpus callosum (CC) area using a box plot. The CC area in patients with Alzheimer’s disease is significantly smaller than in patients with mild cognitive impairment and the healthy controls. There is no significant difference in the CC area between patients with mild cognitive impairment and the healthy controls. VOL, brain volume; AD, Alzheimer disease; MCI, mild cognitive impairment; HC, healthy control.](image)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AD* [n = 11]</th>
<th>MCI* [n = 17]</th>
<th>HC* [n = 28]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>75.7 ± 3.8</td>
<td>60.9 ± 11.7</td>
<td>66.4 ± 11.6</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>3/8</td>
<td>8/9</td>
<td>11/17</td>
</tr>
<tr>
<td>MMSE ³</td>
<td>17.5 ± 5.5</td>
<td>27.8 ± 1.4</td>
<td>NA ³</td>
</tr>
<tr>
<td>CDR ³</td>
<td>1.5 ± 0.5</td>
<td>0.5 ± 0.0</td>
<td>NA ³</td>
</tr>
</tbody>
</table>

Values are expressed as means ± S.D

*AD, Alzheimer dementia; MCI, mild cognitive impairment; HC, Healthy control

³MMSE = mini-mental status examination; CDR = clinical dementia rating

NA = not analyzed

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AD* [cm³]</th>
<th>MCI* [cm³]</th>
<th>HC* [cm³]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>715.4 ± 107.3</td>
<td>844.1 ± 85.5</td>
<td>818.9 ± 109.7</td>
</tr>
<tr>
<td>Minimum</td>
<td>591.8</td>
<td>715.2</td>
<td>632.1</td>
</tr>
<tr>
<td>Maximum</td>
<td>991.3</td>
<td>1008.6</td>
<td>1029.4</td>
</tr>
</tbody>
</table>

*AD, Alzheimer dementia; MCI, mild cognitive impairment; HC, Healthy control
CC area in AD patients (498.7 ± 72 mm²) was significantly smaller than in MCI patients (595.9 ± 108 mm², p < 0.05) and the HCs (563.2 ± 75 mm², p < 0.05). No significant difference was found between MCI patients and the HCs (Table 3) (Fig. 5).

Discussion

Patients with AD complain of memory impairment that is abnormal for aging, in addition to impairment of at least one other cognitive function such as attention, language, visuospatial skills, or problem solving. These deficits in AD patients are sufficiently severe to compromise daily activities. Patients with MCI complained of memory impairment that is abnormal for aging; however, unlike AD patients have generally normal cognition and the ability to function independently in their daily activities. The evaluation of the clinical course of patients with MCI is important because individuals with MCI are at increased risk for developing AD; 10–15% of patients develop AD per year. MCI is thought to be a transitional stage between normal aging and dementia (1, 5, 6). Therefore, the treatment of patients with MCI may be effective in delaying the progression to AD, although management of patients with MCI is currently nonspecific (7).

Many studies have examined the structural and functional changes of the brain in patients with AD and MCI using various MR techniques. For example, studies have been performed on cross-sectional or longitudinal studies of regional brain areas and volume (8, 20), the apparent diffusion coefficient (ADC) and diffusion tensor index (DTI) (21, 22), and the magnetization transfer ratio (MTR) (23, 24). Based on the histopathological evidence that the entorhinal cortex (ERC) and hippocampus are early sites affected by AD, most structural MRI studies in patients with AD and MCI have focused on these two structures located in the medial temporal lobe (25). An increase in the ADC and a decrease in the fraction anisotropy have been reported in the temporal lobe, hippocampus, and corpus callosum (21, 22). Although the volumetric and functional MR techniques need to be reproducible and ubiquitous for use in a clinical setting, the measurements of the changes in these small structures are laborious and hard to replicate (8). The authors of a recent study noted the need for uniformity in the use of structural measures for the diagnosis and evaluation of patients with cognitive impairment (26).

Studies on brain activity using altered cerebral glucose metabolism with PET have also been reported (25). The hypometabolism observed on PET scans can help differentiate AD, frontotemporal dementia, and vascular dementia (27). The 18F-FDG PET may provide an objective and sensitive imaging technique for the clinical diagnosis of early dementia (28). Recent use of the amyloid PET imaging tracer ligands offer the possibility of measuring fibrillar beta amyloid (Aβ) and the evaluation of the progression of amyloid in the brain (29). However, these functional neuro-imaging procedures are not as cost effective for the diagnosis of AD (30, 31).

