Neurobiology of Aging 34 (2013) 1740–1747

Contents lists available at SciVerse ScienceDirect

Neurobiology of Aging

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

Changes in subcortical structures in early- versus late-onset Alzheimer's disease

Hanna Cho [a], Sang Won Seo [a,*], Jeong-Hun Kim [b], Changsoo Kim [c], Byoung Seok Ye [a], Geon Ha Kim [a], Young Noh [a], Hee Jin Kim [a], Cindy W. Yoon [a], Joon-Kyung Seong [d], Chang-Hun Kim [e], Sue J. Kang [a], Juhee Chin [a], Sung Tae Kim [f], Kyung-Han Lee [g], Duk L. Na [a]

[a] Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[b] Department of Computer and Radio Communications Engineering, Korea University, Seoul, Korea
[c] Department of Preventive Medicine and the Institute for Environmental Research, Yonsei University College of Medicine, Seoul, Korea
[d] Department of Biomedical Engineering, Korea University, Korea
[e] Department of Brain and Cognitive Engineering, Korea University, Korea
[f] Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[g] Department of Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

ARTICLE INFO

Article history:
Received 28 August 2012
Received in revised form 28 December 2012
Accepted 2 January 2013
Available online 8 February 2013

Keywords:
Alzheimer's Disease
Onset age
Early onset
Subcortical structure
Longitudinal study
Amygdala
Hippocampus
Thalamus
Putamen
Globus pallidus
Caudate nucleus
Basal ganglia

ABSTRACT

Patients with early-onset Alzheimer's disease (EOAD) are reported to be different from those with late-onset Alzheimer's disease (LOAD) in terms of neuropsychological and neuroimaging findings. In this study, we aimed to compare the longitudinal volume changes of 6 subcortical structures (the amygdala, hippocampus, thalamus, putamen, globus pallidus, and caudate nucleus) between patients with EOAD and LOAD for 3 years. We prospectively recruited 36 patients with probable Alzheimer's disease (14 EOAD, 22 LOAD) and 14 normal control subjects. We analyzed the volume of subcortical structures using an automatic surface-based method. At baseline, there were no differences in the volumes of subcortical structures between patients with EOAD and LOAD. However, over 3 years of longitudinal follow-up, patients with EOAD showed more rapid volumetric decline in the caudate, putamen, and thalamus than patients with LOAD, which is consistent with neuropsychological results. Our findings suggested that the cognitive reserve theory might be applicable to explain different decline rates of the volumes of the basal ganglia and thalamus according to onset age.

1. Introduction

Alzheimer's disease (AD) is the most common cause of degenerative dementia. In typical cases, AD changes initially affect memory, then language and visuospatial, and frontal functions as AD progresses. However, there might be some differences in the clinical manifestations between patients with early-onset AD (EOAD) and late-onset AD (LOAD) (Koedam et al., 2010; Mendez et al., 2012; van der Flier et al., 2011). Patients with EOAD tend to display more diverse cognitive impairments and neurological deficits than those with LOAD, such as language, visuospatial, and executive dysfunctions (Chui et al., 1985; Fujimori et al., 1998; Mendez et al., 2012; Ossenkoppele et al., 2012; Seltzer and Sherwin, 1983; Smits et al., 2012), and extrapyramidal signs (Chui et al., 1985), whereas patients with LOAD present cognitive impairment of the amnesia-predominant type (Binetti et al., 1993; Mendez et al., 2012; Ossenkoppele et al., 2012; Smits et al., 2012).

In line with these clinical differences, cross-sectional neuroimaging studies have also shown greater cortical atrophy, particularly in the lateral parietal and precuneus in patients with EOAD than in those with LOAD, whereas more medial temporal lesions have been documented in patients with LOAD than in those with EOAD (Frisoni et al., 2005, 2007; Ishii et al., 2005). Although recent studies of subcortical structural volume differences have been reported in AD patients (de Jong et al., 2008; Pievani et al., 2012; Roh et al., 2011), of these, only 1 study compared EOAD with LOAD in terms of volume and shape of subcortical structures (Pievani et al., 2012). The authors suggested that the presence of significant differences in shape changes in the caudate nucleus between

* Corresponding author at: Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea. Tel.: +82 2 3410 1233; fax: +82 2 3410 0052.
E-mail address: sangwonseo@empal.com (S.W. Seo).

0197-4580/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2013.01.001

patients with EOAD and young controls. These findings were consistent with previous studies showing that patients with EOAD had more extrapyramidal signs and frontal dysfunction than patients with LOAD (Chui et al., 1985; Frisoni et al., 2007; Kim et al., 2005). Volumes of the basal ganglia and thalamus are the main structures of the frontal-subcortical circuits, which are responsible for frontal dysfunction. To our knowledge, however, there has not been any longitudinal study comparing volume changes in subcortical structures between patients with EOAD and LOAD.

