Psychiatry Research: Neuroimaging 221 (2014) 86–91

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Depressive symptoms and regional cerebral blood flow in Alzheimer's disease

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ARTICLE INFO

Article history:
Received 31 December 2012
Received in revised form
23 October 2013
Accepted 9 November 2013
Available online 15 November 2013

Keywords:
Alzheimer's disease (AD)
Depression
Depressive symptom
Regional cerebral blood flow (rCBF)

ABSTRACT

Depressive symptoms are common in patients with Alzheimer's disease (AD) and increase the caregiver burden, although the etiology and pathologic mechanism of depressive symptoms in AD patients remain unclear. In this study, we tried to clarify the cerebral blood flow (CBF) correlates of depressive symptoms in AD, excluding the effect of apathy and anxiety. Seventy-nine consecutive patients with AD were recruited from outpatient units of the Memory Clinic of Okayama University Hospital. The level of depressive symptoms was evaluated using the depression domain of the Neuropsychiatric Inventory (NPI). The patients underwent brain SPECT with 99mTc-ethylcysteinate dimer. After removing the effects of age, anxiety and apathy scores of NPI, and five subscales of Addenbrooke's Cognitive Examination-revised (ACE-R), correlation analysis of NPI depression scores showed a significant cluster of voxels in the left middle frontal gyrus (Brodmann area 9), similar to the areas in the simple correlation analysis. The dorsolateral prefrontal area is significantly involved in the pathogenesis of depressive symptoms in AD, and the area on the left side especially may be closely related to the depressive symptoms revealed by NPI.

1. Introduction

Alzheimer's disease (AD) is the leading cause of late-onset dementia worldwide. Depressive symptoms are common in patients with AD and increase the caregiver burden (Akiyama et al., 2008; Kataoka et al., 2010). Although the etiology and pathologic mechanism of depressive symptoms in AD patients remain unclear, a biological marker that objectively evaluates depressive symptoms might be useful (Kataoka et al., 2010).

There have been several studies on the relationship of depressive symptoms to regional cerebral blood flow (rCBF) or regional cerebral glucose metabolism in AD (Hirono et al., 1998; Liao et al., 2003; Holthoff et al., 2005; Lee et al., 2006; Levy-Cooperman et al., 2008; Akiyama et al., 2008). Data from previous functional imaging studies have mainly supported the role of the dorsolateral prefrontal region (Hirono et al., 1998; Holthoff et al., 2005; Lee et al., 2006; Levy-Cooperman et al., 2008; Akiyama et al., 2008). Associations with the anterior cingulate have been described inconsistently (Hirono et al., 1998; Liao et al., 2003). However, most of these studies did not exclude AD patients with apathy or anxiety, although depression commonly coexists with apathy and anxiety (Kataoka et al., 2010). The presence of apathy is particularly germane as anterior cingulate and prefrontal hypoperfusion has been associated with apathy symptoms in AD patients (Lanctôt et al., 2007). Moreover, almost all studies were performed in a cross-sectional setting (Hirono et al., 1998; Holthoff et al., 2005; Lee et al., 2006; Levy-Cooperman et al., 2008; Akiyama et al., 2008).

In this study, we tried to identify the cerebral blood flow correlates of depressive symptoms in AD without the effect of apathy and anxiety by correlation analysis. We predicted a significant relationship between depressive symptoms and rCBF in the dorsolateral prefrontal regions of AD patients.

