Neurobiology of Aging 55 (2017) 20–26

Contents lists available at ScienceDirect

Neurobiology of Aging

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

Regional amyloid burden and lacune in pure subcortical vascular cognitive impairment

Yun Jeong Hong [a], Chan-Mi Kim [b,c,d], Ji Eun Kim [a,e], Jee Hoon Roh [a], Jae Seung Kim [f], Sang Won Seo [g], Duk L. Na [g], Jae-Hong Lee [a,*]

[a] Department of Neurology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea
[b] Department of Biomedical Engineering, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea
[c] MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA
[d] Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[e] Department of Neurology, University of Ulsan College of Medicine, Gangneung Asan Medical Center, Gangneung, Korea
[f] Department of Nuclear Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea
[g] Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

ARTICLE INFO

Article history:
Received 17 June 2016
Received in revised form 6 March 2017
Accepted 8 March 2017
Available online 16 March 2017

Keywords:
Vascular cognitive impairment
Pittsburgh compound B
Amyloid
Subcortical vascular mild cognitive impairment
Subcortical ischemic vascular dementia
Cerebral small vessel disease

ABSTRACT

We investigated the amyloid and vascular burden in Pittsburgh compound B (PiB)–negative subcortical vascular mild cognitive impairment (svMCI) and PiB-negative subcortical ischemic vascular dementia (SIVD) to elucidate the potential roles of amyloid deposition and small vessel disease (SVD). Thirty-eight svMCI patients and 42 SIVD patients were enrolled. The regional PiB uptake values and SVD markers were obtained and compared between groups. Additionally, correlations among amyloid burden, SVD, and cognition were made. Patients with PiB-negative SIVD showed more amyloid deposition than those with PiB-negative svMCI, particularly in the cuneus, lingual gyrus, supramarginal, and angular gyri. Despite subthreshold levels for amyloid deposition, our findings showed a marked regional difference in amyloid uptake between svMCI and SIVD, particularly in posteriorly located brain areas. However, lacune, a proxy for vascular burden, showed a broader association with cognition and had more impacts on developing dementia than amyloid burden. The topographical pattern of amyloid deposition and its impact on clinical status in pure subcortical vascular cognitive impairment were different from those in Alzheimer's disease.

1. Introduction

Subcortical vascular cognitive impairment (SVCI) is caused by cerebral small vessel disease (SVD), such as lacune, white matter hyperintensity, and cerebral microbleeds (Roman et al., 2002), and encompasses both subcortical vascular mild cognitive impairment (svMCI) and subcortical ischemic vascular dementia (SIVD). Factors involved in progression from svMCI to SIVD are largely unknown. Cognitive decline especially in the elderly individuals is generally thought to be due to underlying Alzheimer's pathology. In the setting of SVCI, SVD and Alzheimer's pathology may coexist and interact with each other, leading to cognitive decline. With the availability of amyloid positron emission tomography (PET) which allows for in vivo detection of cerebral amyloidosis (Klunk et al., 2004), these controversial issues can be explored more than ever. Pure SVCI is, by definition, rich in vascular lesion but free of amyloid burden. Clinically diagnosed SVCI with a global amyloid uptake ratio below 1.5 has been regarded as Pittsburgh compound B (PiB)–negative pure SVCI. As such, no attempts have been made to look at the regional distribution of amyloid deposit and its potential role in cognitive decline in this population, in contrast to the plethora of studies in patients with Alzheimer's disease (AD) and PiB-positive SVCI (Lee et al., 2011, 2014; Noh et al., 2014; Park et al., 2014; Ye et al., 2015). Low levels of PiB binding or focal uptake of amyloid tracer may be passed off as negative for amyloid retention but might have an impact on cognitive decline in combination with vascular lesion in people with SVCI. In clinical practice, we often encounter patients with different clinical status (svMCI vs. SIVD) despite apparently the similar vascular burden of cerebral SVD. We wondered whether the subcortical vascular lesion or the underlying subthreshold level of amyloid burden makes the difference in determining the clinical status. This study aimed to compare the amyloid burden represented by the degree of global and regional amyloid deposition and vascular burden as indicated by magnetic resonance imaging (MRI) markers of SVD between PiB-negative

* Corresponding author at: Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea. Tel.: +82-2-3010-3446; fax: +82-2-474-4691.
E-mail address: jhlee@amc.seoul.kr (J.-H. Lee).

0197-4580/$ – see front matter © 2017 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2017.03.010

svMCI and PiB-negative SIVD. We planned to exclude PiB-positive SVCI patients because they are mainly considered as AD continuum disorders. Additionally, we assessed whether the amyloid or vascular burden affects the cognition and the diagnosis of PiB-negative SIVD to confirm the potential roles of amyloid deposition and SVD in pure SVCI. We thought that the topographical pattern of amyloid deposition and its impact on clinical status in SVCI would be different from those in AD continuum disorders.

