NeuroImage: Clinical 17 (2018) 751–760

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Regional association of pCASL-MRI with FDG-PET and PiB-PET in people at risk for autosomal dominant Alzheimer's disease

Lirong Yan[a,b,*], Collin Y. Liu[b,c], Koon-Pong Wong[d], Sung-Cheng Huang[d], Wendy J. Mack[e], Kay Jann[a,b], Giovanni Coppola[f], John M. Ringman[b,c], Danny J.J. Wang[a,b]

[a] Laboratory of FMRI Technology (LOFT), USC Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
[b] Department of Neurology, University of Southern California, Los Angeles, CA, USA
[c] Alzheimer's Disease Research Center, University of Southern California, Los Angeles, CA, USA
[d] Molecular and Medical Pharmacology, University of California Los Angeles, Los Angeles, CA, USA
[e] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
[f] Semel Institute of Psychiatry and Biobehavioral Sciences UCLA, USA

ARTICLE INFO

Keywords:
Autosomal dominant Alzheimer's disease
Arterial spin labeling
MRI
FDG pet
PiB PET
Cerebral perfusion
Glucose metabolism
Amyloid deposition

ABSTRACT

Autosomal dominant Alzheimer's disease (ADAD) is a small subset of Alzheimer's disease that is genetically determined with 100% penetrance. It provides a valuable window into studying the course of pathologic processes that leads to dementia. Arterial spin labeling (ASL) MRI is a potential AD imaging marker that non-invasively measures cerebral perfusion. In this study, we investigated the relationship of cerebral blood flow measured by pseudo-continuous ASL (pCASL) MRI with measures of cerebral metabolism (FDG PET) and amyloid deposition (Pittsburgh Compound B (PiB) PET). Thirty-one participants at risk for ADAD (age 39 ± 13 years, 19 females) were recruited into this study, and 21 of them received both MRI and FDG and PiB PET scans. Considerable variability was observed in regional correlations between ASL-CBF and FDG across subjects. Both regional hypo-perfusion and hypo-metabolism were associated with amyloid deposition. Cross-sectional analyses of each biomarker as a function of the estimated years to expected dementia diagnosis indicated an inverse relationship of both perfusion and glucose metabolism with amyloid deposition during AD development. These findings indicate that neurovascular dysfunction is associated with amyloid pathology, and also indicate that ASL CBF may serve as a sensitive early biomarker for AD. The direct comparison among the three biomarkers provides complementary information for understanding the pathophysiological process of AD.

1. Introduction

Alzheimer's disease (AD), as the most common form of dementia, is one of the leading causes of death in the United States. Converging evidence indicates that AD pathology begins years or decades before the clinical symptoms appear (Bateman et al., 2012; Dubois et al., 2016; Frisoni, 2012). Longitudinal studies of AD biomarkers therefore take many years to capture the full pathologic processes leading to dementia. Fully-penetrant autosomal dominant AD (ADAD) due to *PSEN1*, *PSEN2*, or *APP* mutations provides a valuable window for studying biomarkers across the cascade of AD pathology by taking advantage of the essentially 100% penetrance for the future development of AD with similar age of onset within families and mutation type (Ryman et al., 2014; Bateman et al., 2011; Schindler & Fagan, 2015). Therefore, we can estimate at what point cognitive, behavioral, imaging, and biochemical changes are occurring with respect to the onset of clinical signs. At least some findings in this population will likely be applicable to late-onset AD (LOAD) as ADAD and LOAD have similar, though not identical, clinical features, amyloid plaque and neurofibrillary tangle pathology, and early cerebrospinal fluid changes (Bateman et al., 2012).