2. Methods

2.1. Subjects

Seventy-nine consecutive patients with Alzheimer's disease were recruited from the outpatient units of the Memory Clinic of Okayama University Hospital between September 2008 and April 2012 according to the following criteria. They all (i) underwent general physical and neurological examinations and extensive

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http://dx.doi.org/10.1016/j.pscychresns.2013.11.002

laboratory testing, including thyroid function tests, serum vitamin B12, and syphilis serology; (ii) took the revised Addenbrooke's Cognitive Examination (ACE-R) (Yoshida et al., 2012), the Mini Mental State Examination (MMSE) (Folstein et al., 1975), the Frontal Assessment Battery (FAB) (Kugo et al., 2007); (iii) underwent single photon emission computed tomography (SPECT) with 99mTc-ethylcysteinate dimer of the brain as well as magnetic resonance imaging (MRI) of the head; and (iv) were diagnosed with probable AD according to the criteria formulated by the NINCDS-ADRDA (McKhann et al., 1984). The exclusion criteria were (i) complications from other neurological diseases or illnesses; (ii) history of mental illness or substance abuse prior to the onset of dementia; (iii) evidence of focal brain lesions on head MRI; (iv) treatment with cholinesterase inhibitors, memantine, antipsychotics, antidepressants, or anxiolytic drugs; and (v) left handedness or ambidexterity.

The profile of each subject (age, sex, months of disease duration, and years of education) was obtained. Scores on three subscales (depression, anxiety, and apathy) of the Neuropsychiatric Inventory (NPI), Barthel Index, and Functional Assessment Questionnaire (FAQ) were rated by a trained clinical psychologist, based on the information from family caregivers. The Clinical Dementia Rating (CDR) (Hughes et al., 1982) score was rated by the chief clinician.

2.2. Instruments

NPI is a valid and reliable instrument for measuring non-cognitive symptoms in dementia (Cummings et al., 1994; Hirono et al., 1997). It is a caregiver-based tool that assesses ten different domains in dementia. The NPI gives a composite score for each domain, which is the product of frequency multiplied by severity subscores: scores from 1 to 4 (with 4 being the most severe) for the frequency and from 1 to 3 (with 3 being the most severe) for the severity of each behavior (Akiyama et al., 2008). The maximum attainable score was 12. In this study, three subscales (depression, anxiety, and apathy) were used.

ACE-R was developed to provide a brief test sensitive to early stage dementia, and is capable of differentiating between dementia subtypes including AD, frontotemporal dementia, progressive supranuclear palsy, and other parkinsonian syndromes (Mioshi et al., 2006). ACE-R includes MMSE, but extends it to encompass important areas not covered by MMSE, such as frontal-executive function and visuospatial skills. For this study, we used the Japanese version of ACE-R described by Yoshida et al. (2012).

The Barthel Index consists of 10 items that measure a person's daily functioning, specifically the activities of daily living and mobility (Wade and Collin, 1988). The total Barthel Index score ranges from 0 to 100. A higher score indicates a better performance. The Functional Assessment Questionnaire (FAQ) measures functional activities of older adults using the patient's partner as an informant (Pfeffer et al., 1982). The FAQ consists of ten items, and the score on each item ranges from 0 to 3. A higher score indicates more severe impairment.

2.3. Ethics

This study was approved by the Internal Ethical Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences. After a complete description of the study to the subjects and their relatives, written informed consent was obtained.

2.4. Brain perfusion SPECT imaging

All subjects were examined by brain perfusion SPECT. Patients were examined in a comfortable supine position with their eyes closed in quiet surroundings. Ten minutes after intravenous administration of 99mTc-ethylcysteinate dimer (ECD, 600MBq, Daiichi Radioisotope Laboratories Ltd., Tokyo, Japan), SPECT images were obtained using a triple-head, rotating gamma camera interfaced to a minicomputer (GCA9300A/ DI; Toshiba, Tokyo, Japan) equipped with a fanbeam, low-energy, high-resolution collimator. Sixty projection images over a 360° angle in a 128×128 matrix were acquired. All images were reconstructed using ramp-filtered back-projection and then three-dimensionally smoothed with a Butterworth filter (order 8, cutoff 0.12 cycles/cm). The reconstructed images were corrected for gamma ray attenuation using the Chang method ($\mu = 0.09$).

