Retinal Microvascular Signs and 10-Year Risk of Cerebral Atrophy

The Atherosclerosis Risk in Communities (ARIC) Study

Ryo Kawasaki, MD, MPH, PhD; Ning Cheung, MBBS; Thomas Mosley, PhD; Amirul F.M. Islam, PhD; A. Richey Sharrett, DrPH; Ronald Klein, MD, MPH; Laura H. Coker, PhD; David S. Knopman, MD; Dean K. Shibata, MD; Diane Catellier, DrPH; Tien Y. Wong, MD, MPH, PhD

Background and Purpose—Cerebral atrophy, detected as ventricular enlargement or sulcal widening on MRI, is recognized as a risk factor for vascular dementia or Alzheimer disease. However, its underlying pathophysiology is not known. We examined whether retinal microvascular assessment could provide predictive information on the risk of ventricular enlargement and sulcal widening on MRI.

Methods—A prospective, population-based study was conducted of 810 middle-aged persons without clinical stroke or MRI infarcts. All participants had a first cranial MRI and retinal photography in 1993 to 1995 and returned for a repeated MRI in 2004 to 2006 (median follow-up of 10.5 years). Retinal photographs were graded for presence of retinopathy and retinal microvascular abnormalities, and MRI images were graded for ventricular size and sulcal size according to standardized protocols. Ventricular enlargement and sulcal widening were defined as an increase in ventricular size or sulcal size of ≥3 of 10 grades between baseline and follow-up.

Results—After adjusting for age, gender, and cardiovascular risk factors, retinopathy and arteriovenous nicking at baseline were associated with 10-year ventricular enlargement (OR and 95% CI: 2.03, 1.20 to 4.42 for retinopathy and 2.19, 1.23 to 3.90 for arteriovenous nicking). Retinal signs were not associated with 10-year sulcal widening.

Conclusions—Retinopathy and arteriovenous nicking are predictive of long-term risk of ventricular enlargement, but not of sulcal widening, independent of cardiovascular risk factors. These data support a microvascular etiology for subcortical but not cortical cerebral atrophy. *(Stroke. 2010;41:1826-1828.)*

Key Words: cerebral atrophy ■ retinal microvascular signs ■ sulcal widening ■ ventricular enlargement

Cerebral atrophy, detected on MRI as ventricular enlargement (VE) or sulcal widening (SW), has been shown to be associated with cognitive impairment. Semiquantitative assessment of ventricular size based on MRI is recognized as a risk marker for dementia and Alzheimer disease, and it accelerates during the pre-Alzheimer disease stage of amnestic mild cognitive impairment, thus providing complementary information for diagnosis and monitoring of neurodegenerative diseases. Although neurodegenerative processes clearly play an essential role in the pathophysiology of cerebral atrophy, reduced cerebral perfusion due to microvascular disease may also contribute to the development of cerebral atrophy.

The retina provides a noninvasive window to study microvascular etiology of cerebrovascular disease. Pathological retinal changes may reflect microangiopathic processes in the brain. In the Atherosclerosis Risk in Communities (ARIC) study, we have previously demonstrated cross-sectional associations between retinal signs and VE and SW, and both cross-sectional and longitudinal associations with cognitive decline. In this study, we examine the prospective relationship of retinal microvascular abnormalities to the 10-year incidence of VE and SW in the ARIC cohort.

Methods

Study Population

The ARIC study is a population-based study of cardiovascular disease among 15,792 middle-aged blacks and whites from 4 US

Received March 19, 2010; accepted March 23, 2010.

From the Centre for Eye Research Australia (R.K., N.C., A.F.M.I., T.Y.W.), University of Melbourne, Royal Victorian Eye and Ear Hospital, Melbourne, Australia; the Department of Medicine (T.M.), University of Mississippi Medical Center, Jackson, Miss; the Department of Epidemiology (A.R.S.), Johns Hopkins University Bloomberg School of Public Health, Baltimore, Md; the Department of Ophthalmology and Visual Sciences (R.K.), University of Wisconsin School of Medicine and Public Health, Madison, Wis; the Division of Public Health Sciences (L.H.C.), Wake Forest University School of Medicine, Winston-Salem, NC; the Department of Neurology (D.S.K.), Mayo Clinic, Rochester, Minn; the Department of Radiology (D.K.S.), University of Wisconsin Medical Center, Seattle, Wash; the Department of Biostatistics (D.C.), University of North Carolina, NC; and the Singapore Eye Research Institute (T.Y.W.), National University of Singapore, Singapore.

