White Matter Perivascular Spaces on Magnetic Resonance Imaging
Marker of Cerebrovascular Amyloid Burden?

Andreas Charidimou, PhD; Young T. Hong, PhD; Hans R. Jäger, MD; Zoe Fox, PhD; Franklin I. Aigbirhio, PhD; Tim D. Fryer, PhD; David K. Menon, PhD; Elizabeth A. Warburton, MD; David J. Werring, PhD; Jean-Claude Baron, ScD

Background and Purpose—We investigated the relationship between magnetic resonance imaging-visible centrum semiovale perivascular spaces (CSO-PVS), a biomarker of impaired interstitial fluid drainage, and positron emission tomography-based amyloid-β burden across a wide range of cerebrovascular amyloid deposition.

Methods—Thirty-one nondemented subjects (11 probable cerebral amyloid angiopathy patients and 10 healthy subjects ≥60 years; 10 older individuals, <60 years) had brain magnetic resonance imaging and Pittsburgh compound B-positron emission tomography. CSO-PVS was evaluated on T2-magnetic resonance imaging using a 4-point scale. The association between Pittsburgh compound B and CSO-PVS was assessed in linear regression.

Results—In multivariable analyses adjusted for age, microbleeds and white matter hyperintensities, whole cortex Pittsburgh compound B binding was associated with CSO-PVS degree both as continuous (coefficient, 0.11; 95% confidence interval, 0.01–0.22; \( P = 0.040 \)) and as dichotomous variable (coefficient, 0.27; 95% confidence interval, 0.11–0.44; \( P = 0.002 \)). The median Pittsburgh compound B retention was higher in high versus low CSO-PVS degree (\( P = 0.0007 \)).

Conclusions—This pilot study suggests a possible association between cerebrovascular amyloid deposition and CSO-PVS, with potential pathophysiological implications. (Stroke. 2015;46:00–00. DOI: 10.1161/STROKEAHA.115.009090.)

Key Word: cerebral amyloid angiopathy

Accumulating evidence suggests that magnetic resonance imaging (MRI)-visible perivascular spaces in the centrum semiovale (CSO-PVS) and basal ganglia (BG-PVS) are neuroimaging markers of cerebral small-vessel disease. CSO-PVS are attracting attention as a promising marker of cerebrovascular amyloid deposition, a common age-related neuropathological process characterized by progressive amyloid-β accumulation in leptomeningeal and cortical small arteries.

In this pilot study, we examine the association between overall CSO-PVS burden and cortical retention of \(^{11}\)C-Pittsburgh compound B (PiB) positron emission tomography (PET; a radioligand that binds both parenchymal and vascular fibrillar amyloid-β deposits). To analyze this relationship across a wide range of cerebrovascular amyloid burden and CSO-PVS, we merged cerebral amyloid angiopathy (CAA) patients and healthy subjects across the adult age span.

Methods

Study Subjects
The present analysis was based on a prospective PiB-PET imaging research study (ie, not performed for clinical indications) on CAA-related intracerebral hemorrhage (ICH) and healthy subjects.

Consecutive nondemented ICH patients fulfilling the original Boston criteria for probable CAA (ie, ≥2 lobar macrobleeds or microbleeds with no secondary causes, in patients aged ≥55 years) were recruited through the Addenbrooke’s Hospital Stroke Unit or intracerebral hemorrhage clinic. All included CAA patients lived independently and their Mini-Mental State Examination was ≥23.

Medication-free healthy subjects (both individuals ≥60 years and adults <60 years) with no cognitive complaints and normal Mini-Mental State Examination results (≥29) were also enrolled. The protocol was approved by the Cambridgeshire Ethics Committee, and all subjects gave informed consent.

Imaging Acquisition and Analysis

\(^{11}\)C-PiB production, PET scanning, and PET data analysis (including correction for cerebrospinal fluid spaces) methodology in our center has previously been described. On the same day as the PiB-PET, each subject underwent 3T MRI (slice thickness, 4 mm; slice gap, 5 mm), including T2-weighted, T1-weighted magnetization-prepared rapid gradient-echo, fluid-attenuated inversion recovery, and gradient-recalled echo, using standard T2* sequences. MRIs were reviewed blinded to clinical and PET data. CSO-PVS and BG-PVS were rated on axial T2-weighted images, using a validated 4-point visual rating scale (0=no PVS; 1≤10, 2=11–20, 3=21–40, 4=40 PVS). White matter hyperintensities were assessed using the age-related white matter changes scale. Cerebral microbleeds were evaluated on T2*-gradient-recalled echo (echo time>20 ms).