2.5. Data analysis

Spatial reprocessing and statistical analysis of images was performed on a voxel-by-voxel basis using Statistical Parametric Mapping 8 (SPM8, Wellcome Department of Imaging Neuroscience, UK) running on MATLAB (The Mathworks, Inc., Natick, MA, USA). All SPECT images of each subject were normalized to the standard brain of the Montreal Neurological Institute (MNI), and spatial normalization was performed with 12-parameter affine and non-linear transformations (Friston et al., 1995). The voxel sizes of the reslice option were 2 mm × 2 mm × 2 mm. The non-linear parameters were set at 25 mm cut-off basis functions and 16 iterations. All the normalized SPECT images were then smoothed with an isotropic Gaussian kernel filter (12 mm full-width at half-maximum).

We applied a simple regression method using SPM8 to obtain the correlation between NPI-dep scores and rCBF imaging data from SPECT among 79 AD subjects. The analysis used a threshold of $p < 0.001$ (uncorrected) at the voxel level, and results were considered significant at 100 voxels at the cluster level (simple correlation analysis). Thereafter, to remove the effect of other factors, age, five subscale scores of ACE-R and two subscale scores (anxiety, apathy) of NPI were entered into the model as nuisance covariates, and we performed a simple regression method using SPM8 to obtain the correlation between NPI-dep and rCBF imaging data from SPECT. The specific effects of depressive symptoms were tested using [−1] t-contrast with an additional zero for the scores of other factors, assuming that the presence of the symptoms would be uniquely associated with decreased rCBF. In the latter analysis, a threshold of $p < 0.001$ (uncorrected) was used at the voxel level, and results were considered significant at 100 voxels at the cluster level. In both analyses, global normalization was performed by proportional scaling with the mean voxel value. Masking was applied using the threshold method (0.8 times the global value). In both analyses, global normalization was performed by proportional scaling with the mean voxel value. Masking was applied using the threshold method (0.8 times the global value).

2.6. Statistical analysis

Statistical analysis was performed using the SPSS 14.0J software program (SPSS Inc., Chicago, IL). The correlation analysis of NPI-dep scores to other clinical characteristics was done by Pearson's correlation coefficiency. A value of $p < 0.05$ was accepted as significant.

3. Results

3.1. Demographic characteristics

Demographic characteristics are shown in Table 1. Among 79 AD patients, 45 were women and 34 were men. For dementia severity, 47 patients had CDR scores 0.5, 31 had CDR 1, and one patient had CDR 2. On the NPI depression score, 51 patients had a score of 0, seven patients scored 1, ten patients scored 2, ten patients scored 3, and one patient had a score of 6.

Table 1
Clinical characteristics ($n = 79$).

	Mean	S.D.	Range
Age (years)	76.2	7.6	49–89
Duration	28.3	16.6	4–79
Education	11.0	2.5	4–16
NPI-dep	0.8	1.3	0–6
NPI-anxiety	0.2	0.7	0–4
NPI-apathy	2.0	2.8	0–12
MMSE	21.4	4.2	8–27
ACE-R	65.4	13.3	32–91
Attention	13.7	3.2	3–18
Memory	10.3	5.0	1–23
Fluency	6.4	2.9	0–13
Language	22.0	3.3	10–26
Visuospatial	12.9	3.0	4–16
FAB	10.3	2.8	3–16
Barthel	96.9	5.4	80–100
FAQ	12.0	7.2	0–27

Duration, disease duration (months);
Education, years of education;
NPI-Dep, depression scores of neuropsychiatric inventory;
Duration, duration of disease;
Education, years of education;
MMSE, mini mental state examination;
ACE-R, revised Addenbrook's cognitive examination;
Attention, attention and orientation scores of ACE-R;
Memory, memory scores of ACE-R;
Fluency, word fluency scores of ACE-R;
Language, language scores of ACE-R;
Visuospatial, visuospatial scores of ACE-R;
FAB, frontal assessment battery;
Barthel. Barthel index;
FAQ, functinal assessment questionnaire.