Longitudinal studies on EOAD versus LOAD were available for cognitive decline, total brain volumes, and cortical thinning (Chan et al., 2003; Cho et al., 2012a; Jacobs et al., 1994; Koss et al., 1996; Seltzer and Sherwin, 1983) and showed that patients with EOAD progress more rapidly in terms of cognition and brain atrophy. Previous studies suggested that more rapid progression in EOAD than in LOAD might be in accord with the cognitive reserve theory. More specifically, younger patients have more cognitive reserve than older patients such that younger patients are better at coping with brain damage by effectively recruiting pre-existing cognitive networks or by enlisting compensatory strategies (Katzman et al., 1988; Stern, 2002). Therefore, more widespread atrophy in the brain should have occurred for patients with EOAD to have the same level of cognitive impairment as in LOAD. However, when AD starts to progress, it progresses more rapidly in patients with EOAD than LOAD, because AD pathology in EOAD is already more severe so that there is generally less brain substrate left to function properly. This cognitive reserve theory can also be applied to the decline rate of subcortical structures according to onset age. Specifically, it is possible that patients with EOAD might show more rapid decline in the volume of subcortical structures than patients with LOAD. In contrast, regarding the volume of the hippocampus, because patients with LOAD display more severe memory impairment and hippocampal atrophy than patients with EOAD (Binetti et al., 1993; Frisoni et al., 2007), hippocampal volume reduction over time might be more rapid in patients with LOAD than in those with EOAD.

In this study, we aimed to test our hypotheses based on the Alzheimer Disease and Positron Emission Tomography (ADAPET) cohort, which is a 5-year longitudinal study. At the 3-year follow-up, we hypothesized that patients with EOAD will have progressed more rapidly than patients with LOAD in terms of volume changes in the basal ganglia and thalamus, along with more rapid decline of frontal function. Likewise, patients with LOAD might undergo more rapid volume reduction of the amygdala and hippocampus along with more rapid decline of memory function than those with EOAD.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Board of Samsung Medical Center. We obtained informed consent from all the patient and control participants.

We prospectively recruited 36 patients with AD to participate in the ADAPET study conducted by the Memory Disorder Clinic at Samsung Medical Center from March 2006 to December 2006. The patients fit the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 1994) and the criteria for probable AD proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984). The enrolled patients were eligible if they had early-stage dementia with a Clinical Dementia Rating score of 0.5 or 1, were cooperative candidates for this longitudinal study, and had a caregiver. None had a family history suggestive of an autosomal dominant disease. We excluded patients with other structural lesions found using brain magnetic resonance imaging (MRI), such as territorial infarction, intracranial hemorrhage, brain tumor, hydrocephalus, or severe white matter hyperintensities.

At the initial visit, the patients underwent clinical interviews, neurological examination, a battery of neuropsychological tests collectively termed the Seoul Neuropsychological Screening Battery (SNSB, see *2.2. Neuropsychological tests*), conventional brain MRI scans, and F-18 fluorodeoxyglucose positron emission tomography scans. The possibility of secondary causes of cognitive deficits was ruled out by laboratory tests including complete blood count, blood chemistry, vitamin B_{12}, folate, syphilis serology, and thyroid function tests.

Onset age of dementia was determined from information obtained from family members or caregivers at the patient's first visit to our memory disorder clinic. The patients were arbitrarily divided into 2 subgroups according to an arbitrary cutoff age at onset of 65 years: 14 patients were categorized into the EOAD group (onset age $<$65 years; mean $\pm$ SD onset age, 57.8 $\pm$ 6.7 years, and range, 45–64 years) and 22 patients into the LOAD group (onset age $\geq$65 years; mean $\pm$ SD onset age, 71.5 $\pm$ 3.8 years, and range, 66–78 years).

During the study period, a total of 111 patients with AD were candidates, and only 36 patients agreed to participate in this study. The 36 patient participants did not differ significantly from those who did not participate in terms of age (participants vs. nonparticipants: 70.2 $\pm$ 8.0 vs. 70.5 $\pm$ 7.9 years, respectively), sex (male 38.9% vs. 30.7%), education (11.0 $\pm$ 4.6 vs. 9.4 $\pm$ 5.3 years), with the exception of the Mini Mental State Examination (MMSE) score (20.9 $\pm$ 3.3 vs. 18.1 $\pm$ 4.8).

We recruited 14 healthy volunteers to serve as normal control subjects (NCs) who were spouses of the AD patients and who had no history of neurological or psychiatric illnesses and no abnormalities on neurological examination. The NCs exhibited normal cognition on the MMSE and neuropsychological tests (SNSB). In the comparison of AD with onset age, the NCs were divided into 2 subgroups according to the age of 65: 6 NCs in the young control subjects (YCs) group and 8 normal control subjects in the old control subjects (OCs) group.

2.2. Neuropsychological tests

The patients and NCs underwent the SNSB standardized neuropsychological battery of tests (Ahn et al., 2010). The SNSB consists of tests for verbal and visual memory, attention, language, praxis, 4 elements of Gerstmann syndrome, visuoconstructive function, frontal executive function, and the MMSE. Based on the SNSB results, we calculated SNSB-Dementia version (SNSB-D) memory and frontal subscores and total score, previously described in detail (Ahn et al., 2010, 2011).

2.3. Image acquisition and processing

Three-dimensional T1-weighted Turbo Field Echo MRI images from 50 participants (36 patients with probable AD and 14 NCs) were acquired using the same Philips 3.0T Achieva MRI scanner with the same imaging parameters (sagittal slice thickness, 1.0 mm, over contiguous slice acquisition with 50% overlap; no gap; repetition time 9.9 ms; echo time 4.6 ms; flip angle 8°; and matrix size 240 $\times$ 240 pixels reconstructed to 480 $\times$ 480 over a field of view of 240 mm). The T1 images of each subject were processed to obtain the anatomical parcellations of subcortical structures by the FreeSurfer software package (Version 5.0, Athinoula A. Martinos Center at the Massachusetts General Hospital, Harvard Medical School;