Over the past decade, various imaging modalities including positron emission tomography (PET) and magnetic resonance imaging (MRI) have been investigated as surrogate biomarkers of AD (S Zhang et al., 2014a; Vlassenko et al., 2012; Ewers et al., 2011; Mosconi et al., 2010; Smailagic et al., 2015; Fennema-Notestine et al., 2009; Frisoni et al., 2010; Berti et al., 2010). Brain atrophy (Frisoni et al., 2010; McDonald et al., 2009; Vemuri, 2010), cerebral perfusion (Binnewijzend et al.,

* Corresponding author at: Laboratory of FMRI Technology (LOFT), USC Stevens Neuroimaging and Informatics Institute, Department of Neurology, Keck School of Medicine, University of Southern California, 2025 Zonal Ave, Los Angeles, CA, 90033, USA.
E-mail address: lyan@ini.usc.edu (L. Yan).

https://doi.org/10.1016/j.nicl.2017.12.003
Received 28 June 2017; Received in revised form 27 November 2017; Accepted 2 December 2017
Available online 06 December 2017

2013; Binnewijzend et al., 2016), metabolism (Mosconi et al., 2010; Mosconi, 2005), and amyloid and Tau deposition (Forsberg et al., 2008; Small et al., 2006) have been extensively quantified. ^{18}F-FDG PET is used to assess the neurodegenerative processes in AD by measuring glucose metabolism (Smailagic et al., 2015; Mosconi, 2005). Reduction of regional cerebral metabolism has been well characterized in AD patients, and even in MCI patients (Alexander et al., 2002; Mosconi et al., 2009). Many studies suggest cerebral metabolic changes measured using FDG PET can occur as early as the third decade of life (Reiman et al., 2004; Loessner et al., 1995). [^{11}*C*]Pittsburgh compound B ([^{11}*C*]PiB) PET amyloid imaging (Klunk et al., 2004) has been widely used since the accumulation of amyloid β plaques in the brain is thought to play a causative role in AD based on the amyloid cascade hypothesis (Hardy & Higgins, 1992). Specifically, the tracer kinetic modeling of PiB PET yields multiple parameters, including the distribution volume ratio (DVR) of PiB, which is used for the assessment of amyloid deposition, and R1, which is related to tracer delivery, providing information on regional perfusion (Lammertsma & Hume, 1996; Logan, 2000).

While the presence of amyloid plaques is recognized as a central event in the pathogenesis of AD, there is growing evidence that vascular factors play an important role as well (Dickstein et al., 2010; Murray et al., 2011). Decreased regional cerebral blood flow (CBF) has been extensively studied as a possible biomarker of AD (Hays et al., 2016). Arterial spin labeling (ASL) provides a noninvasive means of quantifying regional CBF by MRI, which utilizes magnetically labeled arterial blood water as an endogenous tracer (Detre et al., 2009). Compared to ^{15}O-water PET perfusion imaging, ASL does not involve radiation or contrast injection, and provides absolute CBF measurement and allows easy registration with structural MRI. Over the past few years, several groups have successfully applied ASL MRI to AD (Alsop et al., 2010; Z Wang et al., 2013a; Alsop et al., 2000; Johnson et al., 2005; Dai et al., 2009; WT et al., 2010). Characteristic patterns of cerebral hypoperfusion were detected using ASL MRI, mostly in late-onset AD patients (Alsop et al., 2010; Z Wang et al., 2013a; Alsop et al., 2000; Johnson et al., 2005; Dai et al., 2009; WT et al., 2010). A good correlation has been demonstrated between ASL MRI and ^{15}O-water PET in both resting state and activation studies (Ye et al., 2000; K Zhang et al., 2014b; Kilroy et al., 2014). More recently, a few groups began to investigate the relationship between cerebral perfusion by ASL MRI and metabolism by FDG PET (Cha et al., 2013; Chen et al., 2011), as well as between ASL MRI and PiB PET (McDade et al., 2014; Mattsson et al., 2014). However, we are unaware of any studies that have directly compared CBF measured by ASL MRI with both metabolism and amyloid deposition measured by PET in persons at risk for ADAD. Therefore, the aim of this study was to enhance our understanding of the contributions of both vascular, metabolic and biochemical dysfunction to the amyloid pathology of AD by investigating the relationship among cerebral perfusion, glucose metabolism, and amyloid deposition in a cohort of individuals at risk for ADAD.