Correspondence to Tien Yin Wong, MD, MPH, PhD, Singapore Eye Research Institute, National University of Singapore, 11 Third Hospital Avenue, Singapore 168751, Singapore. Email opwty@nus.edu.sg

© 2010 American Heart Association, Inc.

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

DOI: 10.1161/STROKEAHA.110.585042
Table. Retinal Microvascular Changes and Vₑ or SW (≥3 Grade Increase in Ventricular Size or Sulcal Size, Respectively)

<table>
<thead>
<tr>
<th>Retinal Microvascular Abnormalities</th>
<th>Vₑ (N=147; 18.4%)</th>
<th>SW (N=94; 11.8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. at Risk, (% Vₑ)</td>
<td>Age–Gender–Race–Study Center-Adjusted OR</td>
</tr>
<tr>
<td>Any retinopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>748 (17.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Present</td>
<td>53 (27.5)</td>
<td>1.76 (0.92–3.40)</td>
</tr>
<tr>
<td>Microaneurysm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>689 (17.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Present</td>
<td>26 (23.1)</td>
<td>1.34 (0.52–3.46)</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>739 (17.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Present</td>
<td>22 (27.3)</td>
<td>1.77 (0.67–4.68)</td>
</tr>
<tr>
<td>Cotton wool spot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>766 (17.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Present</td>
<td>13 (38.5)</td>
<td>3.06 (0.97–9.71)</td>
</tr>
<tr>
<td>Hard exudates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>743 (17.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Present</td>
<td>10 (30.0)</td>
<td>2.17 (0.54–8.68)</td>
</tr>
<tr>
<td>Arteriovenous nicking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>685 (17.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Present</td>
<td>98 (27.6)</td>
<td>1.78 (1.08–2.92)</td>
</tr>
<tr>
<td>Focal arteriolar narrowing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>654 (18.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Present</td>
<td>110 (18.2)</td>
<td>0.94 (0.55–1.59)</td>
</tr>
</tbody>
</table>

*Further adjusted for cigarette smoking, 6-year mean arteriolar blood pressure, antihypertensive medication, education, fasting glucose, total cholesterol, triglycerides, and carotid intima-media thickness.

Results

Over a median follow-up of 10.5 years, 147 (18.4%) had 10-year incident Vₑ, and 94 (11.8%) had 10-year incident of SW. The Table shows that retinopathy and arteriovenous nicking were associated with increased odds of 10-year Vₑ (OR 2.03 and OR 2.19, respectively) after adjusting for arteriovenous nicking and focal arteriolar narrowing were separately defined as present if graded definite or probable. Retinal vessel diameters were measured using standardized semiautomated imaging software. Participants underwent standardized examinations. Mean arterial blood pressure was computed as 2/3 of [diastolic blood pressure] + [systolic blood pressure]. Diabetes mellitus was defined as fasting/nonfasting glucose level of ≥126 mg/dL/≥200 mg/dL, or a self-report of physician-diagnosed diabetes or treatment for diabetes.

Kawasaki et al Retinal Signs and Cerebral Atrophy 1827

Statistical Analysis

We constructed multiple logistic regression models to determine OR for 10-year cumulative incidence of Vₑ or SW in relation to retinal microvascular signs adjusting for age, gender, race/ethnicity, and study center and further adjusted for cigarette smoking, 6-year average of mean arterial blood pressure between 1987 to 1989 and 1993 to 1995, antihypertensive medication, education, fasting glucose, total cholesterol, triglycerides, and carotid intima-media thickness.

participants who underwent a third examination in 1993 to 1995 for cerebral MRI and retinal photography, when participants were 51 to 72 years of age, were included for this study. Cerebral MRI was performed for persons aged ≥55 years in 2 ARIC centers. Of the 1684 participants who had completed cerebral MRI and retinal examinations at the third visit, 1031 (61%) had a repeated MRI examination in 2004 to 2006 (median follow-up of 10.5 years). Of these, 810 participants were included after excluding those with a history of clinical/MRI-defined stroke or incomplete examinations. Although there were no significant differences in gender, race/ethnicity, or lipid profile, included participants were younger and had less hypertension, diabetes, and smoking and less carotid intima-media thickness. Institutional Review Boards at each study site approved the study and informed consent was obtained from all participants.