The CC is the largest connective pathway in the human brain. It consists of more than 200 million nerve fibers that connect the right and left hemispheres of the brain (13, 14). The midsagittal cross-sectional area of the corpus callosum correlates with the number of callosal fibers (32). Several studies have showed a significant relationship between the CC area and brain volume in healthy and relatively young individuals (15–17). Our study revealed a stronger positive correlation, not only in healthy individuals with a wide age range, but also in patients with memory impairment (r = 0.64 and 0.66, respectively).

The regional degeneration of the cerebral cortex may cause atrophy of the CC due to the underlying pathology (18, 33, 34). In patients with AD, it has been shown that the accumulation of β-amyloid plaques and neurofibrillary tangles in the cerebral cortex with neuronal and synaptic loss, produce cerebral atrophy (8). The CC atrophy is assumed to be the anatomical correlate of inter-hemispheric disconnection; namely, Wallerian degeneration of the interhemispheric commissural nerve fibers due to cerebral atrophy (35). In addition, Teipel et al. (19) reported that the CC size was significantly reduced in AD patients. Accordingly, the annual rates of atrophy of the CC were significantly greater in the AD patients than in the HCs. Wang et al. (36), as well as Thomann et al. (37), recently reported that the CC area was significantly smaller in patients with AD than in comparison to patients with MCI and the HCs. Moreover, there was no significant difference between
MCI patients and the HCs. The results of this study are consistent with the aforementioned reports (Citations??). However, this is the only study that included a simultaneous comparison of the forebrain volume and CC area among AD and MCI patients and the HCs.

This study has several limitations. The mean age of the patients with AD was significantly greater than the patients with MCI (Table 1). Age is an important factor affecting brain volume [38, 39]. Therefore, the older age of the patients with AD may be a confounding factor in the finding of a smaller brain volume and CC area in the patients with AD. The wide age difference between the patients with AD and those with MCI was reflected in an older mean age of the HCs compared to the patients with MCI. The smaller brain volume and CC area in the HCs compared to the patients with MCI may also have been influenced by the age differences; although, upon comparison of patients with MCI and the HCs, there were no statistically significant differences between the brain volume and CC area.

In conclusion, the results of this study suggest that the CC area was significantly correlated with brain volume in patients with or without memory impairment. In addition, CC atrophy was significant in the patients with AD compared to patients with MCI and the HCs.

References

알츠하이머병, 경도인지장애 및 정상 대조군의 뇌량 면적과 뇌용적의 비교

 목적: 알츠하이머병과 경도 인지장애 그리고 정상 대조군에서 뇌량 면적과 뇌용적의 관계를 알아보는 것을 목적으로 하였다.

 대상과 방법: 뇌량 면적과 뇌용적의 상관관계를 알아보기 위해, 기억력 장애가 없는 111명 (남: 여 = 48:63; 평균 연령 56.9세)과 기억력 장애가 있는 28명 (남: 여 = 11:17; 66.7세)을 분석하였다. 그리고 알츠하이머병과 경도 인지장애 그리고 정상 대조군 사이의 뇌량 면적과 뇌용적을 비교하기 위해, 11명의 알츠하이머병 환자 (남: 여 = 3:8; 75.7세), 17명의 경도 인지장애 환자 (남: 여 = 8:9; 60.9세) 그리고 28명의 선택된 정상 대조군 (남: 여 = 11:17; 66.4세)을 대상으로 하였다.

 결과: 기억력 장애가 없는 군과 기억력 장애가 있는 환자군 모두에서 뇌량 면적과 뇌용적 사이에 양적 선형 관계가 있었다 (r = 0.64 and 0.66, respectively, p < 0.01). 알츠하이머병 환자 (498.7 ± 72 mm\(^2\), 715.4 ± 107 cm\(^3\))에서 뇌량 면적과 뇌용적은 경도 인지장애 환자 (595.9 ± 108 mm\(^2\), 844.1 ± 85 cm\(^3\)) 및 정상 대조군에 비해 유의하게 작았다 (563.2 ± 75 mm\(^2\), 818.9 ± 109 cm\(^3\)) (p < 0.05). 경도 인지장애 환자 및 정상 대조군 사이에 의미 있는 차이는 없었다.

 결론: 뇌량 면적은 뇌용적과 의미 있는 상관관계를 보이며, 알츠하이머병 환자에서 의미 있게 감소한다.