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Neurobiology of Aging 34 (2013) 1–12

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Apolipoprotein E ε4 and age effects on florbetapir positron emission tomography in healthy aging and Alzheimer disease

Adam S. Fleisher[a,b,c,*], Kewei Chen[a,c,d], Xiaofen Liu[a], Napatkamon Ayutyanont[a], Auttawut Roontiva[a], Pradeep Thiyyagura[a], Hillary Protas[a], Abhinay D. Joshi[e], Marwan Sabbagh[c,m], Carl H. Sadowsky[f], Reisa A. Sperling[g], Christopher M. Clark[e,h], Mark A. Mintun[e,i], Michael J. Pontecorvo[e], R. Edward Coleman[j], P. M. Doraiswamy[j], Keith A. Johnson[g,k], Alan P. Carpenter[e], Daniel M. Skovronsky[e,h], Eric M. Reiman[a,c,l,m]

[a] *The Banner Alzheimer's Institute, Phoenix, AZ, USA*
[b] *Department of Neurosciences, The University of California, San Diego, CA, USA*
[c] *Arizona Alzheimer's Consortium, AZ, USA*
[d] *Department of Mathematics, Arizona State University, Tempe, AZ, USA*
[e] *Avid Radiopharmaceuticals, Philadelphia, PA, USA*
[f] *Nova SE University, Fort Lauderdale, FL, USA*
[g] *Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[h] *University of Pennsylvania School of Medicine, Philadelphia, PA, USA*
[i] *Washington University School of Medicine, St. Louis, MO, USA*
[j] *Department of Radiology, Duke University Medical Center, Durham, NC, USA*
[k] *Departments of Neurology and Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
[l] *Department of Psychiatry, University of Arizona College of Medicine, Phoenix, AZ, USA*
[m] *Banner Sun Health Research Institute, Phoenix, AZ, USA*

Received 5 December 2011; received in revised form 24 April 2012; accepted 28 April 2012

Abstract

Objectives: Investigate apolipoprotein E ε4 (APOE4) gene and aging effects on florbetapir F18 positron emission tomography (PET) in normal aging and Alzheimer's disease (AD). Methods: Florbetapir F18 PET images were analyzed from 245 participants, 18–92 years of age, from Avid Radiopharmaceutical's multicenter registered trials, including 86 younger healthy control volunteers (yHC), 61 older healthy control volunteers (oHC), 53 mild cognitive impairment (MCI) patients, and 45 AD dementia patients (DAT). Mean florbetapir standard uptake value ratios (SUVRs) were used to evaluate the effects of APOE4 carrier status, older age, and their interaction in each of these groups. Results: In comparison with non-carriers, the APOE4 carriers in each of the oHC, MCI, and DAT groups had higher mean cortical-to-cerebellar florbetapir SUVRs, patterns of florbetapir PET elevations characteristic of DAT, and a higher proportion meeting florbetapir PET positivity criteria. Only the oHC group had a significant association between mean cortical florbetapir SUVRs and age. In cognitively normal adults, without regards to APOE4 genotype, amyloid began to increase at age 58 (95% confidence interval [CI]: 52.3–63.7), with a predicted typical age of florbetapir positivity occurring around age 71 years. Presence of the APOE4 gene reduced the age of predicted florbetapir positivity in normal aging to around age 56 years, approximately 20 years younger than non-carriers. Interpretation: Cerebral amyloid deposition is associated with APOE4 carrier status in older healthy control subjects and symptomatic AD patients, and increases with age in older cognitively normal individuals. Amyloid imaging positivity appears to begin near age 56 years in cognitively intact APOE4 carriers and age 76 years in APOE4 non-carriers.

Keywords: Florbetapir; PET; Amyloid PET; Apolipoprotein; Alzheimer; Alzheimer risk; Aging

* Corresponding author at: The Banner Alzheimer's Institute, Phoenix, AZ, USA. Tel.: +1 602 839 6979.
E-mail address: Adam.fleisher@bannerhealth.com (A.S. Fleisher).

0197-4580/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2012.04.017

1. Introduction

The advent of amyloid imaging provides an opportunity to expedite and guide development and use of early, even preclinical, treatments for Alzheimer's disease. To best identify patients for which amyloid imaging will provide interpretable information, we must first understand the influence of other risk factors that portend dementia due to Alzheimer's disease (DAT). These risk factors assist clinicians and researchers in stratifying patients by degree of probability of the presence of underlying cortical amyloid, a pathological hallmark of Alzheimer's disease (AD) (Braak and Braak, 1997; Jack et al., 2010a; Selkoe, 2008; Shaw et al., 2009). New diagnostic criteria are now proposed to better capture the utility of biomarkers in clinical research and diagnosis (Albert et al., 2011; Dubois et al., 2007; McKhann et al., 2011; Sperling et al., 2011). Furthermore, earlier more accurate biomarker-based diagnosis would likely offer greater opportunity for initiation of disease-modifying therapies prior to the end-stages of brain failure and dementia.