2. Materials and methods

2.1. Subjects

All patients who underwent standardized dementia work-ups and diagnosed as SVCI were consecutively recruited from memory clinic. Among the 190 candidates with SVCI, 53 patients were excluded due to refusal to participate in the study. A total of 137 patients with clinically diagnosed svMCI or SIVD were prospectively recruited and underwent PiB-PET scans at Asan Medical Center or Samsung Medical Center between September 2008 and August 2011. All patients underwent a neurological examination, a detailed neuropsychological tests battery (Kang and Na, 2003) and a brain MRI. Apolipoprotein-ε genotyping was performed if both patients and their caregivers consented. All diagnostic work-up procedures were carried out 3 months before or after the PiB-PET scans. Patients with other structural lesions, such as territory infarctions, intracerebral hemorrhage, hydrocephalus, or high signal abnormalities on the MRI that resulted from radiation injury, multiple sclerosis, vasculitis, or leukodystrophy were excluded. Patients were diagnosed with svMCI ($n = 67$) if they met the following requirements that were modified from the Petersen criteria (Petersen, 2004): (1) subjective cognitive complaints by the patient or his/her caregiver; (2) normal activity of daily living; (3) an objective cognitive decline assessment below the 16th percentile on any neuropsychological test; (4) the absence of dementia; and (5) the presence of significant white matter ischemia on MRI with concomitant focal neurological symptoms/signs. Patients were diagnosed with SIVD ($n = 70$) if they met the diagnostic criteria for vascular dementia established by the diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994) and showed significant ischemia on MRI with focal neurological symptoms/signs. Significant white matter hyperintensity was defined as a cap or band $\geq$10 mm with a deep white matter lesion $\geq$25 mm in the longest diameter (Fazekas et al., 1993). Focal neurological signs suggestive of cerebrovascular disease were operationally defined as at least 2 of the followings: corticobulbar signs (facial palsy, dysarthria, dysphagia, or pathologic laughing or crying), pyramidal signs (hemiparesis, increased deep tendon reflexes or extensor plantar responses), or parkinsonism (short-stepped gait, festinating gait, shuffling gait, decreased arm swing while walking, rigidity, bradykinesia, or postural instability).

Forty-five patients with positive findings (global PiB uptake ratio >1.5) on a PiB-PET scan were excluded from this study. Additionally, 12 patients were excluded because of an inappropriately low dose of ^{11}C PiB ($n = 9$) or coregistration errors ($n = 3$) during the imaging analysis. Finally, 38 patients with PiB-negative svMCI and 42 patients with PiB-negative SIVD were enrolled (Fig. 1).

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

2.2. PiB-PET imaging acquisition

All ^{11}C PiB-PET scans were examined at Asan Medical Center or Samsung Medical Center. Each subject completed the same type of PET scan with a Discovery STe PET/computed tomography scanner (GE Medical Systems, Milwaukee, WI). ^{11}C PiB was injected into the antecubital vein as a bolus at a mean dose of 535 MBq (range 370–700 MBq). A computed tomography scan was performed 60 minutes after injection for a total of 30 minutes.

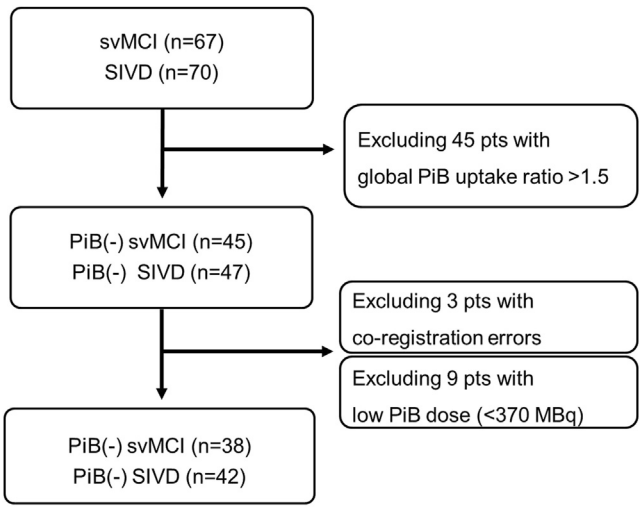

Fig. 1. A graphical flowchart of the patients' enrollment. Abbreviations: PiB, Pittsburgh compound B; SIVD, subcortical ischemic vascular dementia; svMCI, subcortical vascular mild cognitive impairment.

2.3. PiB-PET imaging analysis

The MRI scan was performed using the same 3T MRI scanner (Philips 3.0T 164 Achieva, Eindhoven, The Netherlands). Individual T1-weighted MRI images were estimated to correct any nonhomogeneous biased fields using an N3 algorithm (Sled and Pike, 1998) and then were coregistered into corresponding PiB-PET images by rigid body registration. Each individual MRI image was normalized to a standardized stereotaxic space using an affine transformation and then was classified into probabilistic tissue maps, such as gray matter, white matter (WM), and cerebral spinal fluid (Collins et al., 1994). A volume-based automated anatomical labeling template (Tzourio-Mazoyer et al., 2002), including 90 regions-of-interest (ROI), was inversely aligned to each individual T1-weighted MRI image by applying an inverse linear transformation. Subsequently, whole voxels of PiB-PET images were scaled using the mean uptake value in the cerebellar cortex to calculate the PiB standardized uptake value ratio (SUVR) (Johnson et al., 2007; Lee et al., 2011). The voxels, which were located in the WM areas as well as in the gray matter with a probability of less than 20%, were discarded to estimate any partial volume effects in each PiB-PET image. We measured the partial volume-corrected regional mean PiB SUVR within 90 ROIs using an automated anatomical labeling template in native space. The global amyloid uptake ratio was calculated from the volume-weighted average uptake ratios of 90 bilateral cerebral regions.

2.4. Measurements of white matter hyperintensities volume, lacunes, and microbleeds

WM hyperintensities (WMH) volumes were measured quantitatively using automated method on fluid-attenuated inversion recovery images. The detailed method was described previously (Jeon et al., 2011). Lacunes of presumed vascular origin were defined as small lesions ($\geq$3 mm and $\leq$15 mm in diameter) with high signal intensities on T2- and low signal intensities on