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The short-term effect of acetylcholinesterase inhibitor on the regional cerebral blood flow of Alzheimer's disease

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ABSTRACT

This study is to investigate changes in regional cerebral blood flow (rCBF) of Alzheimer's disease (AD) in short-term treatment with acetylcholinesterase inhibitor (ChEI). rCBF was measured by single photon emission computed tomography (SPECT). CBF measurements were performed in 13 AD patients before treatment and 4 months later, while the control group with syncope or headache consisted of 17 patients. The clinical diagnosis of AD was based on the NINCDS-ADRDA criteria. Significant increases in rCBF were noted in the left angular, the right superior frontal gyrus, the right occipital, the left temporal lobe and the left orbital gyrus at the end of short-term therapy. Reduction in the rCBF before treatment is more profound in the left superior temporal, the right precentral and the both inferior frontal gyri compared with the control group. It achieved increase of rCBF after ChEI treatment. Also it overall increased in global cognitive functions including Korean Version Mini Mental State Examination (K-MMSE) and Clinical Dementia Rating (CDR). Treatment with ChEI for 4 months could increase rCBF and improve cognitive function of patients with AD.

1. Introduction

AD is characterized by deficient cholinergic innervation of the cerebral cortex and subcortical structures (Francis et al., 1999; Jansen Steur and Wevers, 2002). ChEI is used as a therapeutic agent for AD. Intracerebral acetylcholine receptors are distributed throughout the brain, and ChEI influences both the pre- and the postsynaptic acetylcholinesterase (AChE)-positive structures in the human central nervous systems. During periods of high attentional demand, acetylcholine is released diffusely throughout neocortex to modulate processing within sensory and prefrontal–parietal cortices. Thus, ChEI improves the behavioral and attentional symptoms of AD (Kasa et al., 2000; Kaasinen et al., 2002).

There are various studies with SPECT assessment of the short-term effects of ChEI on rCBF in patients with AD by such action (Nakano et al., 2001; Nobili et al., 2002a,b; Annalena, 2007; Tonini et al., 2003). Some studies indicate that ChEI could enhance cognitive functions and/or rCBF by comparing patients actively treated with non-treated (Staff et al., 2000; Seigo et al., 2001; Nobili et al., 2002a,b).

SPECT is a generally accepted tool in studies of rCBF in neurology and psychiatry (Andrew et al., 2006). It may be useful for diagnosis of dementia and for the estimation of the effects of the ChEI therapy in AD. In the present study, we administered ChEI to AD and evaluated changes in rCBF 4 months later.

2. Materials and methods

2.1. Participants

We investigated 13 patients diagnosed as having AD according to the NINCDS-ADRDA criteria (McKhann et al., 1984). All these subjects had Hachinski ischemic scale (HIS) scores of less than 4 (Hachinski et al., 1975). Most of them had experienced a progressive memory loss for at least 1 year. All patients were subjected to a comprehensive medical evaluation, computed tomography (CT) or magnetic resonance imaging (MRI), as well as neuropsychological tests: K-MMSE and CDR (Kang et al., 1997; Choi et al., 2001). The CT or MRI images for patients with AD were normal or revealed generalized or temporal lobe atrophy and they were free of any significant medical illnesses. The control group from non-demented patients with headache or syncope ranged in age from 60 to 75 years was included for normal SPECT database of our center.

ChEI therapy (donepezil, 5 mg/day, in 7 patients and galantamine, 8 mg/day, in 6 patients) was introduced at the onset of study

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Table 1
Scores on neuropsychological tests of K-MMSE and CDR before treatment and 4 months later follow-up for 13 patients with AD (mean ± S.D.).

	Before treatment	4 months follow-up
K-MMSE	18.77 ± 6.46	19.85 ± 7.24
CDR	1.38 ± 0.51	1.12 ± 0.55

in 13 patients with AD. They did not receive any other drugs improving rCBF. The measurement of rCBF was repeated in all patients before treatment and 4 months later. In the control group, SPECT was done at the onset of the symptom.

2.2. SPECT imaging

The SPECT images were obtained 20 min after an intravenous injection of approximately 740–925 MBq of ^{99m}Tc-ECD and by using a multi-detector scanner (ECAM plus; Siemens, Erlangen, Germany) that was equipped with a low-energy, fan-beam collimator. The head unit consists of two rings of 59 probe-type detectors. The data were acquired on 128 × 128 matrices with a 20% symmetric window at 140 keV. The continuous transaxial

Table 2
Brain areas showing increases in rCBF for the patients after short-term treatment compared with before treatment.

