Frontal Dysfunction Underlies Depressive Syndrome in Alzheimer Disease: A FDG-PET Study

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Objective: *This study aimed to investigate the regional cerebral dysfunction associated with depressive syndrome in patients with Alzheimer disease (AD).* **Method:** *Twelve patients with AD with depressive syndrome (ADD) and 12 age-, gender-, and severity-matched patients with AD without depressive syndrome (ADND) underwent FDG-PET scanning. The regional cerebral glucose metabolism in the two groups was compared using a voxel-based method.* **Results:** *The ADD group showed lower glucose metabolism in the right superior frontal gyrus than the ADND group.* **Conclusions:** *These results indicate that frontal dysfunction, known to be associated with primary or other secondary depressive syndromes, underlies the depressive syndrome of patients with AD patients as well.* (Am J Geriatr Psychiatry 2006; 14:625–628)
Key Words: Alzheimer's disease, depressive syndrome, frontal dysfunction, FDG-PET

Depressive syndrome is a very common and significant psychiatric complication that affects 30% to 50% of patients with Alzheimer disease (AD).[1] The syndrome increases the suffering of patients with AD and their families, produces excess disability, promotes institutionalization, and hastens death.[1] Nevertheless, there has been no functional imaging study targeted specifically to a depressive syndrome appearing in AD, although there are some reports on regional brain dysfunction related to the elementary symptoms of the depressive syndrome.[2,3]

The aim of this study was to elucidate the specific regional cerebral metabolic abnormalities associated with depressive syndrome appearing in patients with AD.

MATERIALS AND METHODS

Subjects

The subjects for this study were recruited from patients with AD who visited the Dementia and Age-Associated Cognitive Decline Clinic of Seoul National University Hospital in Seoul. Twelve female AD cases with depressive syndrome (ADD) and their age-, gender-, and Clinical Dementia Rating (CDR) index-matched 12 AD cases with no present depressive symptom and no history of depressive syndrome (ADND) were enrolled in this study. To reduce the problems associated with self-reporting about their own depressive symptoms, patients only with a very mild or mild functional severity, i.e., CDR index 0.5 or 1.0, were selected. Twelve cognitively intact, age- and gender-matched healthy normal comparison (NC) subjects were also selected from a pool of volunteers with a normal neurologic and psychiatric history and examination and a normal brain magnetic resonance image. All the AD subjects included in this study met both the *Diagnostic and Statistical Manual of Mental Disorders, Fourth*

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Edition criteria for dementia and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer disease and Related Disorder Association (NINCDS-ADRDA) criteria for probable AD. Depressive syndrome was diagnosed by the provisional diagnostic criteria for depression of AD that was recently proposed by the NIMH workgroup.[1] The exclusion criteria for this study were any present serious medical, psychiatric, and neurologic disorders that could affect the mental function; history of any mood disorders; evidence of focal brain lesions on magnetic resonance imaging; the presence of severe behavioral or communication problems that would make a clinical or positron emission tomography (PET) examination difficult; both- or left-handedness; and an absence of a reliable informant. The Institutional Review Board of the Seoul National University Hospital, Korea, approved the study protocol and informed consent was obtained from all the subjects as well as their relatives.

Clinical Assessments

All the subjects were examined by neuropsychiatrists who had advanced training in neuropsychiatry and dementia research according to the protocol of the Korean Version of the Consortium to Establish a Registry for Alzheimer disease Assessment Packet (CERAD-K).[4] The CERAD evaluation section for depression was modified to collect the clinical information adequate to NIMH criteria for depression of AD. Reliable informants were necessarily interviewed and a panel consisting of four neuropsychiatrists with expertise in dementia research made the clinical decisions after reviewing all the available raw data. Every clinical assessment was carried out within 3 weeks of the PET examination. None of the subjects were receiving an antidepressant or other psychotropic medication except donepezil when recruited to our study. Only two patients (one ADD and one ADND), who were having donepezil, stopped the medication for 2 weeks before PET imaging. For the two, the data from the clinical assessment done on 1 day before PET imaging were used.

