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Excessive tau accumulation in the parieto-occipital cortex characterizes early-onset Alzheimer's disease

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ABSTRACT

Early-onset Alzheimer's disease (EOAD) is characterized by greater nonmemory dysfunctions, more rapid progression, and greater hypometabolism and atrophy than late-onset AD (LOAD). We sought to investigate the differences in tau accumulation patterns between early- and late-onset patients with AD and mild cognitive impairment (MCI). In 90 patients who completed ^{18}F-AV-1451 and ^{18}F-florbetaben positron emission tomography scans, only 59 amyloid-positive patients (11 EOAD, 10 EOMCI, 21 LOAD, and 17 LOMCI) were included in this study. We compared cortical ^{18}F-AV-1451 binding between each patient group and corresponding amyloid-negative age-matched controls. In contrast to no difference in cortical binding between the EOMCI and LOMCI groups, EOAD showed greater binding in the parieto-occipital cortex than LOAD. The parieto-occipital binding correlated with visuospatial dysfunction in the EOAD spectrum, whereas binding in the temporal cortex correlated with verbal memory dysfunction in the LOAD spectrum. Our findings suggest that distinct topographic distribution of tau may influence the nature of cognitive impairment in EOAD patients.

1. Introduction

Early-onset Alzheimer's disease (EOAD) has a greater impact on occupational and socioeconomic status (Werner et al., 2009), undergoes more rapid progression, and is associated with a shorter survival period than late-onset AD (LOAD) (Heyman et al., 1987; Koss et al., 1996). EOAD is also characterized by greater impairment of various nonmemory functions including attention, visuospatial, language, praxis, and executive functions than LOAD, which is predominantly associated with memory impairment (Frisoni et al., 2007; Jacobs et al., 1994; Koss et al., 1996; Smits et al., 2012). Accompanying these distinct patterns of neuropsychological dysfunction, EOAD patients show more severe hypometabolism and cortical atrophy, particularly in the parietal, posterior cingulate, and precuneus cortices (Cho et al., 2013a; Frisoni et al., 2007; Kim et al., 2005; Rabinovici et al., 2010).

Postmortem pathologic studies have reported greater burden of amyloid-β plaques and neurofibrillary tangles (NFTs) in the parieto-frontal association cortices of EOAD patients than that in LOAD patients (Hansen et al., 1988; Ho et al., 2002). In a study using a cutoff of 62 years, EOAD patients showed greater ^{11}C-Pittsburgh Compound B (PIB) binding in the parietal cortex than LOAD patients (Ossenkoppele et al., 2012). However, unlike these postmortem and in vivo imaging studies, no difference in cortical ^{11}C-PIB binding has been shown between EOAD and LOAD patients dichotomized by the age cutoff of 65 years at onset (Cho et al., 2013b; Rabinovici et al., 2010).

^{18}F-AV-1451 is a recently developed radiotracer specific for paired helical filaments of hyperphosphorylated tau protein (Marquie et al., 2015) and enables the in vivo visualization of tau pathology (Johnson et al., 2016). Cortical ^{18}F-AV-1451 binding patterns clearly mirror the known topographic distribution of NFT pathology in AD (Cho et al., 2016; Schwarz et al., 2016).

In the present study, we sought to investigate differences in ^{18}F-AV-1451 binding patterns between early- and late-onset patients with AD and mild cognitive impairment (MCI). We also investigated the cortical regions in which ^{18}F-AV-1451 binding correlates with specific neuropsychological function in each age-related group.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Board of Gangnam Severance Hospital, and written informed consent was obtained from all participants.

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Between January 2015 to February 2016, 90 MCI and mild to moderate AD dementia patients who had been clinically diagnosed at the Memory Disorder Clinic of Gangnam Severance Hospital were recruited. Clinical interviews, neurological examination, laboratory blood tests, apolipoprotein E (APOE) genotyping, neuropsychological tests, conventional brain magnetic resonance (MR) imaging, and ^{18}F-florbetaben (for amyloid-β) and ^{18}F-AV-1451 (for tau) positron emission tomography (PET) scans were conducted for all patients.

AD patients were required to meet the criteria for probable AD as 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). Amnestic MCI was diagnosed based on Petersen's criteria (Petersen et al., 1999); performance of verbal or visual memory function tests was below −1.5 standard deviation of age- and education-adjusted norm. Patients were excluded if they exhibited other structural lesions identified by brain MRI, including territorial infarction, intracranial hemorrhage, brain tumor, hydrocephalus, or severe white matter hyperintensities (Fazekas scale 3) (Fazekas et al., 1987). Potential secondary causes of cognitive deficits were excluded by additional laboratory tests including complete blood count, blood chemistry, vitamin B12, folate, syphilis serology, and thyroid function tests. We also excluded patients who met the diagnostic criteria for psychotic or mood disorders such as schizophrenia or major depressive disorder. There were no patients presenting with atypical features suggesting AD variants (posterior cortical atrophy, logopenic aphasia, or frontal-variant AD). Although we could not perform any genetic tests other than apolipoprotein E genotyping, none of the patients had a family history suspicious for autosomal dominant AD; ≥2 first degree relatives with a history of dementia or ≥1 family member presenting dementia in extremely young age.