To date, advanced age and the apolipoprotein E $\varepsilon 4$ (APOE4) gene are the most potent known risk factors for DAT and subsequent presence of neurofibrillary tangles and amyloid plaques in the brain (Corder et al., 1998, 2004; Fratiglioni et al., 1993; Ghebremedhin et al., 1998, 2001). The APOE4 gene is associated with cerebral and vascular amyloid processing and toxicity (Folin et al., 2006; Jiang et al., 2008; Jordán et al., 1998; Li et al., 2007; Ma et al., 1996; Mahley et al., 2009; Strittmatter et al., 1993; Vemuri et al., 2010). Pathological studies, spinal fluid markers, and amyloid imaging have all shown that amyloid accumulation increases in association with advanced age and presence of the APOE4 allele, even in the absence of cognitive symptoms (Kok et al., 2009; Morris et al., 2010; Price and Morris, 1999; Reiman et al., 2009; Rowe et al., 2010; Sojkova et al., 2011; Vemuri et al., 2010; Villemagne et al., 2011). However, it is not clear when cognitively normal individuals begin to accumulate fibrillar amyloid in the brain, how rapidly it increases in association with age, and how the APOE4 gene and age interact to affect the patterns and degree of cortical amyloidosis.

In this study, we pooled data from five registered trials of florbetapir-positron emission tomography (PET), establishing a large convenience sample of cognitively normal individuals in a wide age range, as well as mild cognitive impairment (MCI) and DAT patients. Voxel-wise and region of interest (ROI) measures were assessed to evaluate the influences of APOE4 gene carrier status, gene dose, and age on regional patterns and degree of cortical amyloidosis within and between diagnostic and age groups. In addition, we sought to predict the trajectory of age-associated cortical fibrillar amyloid accumulation and the age at which cognitively normal individuals develop cortical amyloidosis in relationship to APOE4 genotype.

2. Methods

2.1. Participants

A total of 245 participants, including cognitively normal younger healthy control (yHC) volunteers (n = 86; 18–49 years old, 75 with APOE genotyping), older healthy control (oHC) volunteers (n = 61; ≥ 50 years old), individuals with MCI (n = 53) and DAT (n = 45) were assessed at 31 U.S. sites (Table 1). All healthy control volunteers (HC) were required to have no subjective cognitive complaints as corroborated by an informant report, a Mini-Mental State Examination (MMSE) score ≥ 29, and be cognitively normal on screening psychometric testing. Probable DAT participants met National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984) and had an MMSE score of 10–24. MCI participants had complaints of memory or cognitive decline corroborated by an informant, MMSE score > 24, with an initial diagnosis not more than 1 year from the day of the screening visit. Further inclusion and exclusion details for this cohort have been previously described (Fleisher et al., 2011). Both investigators and participants were blinded to genotype status. Trials were conducted in accordance with good clinical practice guidelines after approval from local institutional review boards. Study procedures were performed after written informed consent was obtained from study participants, authorized representatives, or both, according to local guidelines and degree of cognitive impairment.

2.2. Florbetapir-PET imaging acquisition

Across the study sites, there were 14 different PET scanner models from three manufacturers (Siemens, Munich, Germany; General Electric, Waukesha, WI, USA; Phillips, Amsterdam, Netherlands). Native slice thickness ranged from 2 mm to 4.25 mm, with field of views from 550/153 to 700/153. PET scans involved intravenous injection of approximately 10 mCi of florbetapir F18 50 minutes prior to a 10-minute emission acquisition. An iterative reconstruction algorithm (4 iterations, 16 subsets) was performed using a Gaussian filter of 5-mm full width at half maximum and saved as series of 128 × 128 matrices with voxel size of 2 × 2 × 2 mm. Between-scanner variability in attenuation, scatter, and uniformity was corrected based on Hoffman brain phantom scans acquired on each scanner.

2.3. Image processing

An automated brain mapping algorithm (SPM5, www.fil.ion.ucl.ac.uk/spm/) was used to spatially normalize each participant's PET image into the coordinates of the Montreal Neurological Institute (MNI) brain atlas. The spatially normalized PET scans were manually inspected for proper alignment to a custom MNI template from a subset