Positron Emission Tomography Imaging

PET studies were performed using the ECAT EXACT 47 scanner (Siemens-CTI, Knoxville, TN). The detailed PET imaging methods used in this study were identical with those described in our previous publication.[5]

Positron Emission Tomography Image Analysis

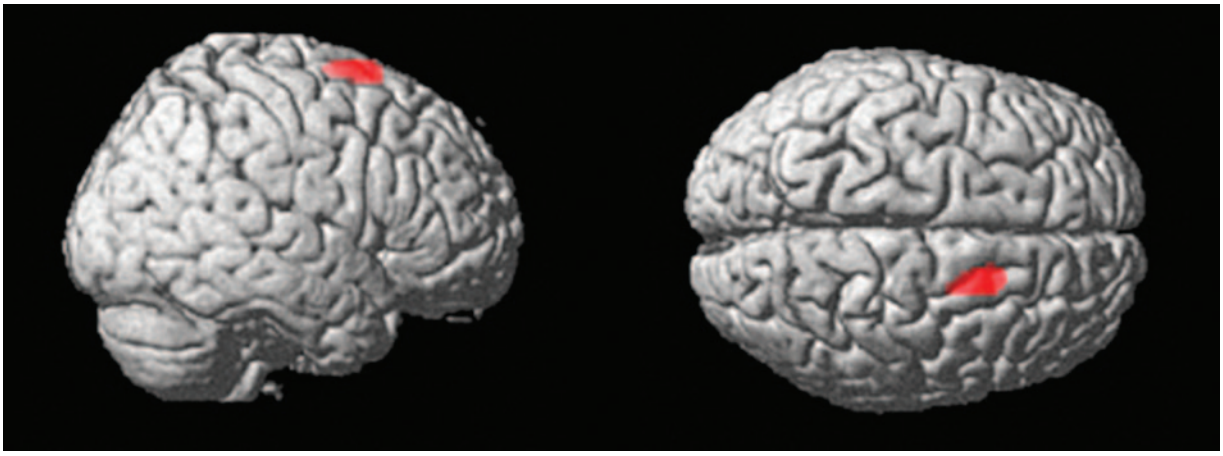
The image data were analyzed by using Statistical Parametric Mapping (SPM) 99. Before the statistical analysis, all of the images were spatially normalized to the Montreal, Quebec, Canada, Neurological Institute (MNI) space to correct for the intersubject anatomic variability. The normalized images were smoothed by convolution with an isotropic Gaussian kernel with 16 mm FWHM. The differences in global metabolism between all subjects were removed by normalizing the count of each voxel to the total count of the brain (proportional scaling to a mean value of 50 mg 100 mL^{-1}/min^{-1} in SPM). The difference in the regional cerebral glucose metabolic rate (rCMRglc) between any two of ADD, ADND, and NC groups was estimated on a voxel-by-voxel basis using a paired t test. For all the comparisons, a height threshold of $p < 0.001$ (uncorrected) and an extent threshold of 20 voxels were applied. The MNI coordinates of the local maximum of each cluster were converted into Talairach coordinates.

RESULTS

Each AD group included five mild patients (CDR 1) and seven very mild patients (CDR 0.5). There was no significant intergroup difference on a paired t test in age (ADD versus ADND: 71.3 ± 5.8 [mean $\pm$ standard deviation] versus 70.6 ± 5.6 years), age at onset (68.6 ± 6.8 versus 67.1 ± 6.6 years), duration of illness (2.7 ± 2.1 versus 3.4 ± 2.1 years), education (6.1 ± 5.3 versus 7.5 ± 6.1 years), and each of the eight neuropsychologic tests (verbal fluency; 15-item Boston naming test; Mini-Mental Status Examination; word list memory; word list recall; word list recognition; constructional praxis; constructional recall) in CERAD-K.[5]

When compared with the ADND group using SPM99, the ADD group showed significant hypometabolism in the right superior frontal gyrus (Brodmann's area [BA] 6: $x, y, z = 20, 17, 62$; number of voxels = 138) (Figure 1). Relative hypometabolism of the