T₁-, T₂-, and proton density-weighted axial cerebral MRI scans oriented parallel to the anterior comissure–posterior commissure line were obtained. Masked neuroradiologists evaluated the digitized MRI scan. Sulcal size and ventricular size were assessed on a semiquantitative 10-point scale by visual comparison with standard images. Incident Vₑ and SW were defined as an increase in ventricular size and sulcal size grade of ≥3 between baseline and follow-up.

Retinal photographs were taken through a nonpharmacologically dilated pupil. Trained graders evaluated the photographs using a standardized protocol. Retinopathy was defined as present if any of the following lesions were detected: retinal microaneurysms, hemorrhages, soft exudates, and other less common lesions. Retinal arteriovenous nicking and focal arteriolar narrowing were separately defined as present if graded definite or probable. Retinal vessel diameters were measured using standardized semiautomated imaging software.
cardiovascular risk factors. Although not significant, cotton wool spots (OR 2.57) and hard exudates (OR 2.43) seemed to have stronger associations with 10-year incident Ve. No retinal signs were associated with 10-year incident Sw. There were no significant associations of retinal arteriolar or venular diameter with 10-year incident Ve or Sw (data not shown).

Discussion
In this prospective population-based study, persons with retinal microvascular signs had a 2-fold risk of incident Ve over a 10-year period. This finding expands our previous cross-sectional observation\(^1\) and suggests that microvascular disease may be a risk factor for Ve.

In contrast, we found no associations between retinal microvascular signs and incident Sw. It is consistent with previous studies reporting that Ve had a stronger association with a test for verbal learning and recent memory compared to Sw.\(^14,15\) This could reflect a closer correlation of retinal microvascular changes with cerebral vessels in deeper parts of the brain responsible for Ve than those affecting the sulci, suggesting that microvascular disease, as expected,\(^11\) plays a more prominent role in the development of subcortical than cortical atrophy. Alternatively, the lack of association of retinal signs with Sw could be due to measurement error, because sulcal size was less reliably measured (κ-value for agreement of ventricular size and sulcal size were 0.89 and 0.66, respectively).\(^1,8\)

In regard to the potential vascular contribution to Alzheimer disease, the pathogenesis of Alzheimer disease principally involves neurodegeneration, but for any level of neurodegeneration, the added effects of ischemia and infarction could be additive and reduce the threshold at which clinical symptoms occur. Alternatively, it is possible that microvascular disease alters the disposition of β-amyloid and leads to higher levels of brain β-amyloid, thereby facilitating the appearance of clinical symptoms. In our study, cotton wool spots (a sign of acute microinfarction) and hard exudates (a sign of disruption in retinal microvasculature from hypoxia) were most strongly associated with Ve, consistent with a microvascular contribution to Alzheimer disease.

The strengths of this study include its prospective design, biracial cohort of blacks and whites, and standardized assessment. Limitations may include possible selection bias because of significant loss to follow-up and confounding effect of unmeasured risk factors.

Summary
Our study showed that retinal microvascular signs are associated with the 10-year incident cerebral atrophy reflected as Ve. This finding suggests that retinal microvascular signs may represent risk factors for subcortical atrophy evident before radiological manifestations or cognitive decline. Our finding also suggests a contribution of microvascular etiology of cerebral atrophy in addition to neurodegenerative pathologies and supports the concept that modification of microvascular disease risk factors (eg, hypertension, diabetes) may reduce progression of cerebral atrophy.

Acknowledgments
We thank the staff and participants of the ARIC study for their important contributions.

Sources of Funding
The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022. This work was also supported by grant R01-HL70825.

Disclosures
None.

References
Retinal Microvascular Signs and 10-Year Risk of Cerebral Atrophy: The Atherosclerosis Risk in Communities (ARIC) Study
Ryo Kawasaki, Ning Cheung, Thomas Mosley, Amirul F.M. Islam, A. Richey Sharrett, Ronald Klein, Laura H. Coker, David S. Knopman, Dean K. Shibata, Diane Catellier and Tien Y. Wong

Stroke. 2010;41:1826-1828; originally published online June 24, 2010;
doi: 10.1161/STROKEAHA.110.585042

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 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/41/8/1826