Received February 11, 2015; final revision received March 15, 2015; accepted March 23, 2015.
From the UCL Institute of Neurology, Queen Square, London, United Kingdom (A.C., H.R.J., Z.F., D.J.W.); Wolfson Brain Imaging Centre (Y.T.H., E.A.W., J.-C.B.), University of Cambridge, Cambridge, United Kingdom; and INSERM U894, Centre Hospitalier Sainte-Anne, Sorbonne Paris Cité, Paris, France (J.-C.B.).
Correspondence to Andreas Charidimou, PhD, Queen Sq, London WC1N3BG, United Kingdom. E-mail andreas.charidimou.09@ucl.ac.uk
© 2015 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.115.009090
Whole brain volume was calculated from magnetization-prepared rapid gradient-echo images using Advanced Normalization Tools.

Statistical Analysis

The relationship between whole cortex PiB distribution volume ratio (DVR) and CSO-PVS degree was explored using Kendall correlation analysis. Linear regression was used to quantify the relationship between PiB DVR and CSO-PVS grade after adjustment for age, white matter hyperintensities and lobar microbleeds, or age and total brain volume. Regression analysis was repeated with CSO-PVS degree dichotomized into high (score≥3) or low (score≤2).

Values below the 10% level considered indicative of a trend. Statistical analyses were performed using STATA (version 12.1; StataCorp).

Results

Eleven CAA patients and 20 healthy subjects (10 older individuals, ≥60 years) were recruited (Table 1). PiB retention was higher in CAA patients versus the whole healthy group (P=0.0082; Table 1), but similar between CAA patients and older healthy subjects (P=0.53).

Across the whole group, there was a nearly linear increase in PiB DVR as CSO-PVS score increased (τ=b=+0.552; P=0.0001; Figure) and a trend when only probable CAA patients and older healthy subjects were analyzed (τ=b=0.3589; P=0.0068). There was a negative trend between PiB retention and whole brain volume (τ=b=0.2172; P=0.087) and a positive correlation with age (τ=b=0.4946; P=0.0001). These associations were not present when only probable CAA patients and older healthy subjects were analyzed. There was no association between brain volume and CSO-PVS. In multivariable linear regression, PiB binding was positively associated with CSO-PVS degree (Table 2).

Across the whole group, whole cortex DVR was higher in subjects with high versus low CSO-PVS degree (median, 1.42; interquartile range, 1.37–1.50 versus 1.14; 1.12–1.23, respectively; P=0.0007). This was also true within the healthy group (1.82; 1.80–1.84 versus 1.13; 1.11–1.18; P=0.023), as well as the healthy older subgroup (1.82; 1.80–1.84 versus 1.17; 1.12–1.36; P=0.037). The same trend was observed in the CAA group.

Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy Subjects (n=20)</th>
<th>Probable CAA Patients (n=11)</th>
<th>Older Healthy Subjects (n=10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>59.5 (34.5–63.5)</td>
<td>71 (63–77)</td>
<td>63.5 (61–68)</td>
<td>0.06</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>15 (75)</td>
<td>9 (81.8)</td>
<td>5 (50)</td>
<td>0.18</td>
</tr>
<tr>
<td>MMSE, median (IQR)</td>
<td>30 (29–30)</td>
<td>26 (25–26)</td>
<td>30 (29–30)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>0</td>
<td>6 (54.6)</td>
<td>0</td>
<td>0.012</td>
</tr>
<tr>
<td>Lobar CMBs presence, n (%)</td>
<td>1 (5)</td>
<td>11 (100)</td>
<td>1 (10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lobar CMBs count, median (IQR range)</td>
<td>0</td>
<td>4 (2–50)</td>
<td>0</td>
<td>0.0002</td>
</tr>
<tr>
<td>WMH, median (IQR)</td>
<td>2.5 (0–4)</td>
<td>11 (9–14)</td>
<td>4 (4–6)</td>
<td>0.0002</td>
</tr>
<tr>
<td>High degree CSO-PVS (&gt;40 PVS), n (%)</td>
<td>2 (10)</td>
<td>7 (63.6)</td>
<td>2 (20)</td>
<td>0.08</td>
</tr>
<tr>
<td>Whole cortex DVR, median (IQR)</td>
<td>1.14 (1.11–1.21)</td>
<td>1.37 (1.23–1.43)</td>
<td>1.21 (1.13–1.65)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

*Three CAA patients had cortical superficial siderosis.
†A healthy older subject had 3 lobar CMBs.

Figure. Whole cortex Pittsburgh compound B retention and centrum semiovale perivascular spaces (CSO-PVS) severity scatter plot. CAA indicates cerebral amyloid angiopathy; and DVR, distribution volume ratio.