FIGURE 1. Statistical Parametric Maps Showing Decrease of Metabolism in Patients With Alzheimer Disease With Depressive Syndrome Compared With Those Without Depressive Syndrome at p <0.001 (uncorrected)



ADD group was also observed in the left superior frontal gyrus (BA 6; −23, 5, 57; uncorrected p <0.005), although not statistically significant. SPM analyses showed that there was no brain region in which the ADD group showed increased rCMRglc compared with the ADND group. When compared with the NC, the ADD patients showed significant regional metabolic reductions in the bilateral posterior cingulate (BA 31), left inferior temporal (BA 37), and right inferior parietal cortex (BA 40). The ADND patients also revealed a similar hypometabolic pattern involving in the right precuneus (BA 31), right parahippocampal gyrus (BA 30), and right middle temporal (BA 39) and left inferior parietal cortex (BA 40).

DISCUSSION

To the best of our knowledge, this is the first report showing frontal dysfunction associated with depressive syndrome of AD through functional brain imaging, although there are some studies that reported regional brain dysfunction related to the elementary symptom of depression, not depression defined as a syndrome. Hirono et al.[2] reported through a FDG-PET study that the depression score of the Neuropsychiatric Inventory (NPI)[6] was correlated with frontal cerebral hypometabolism. In contrast, Craig et al.[3] did not find any relationship between the two. Although the depression score of the NPI relays mainly on dysphoric mood, depressive phenomena is more likely to manifest as a syndrome rather than as a single elementary symptom like dysphoric mood. Furthermore, the NPI assessment for dysphoric mood symptoms is based only on an interview with collateral informant without any direct evaluation of the patient's mood state. In contrast, for a better assessment of the individual depressive symptoms included in the depression of AD, we interviewed both the patient and his or her collateral informant and tried to explore and resolve any apparent inconsistencies between the two. In general, collateral informants tend to overreport depressive symptoms for patients with AD patients, whereas patients with AD tend to underreport the symptoms because of memory and language problems.

Although functional changes in prefrontal areas, including dorsolateral prefrontal cortex, orbitofrontal cortex, or anterior cingulate cortex, have been implicated as neural correlates of primary depression in many studies,[7] BA 6, which has long been recognized as a premotor or high-order motor area, was associated with depressive syndrome of AD in this study. However, this finding does not necessarily indicate that motor system deficit has a close relationship with depression in AD. Recent evidence has revealed that the rostral parts of BA 6, where

depression-related hypometabolism was observed in our study, closely interconnect with prefreontal cortex rather than with primary motor cortex, although the caudal parts of BA 6 has a close relationship with primary motor cortex and send massive corticospinal projections.[8] Therefore, it seems more reasonable that the deficit of rostral BA 6 in depressive AD is related to prefrontal dysfunction rather than motor system dysfunction. There was also a recent report that loss of motivated behavior, including work, activities, appetite, and libido, in primary depression showed significant negative correlation with rCMRglu in BA 6 as well as dorsomedial and dorsolateral prefreontal cortex.[9]

Although the depressive AD group showed frontal hypometabolism when compared with the nondepressive AD group, there was no difference of glucose metabolism found in the same area between the depressive AD and NC groups. This may probably be related to the global normalization process, in which the count of each voxel is normalized to the total count of the brain. Compared with the normal brain, the AD brain has much smaller total rCMRglu count because of the diffuse neuronal dysfunction or loss. As a result, the relatively small but really existing metabolic difference could not be detected between AD and NC.

We included only patients with very mild and mild AD to minimize the underreporting problem. However, it is possible that this may result in missing any potential abnormalities of rCMRglu related specifically to depression of moderate or severe AD.

In conclusion, these results suggest that the functional disruption of the frontal cortex is associated with depressive syndrome in patients with AD. When combined with previous observations of frontal dysfunction for primary and secondary depressive syndrome,[7] these results suggest that frontal dysfunction is probably associated with depressive syndrome regardless of the etiology.

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