2. Materials and methods

2.1. Study participants

Persons known to have *PSEN1*, *PSEN2*, or *APP* mutations in the family were recruited for comprehensive clinical, imaging, and biochemical assessments at UCLA. A total of 31 ADAD subjects (age 39 ± 13 years, 19 females) including 23 mutation carriers (PSEN = 19, and APP = 4) participated in this study after providing written informed consent. Persons with significant medical or psychiatric illnesses with the potential to significantly affect their cognition were excluded.

2.2. MRI protocol

Twenty-seven participants underwent MRI scans on a 3 T Siemens TIM Trio scanner (Erlangen, Germany) using the standard 12-channel head coil. Two participants were excluded from data analysis due to abnormal CBF values of whole brain (e.g. < 20 ml/100 g/min). Pseudo-continuous ASL (pCASL) with 3D background suppressed GRASE sequence (Kilroy et al., 2014) was performed for resting CBF measurement with the following imaging parameters: FOV = 220 × 220 mm^2, matrix size = 64 × 64, TE/TR = 23/3500 ms, GRAPPA rate = 2. Twenty-six 5-mm slices were acquired to cover the whole brain with 60 repetitions. The tagging plane was positioned 90 mm inferior to the center of the imaging slab with a labeling duration of 1500 ms and post-labeling delay (PLD) of 1500 ms. A 3D MPRAGE sequence was performed for T1 weighted structural MRI with the imaging parameters: 192 slices at 1 mm slice thickness, voxel size = 1 × 1 × 1 mm^3, TR/TE = 1620/3 ms, TI = 950 ms, TE = 3 ms, the scan time of 6 min.

2.3. PET protocol

2.3.1. ^{18}F-FDG PET

Twenty-three subjects participated in an ^{18}F-FDG PET/CT scan on a whole body scanner. Metabolic imaging with [18*F*]FDG-PET was performed with a 3D dynamic acquisition beginning 40 min after a bolus injection of approximately 5 mCi of FDG and lasted for 20 min. Images were reconstructed using back of projection with a Gaussian smoothing of 3 mm full width half-maximum (FWHM) after correction for scatter, decay, scanner dead time, and attenuation.

2.3.2. ^{11}C-PiB PET

Twenty-three participants received ^{11}C-PIB PET/CT scans. Subjects received a bolus injection of approximately 15 mCi of [11*C*]PiB. Dynamic ^{11}C-PIB PET/CT scans were acquired in list-mode for 70 min. Raw PiB PET data were rebinned into 6 × 30 s, 4 × 180 s, and 11 × 300 s, and were reconstructed using ordered subset expectation maximization algorithm (6 iterations, 16 subsets) with a post-reconstruction 3D Gaussian smoothing (FWHM: 3 mm × 3 mm × 3 mm). A retrospective image-based movement correction procedure was applied to correct for possible misalignment between CT and PET scans and between PET image frames (Ye et al., 2014).

2.4. Image processing

For pCASL data, motion correction was performed using Statistical Parametric Mapping (SPM) 12 for control and label images, separately. Perfusion weighed images were obtained by pair-wise subtraction between the control and label images. Quantitative CBF maps were subsequently calculated using the averaged perfusion weighted images based on a single compartment model (Kilroy et al., 2014).

All CBF, FDG PET, and PiB PET images of each subject were co-registered to the subject's MPRAGE images, and further warped to MNI single-subject brain template using the Symmetric Diffeomorphic Mapping method implemented in ANTS (Avants et al., 2008). The normalized CBF images were smoothed with a 3 mm FWHM kernel, creating absolute CBF (absCBF) maps. A relative CBF (rCBF) map was also generated by dividing the CBF of each voxel by the mean CBF in the cerebellum for each subject. Summation images were generated from FDG PET data to assess the glucose metabolism, and then were intensity normalized to cerebellar mean intensity, generating relative CMR_{Glc} ($rCMR_{Glc}$) images. For PiB PET images, using the combined transformation from template to PET space, tissue time-activity curve was generated for cerebellar grey matter (reference region), and parametric images of relative perfusion (R1) and distribution volume ratio (DVR) were constructed by simplified reference tissue model (SRTM) (Lammertsma & Hume, 1996) and Logan graphical method (Logan,