Table 2. Univariable and Multivariable Linear Regression of Whole Cortex PiB Retention and CSO-PVS Grade (Nondichotomized Variable) or High CSO-PVS Degree (>40)

<table>
<thead>
<tr>
<th>Group</th>
<th>PiB Retention (CSO-PVS Grade)</th>
<th>Coefficient (95% CI)</th>
<th>P Value</th>
<th>PiB Retention (High CSO-PVS Degree)</th>
<th>Coefficient (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSO-PVS, unadjusted</td>
<td>0.12</td>
<td></td>
<td>&lt;0.0001</td>
<td>0.28</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CSO-PVS, adjusted for age, CMBs and WMH</td>
<td>0.11</td>
<td>0.040</td>
<td>0.27</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSO-PVS, adjusted for age and total brain volume</td>
<td>0.10</td>
<td>0.063</td>
<td>0.20</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Probable CAA+older healthy group | | | |
| CSO-PVS, unadjusted | 0.11 | 0.071 | 0.21 | 0.021 |
| CSO-PVS, adjusted for CMBs and WMH | 0.13 | 0.059 | 0.29 | 0.009 |

CA indicates cerebral amyloid angiopathy; CMBs, cerebral microbleeds; CSO-PVS, centrum semiovale perivascular spaces; DVR, distribution volume ratio; IQR, interquartile range; MMSE, Mini-Mental State Examination; and WMH, white matter hyperintensities.
There was no significant association between BG-PVS and PiB retention: $r_b=0.01; P=1.00$; regression coefficient: $-0.001$, 95% confidence interval, $-0.166$ to $0.149$, $P=0.911$.

**Discussion**

Our data suggest an association between whole cortex amyloid burden and MRI-visible CSO-PVS in a combined group of probable CAA-related ICH patients and healthy elderly subjects free of cognitive complaints and vascular risk factors. This link was also present within the healthy older group alone, and showed similar trends in CAA. This relationship was not present with BG-PVS, in line with previous studies showing different associations and pathophysiology between CSO-PVS and BG-PVS.7,8

Our study design including in the same analysis probable CAA patients and healthy subjects was based on strong neuropathological and in vivo MR evidence that both cerebrovascular amyloid and CSO-PVS are present in the healthy elderly and form a continuum with symptomatic CAA.6 This may partly explain why there was no difference in PiB retention between CAA and healthy subjects (see Baron et al for further discussion).

Although the mechanisms of MRI-visible CSO-PVS remain poorly understood, our findings might indicate a potential pathophysiological link: drainage impairment by progressive vascular amyloid-β deposition, causing retrograde perivascular spaces dilation in the white matter.7 Consistent with this hypothesis, a postmortem study of Alzheimer disease found that the degree of white matter perivascular spaces enlargement on histopathology, correlated with cerebrovascular amyloid burden.8 Despite our best efforts, this link might be somehow confounded by other factors coassociated with CSO-PVS, including age, vascular risk factors, and other small-vessel disease markers.1,5

A main limitation, intrinsic to amyloid imaging, is that incident Alzheimer disease pathology might not only be present in nondemented CAA-ICH patients, particularly given the frequent co-occurrence of these 2 conditions, but also in healthy elderly. The potential selection bias of CAA cases means that our results can only be extrapolated to populations in a similar clinical context, ie, nondemented ICH survivors living independently. Also, the sample size was relatively small, limiting power and raising the chance of false-positives, especially in adjusting for potential confounders. For example, our analyses are not adjusted for hypertension or other vascular risk factors. Hence, our study should be considered preliminary and the $P$ values should be interpreted cautiously. Nonetheless, our results support the idea of CSO-PVS being a useful potential marker of vascular amyloid burden. They require external validation in larger cohorts, adjusting for other factors related to PVS (eg, hypertension, inflammation markers, and additional small-vessel disease features) and amyloid load.

**Sources of Funding**

This study was supported by Cambridge National Institute for Health Research Comprehensive Biomedical Research Centre.

**Disclosures**

None.

**References**

White Matter Perivascular Spaces on Magnetic Resonance Imaging: Marker of Cerebrovascular Amyloid Burden?
Andreas Charidimou, Young T. Hong, Hans R. Jäger, Zoe Fox, Franklin I. Aigbirhio, Tim D. Fryer, David K. Menon, Elizabeth A. Warburton, David J. Werring and Jean-Claude Baron

Stroke. published online April 23, 2015;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2015/04/23/STROKEAHA.115.009090

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/