The controls were healthy volunteers with no history of neurologic or psychiatric illness and no abnormalities detected by neurological examination. All control subjects underwent the same neuropsychological tests and neuroimaging studies as the patients. All showed normal cognition (above −1.5 standard deviation of age- and education-adjusted norm) on detailed neuropsychological tests.

Using the visual assessment method validated with postmortem tissue (Sabri et al., 2015; Villemagne et al., 2011), amyloid positivity was determined by 2 nuclear medicine specialists (Y. H. R. and J. H. L.) who were blinded to the clinical diagnosis. Onset ages were determined by an interview conducted with family members or caregivers. The patients were divided into subgroups according to the age cutoff of 65 years at onset, with 30 patients in the early-onset AD spectrum (EOAD/MCI: onset age <65 years; 12 EOAD and 18 EOMCI) and 60 patients in the late-onset AD spectrum (LOAD/MCI: onset age ≥65 years; 31 LOAD and 29 LOMCI). For this study, we finally included amyloid-positive patients: 11/12 (91.7%) EOAD, 10/18 (55.6%) EOMCI, 21/31 (67.7%) LOAD, and 17/29 (58.7%) LOMCI.

For comparison of the AD/MCI groups, 2 age-matched control groups comprising 15 young controls (YC) and 15 old controls (OC) negative for amyloid were included.

2.2. Neuropsychological tests

All subjects underwent neuropsychological tests using a standardized battery called the Seoul Neuropsychological Screening Battery (Ahn et al., 2010; Kang and Na, 2003). We assessed attention (Digit Span Backward: DS-BW), language (Boston Naming Test: BNT), visuospatial/constructive (Rey-Osterrieth Complex Figure Test: RCFT), verbal memory (Seoul Verbal Learning Test-Delayed Recall: SVLT-DR), visual memory (Rey-Osterrieth Complex Figure Test-Delayed Recall: RCFT-DR), frontal/executive functions (Controlled Oral Word Association Test-Semantics: COWAT), and Clinical Dementia Rating sum-of-boxes (CDR-SB), and also conducted the Mini-Mental State Examination (MMSE).

2.3. Image acquisition and processing

All participants underwent ^{18}F-florbetaben and ^{18}F-AV-1451 PET on separate days using a Biograph mCT PET/CT scanner (Siemens Medical Solutions; Malvern, PA, USA). PET images were acquired for 20 minutes at 80 minutes after the injection of 273.9 ± 31.8 MBq of ^{18}F-AV-1451 and at 90 minutes after the injection of 290.2 ± 30.5 of ^{18}F-florbetaben. Axial T1-weighted MR images were also acquired with 3D-spoiled gradient-recalled (3D-SPGR) sequences in a 3.0 Tesla MR scanner (Discovery MR750, GE Medical Systems, Milwaukee, WI, USA).

Detailed scanning and reconstruction protocols for PET and MR images and image processing steps were described in our previous work (Cho et al., 2016). In brief, we used FreeSurfer 5.3 (Massachusetts General Hospital, Harvard Medical School; http://surfer.nmr.mgh.harvard.edu) and in-house software to create FreeSurfer-generated cortical volumes-of-interest (VOIs) and the extraction of gray and white matter surfaces. By using the cerebellar cortex as the reference region, standardized uptake value ratio (SUVR) images were created. For the VOI-based analysis, we measured regional SUVR values for ^{18}F-AV-1451 and ^{18}F-florbetaben PET by using the subject-specific cortical VOIs. For the surface-based analysis, the cortical SUVR values were mapped on the white matter surface, and then, these SUVR maps were spatially normalized and smoothed on 2-dimensional surface by using the Gaussian kernel with an 8-mm full-width half maximum for statistical analysis.

We primarily used VOI data uncorrected for partial volume effect but additionally analyzed VOI data corrected for partial volume effect by using the region-based voxel-wise partial volume correction method (Thomas et al., 2011).

2.4. Statistical analysis

Demographic data were analyzed using analysis of variance and post hoc comparison for continuous variables and chi-square test for categorical variables. For the comparison of neuropsychological tests, we first used the analysis of covariance (ANCOVA) model with years of education as covariates, and then corrected multiple comparisons of each between-group comparison with the Bonferroni method. We primarily compared between the young and corresponding old groups (e.g., EOAD vs. LOAD, EOMCI vs. LOMCI, and YC vs. OC).

We performed interaction analysis by using the general linear model adjusting for the year of education to observe the interaction of regional ^{18}F-AV-1451 binding values between the onset age (early and late onset) and diagnosis (healthy control, MCI and AD) and also between the onset age and the MMSE score. For the between-group comparison, we compared regional ^{18}F-AV-1451 SUVR values between the 3 diagnostic groups in EOAD/MCI and LOAD/MCI separately by using the analysis of covariance model with age and years of education as covariates. For the group comparisons between the EO and LO groups (EOAD vs. LOAD and EOMCI vs. LOMCI), we used years of education and MMSE as covariates. Bonferroni's correction was used to correct for the multiple comparisons of each between-group comparison, and region-wise multiple comparisons were corrected by using Benjamini-Hochberg's false discovery rate (FDR) method (Benjamini and Hochberg, 1995). With the same method, we also compared ^{18}F-florbetaben SUVR values between the groups.