T	Coordinate			Brain area
	x	*y*	*z*	
6.06	−53	−60	33	Left parietal lobe, angular gyrus
5.67	32	−67	−15	Right occipital lobe, fusiform gyrus
5.59	32	34	54	Right superior frontal gyrus
4.52	−40	−38	−18	Left temporal lobe, fusiform gyrus
4.49	−4	39	−27	Left frontal lobe, orbital gyrus

Note: *t* values of the voxels and the coordinates of the significant (corrected $p < 0.05$) clusters showing increases in rCBF.

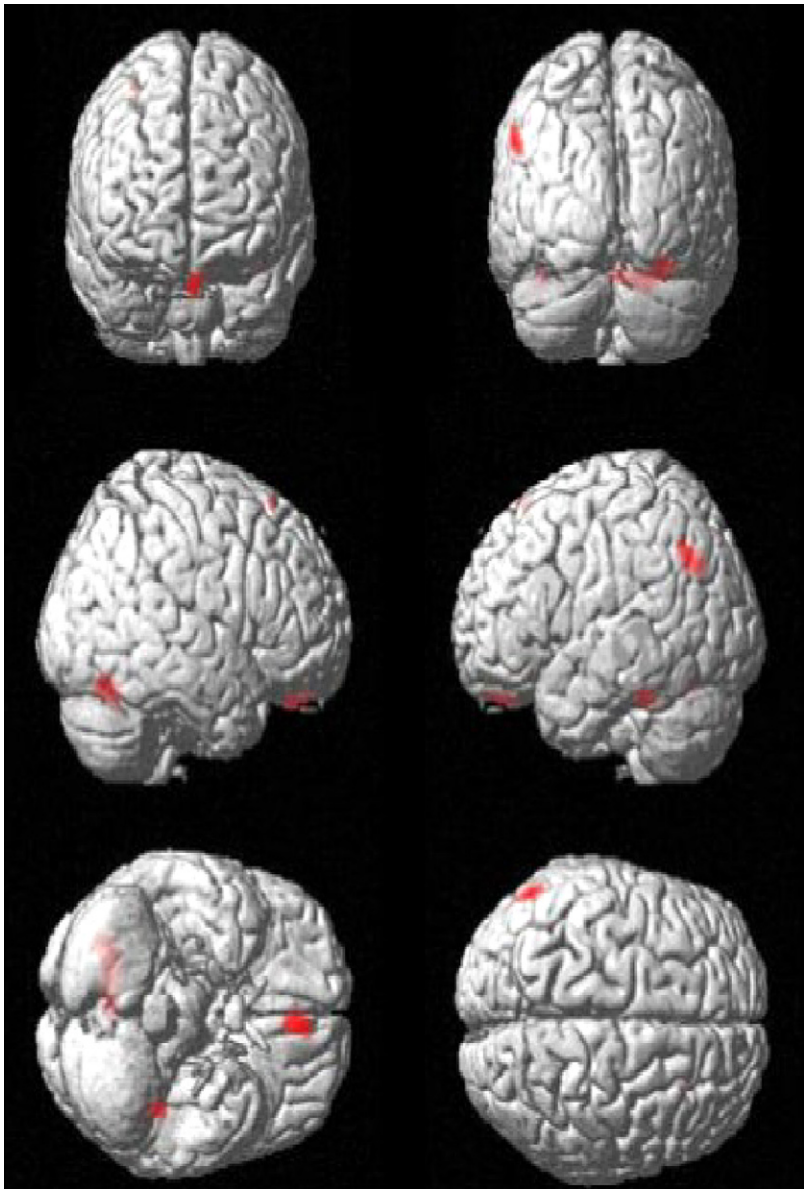

Fig. 1. rCBF increase in AD patients treated with ChEI for 4 months compared with before treatment as shown by SPM. Significant increase is seen as red colored areas superimposed on standard three-dimensional anatomic template (uncorrected $p < 0.001$, corrected $p < 0.05$). The maximum difference is found in the left parietal lobe, angular gyrus ($T = 6.06$, peak Talairach coordinates: −53, −60, 33). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)