Retinal Microvascular Abnormalities and MRI-Defined Subclinical Cerebral Infarction

The Atherosclerosis Risk in Communities Study

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Background and Purpose—Retinal microvascular abnormalities reflect cumulative small vessel damage from elevated blood pressure and may reflect subclinical cerebral microvascular changes. We examined their associations with MRI-defined cerebral infarcts.

Methods—Population-based, cross-sectional study of 1684 persons 55 to 74 years of age without a history of clinical stroke, sampled from 2 US southeastern communities. Retinal photographs were obtained and graded for presence of retinal microvascular abnormalities, including arteriovenous nicking, focal arteriolar narrowing, retinal hemorrhages, soft exudates and microaneurysms. Photographs were also digitized, and retinal vessel diameters were measured and summarized as the arteriole-to-venule ratio (AVR). Cerebral MRI scans were graded for presence of cerebral infarct, defined as a lesion ≥ 3 mm diameter in a vascular distribution with typical imaging characteristics.

Results—There were a total of 183 MRI cerebral infarcts. After adjustment for age, gender, race, 6-year mean arterial blood pressure, diabetes, and other stroke risk factors, cerebral infarcts were associated with retinal microvascular abnormalities, with odds ratios 1.90 (95% CI, 1.25 to 2.88) for arteriovenous nicking, 1.89 (95% CI, 1.22 to 2.92) for focal arteriolar narrowing, 2.95 (95% CI, 1.30 to 6.71) for blot hemorrhages, 2.08 (95% CI, 0.69, 6.31) for soft exudates, 3.17 (95% CI, 1.05 to 9.64) for microaneurysms, and 1.74 (95% CI, 0.95 to 3.21) for smallest compared with largest AVR. In stratified analyses, these associations were only present in persons with hypertension.

Conclusions—Retinal microvascular abnormalities are associated with MRI-defined subclinical cerebral infarcts independent of stroke risk factors. These data suggest that retinal photography may be useful for studying subclinical cerebrovascular disease in population-based studies. (Stroke. 2006;37:82-86.)

Key Words: cerebrovascular disorders ■ cerebral infarction ■ hypertension ■ retinal artery ■ retinal blood vessels ■ stroke

Stroke is an important cause of mortality and morbidity in the United States. Because current stroke risk prediction has inherent limitations, there is a need to search for additional predictors. The retinal vasculature permits noninvasive visualization of long-term, cumulative exposure to elevated blood pressure and other stroke risk factors.1 It is embryologically and anatomically part of the cerebral vasculature.2,3 Recent studies have shown retinal microvascular abnormalities (eg, arteriovenous nicking, focal arteriolar narrowing, and microaneurysms; Figure) are associated with current and past blood pressure4,5 and predict the development of incident clinical stroke, independent of vascular risk factors.5

It is unclear whether retinal microvascular abnormalities are associated with subclinical cerebrovascular disease. Cerebral infarction diagnosed via MRI is correlated with pathologic evidence of infarction7 and is strongly related to stroke risk factors,8,9 motor and cognitive dysfunction,10 and prevalent11 and incident12 clinical stroke. In the current study, we examined the relationship of retinal microvascular abnormalities with MRI-defined subclinical cerebral infarcts.

Methods

Study Population

The Atherosclerosis Risk in Communities (ARIC) Study has been described previously.13 From 1987 to 1989, 15 792 women and men were recruited, selected as probability samples of 45- to 64-year-old residents of 4 US communities in Forsyth County, NC, Jackson,
MRI Procedures and Definition of Cerebral Infarct
The MRI scanning and reading protocols and definition of cerebral infarcts are described in detail previously.15 A standardized protocol was used to scan participants at the field centers. These scans were read at the MRI reading center by trained readers, masked to subject identity. Cerebral infarct was defined as a lesion ≥3 mm in maximum diameter in a vascular distribution with typical imaging characteristics15 and was distinguished from smaller, more common cerebral white matter lesions. Lacunar infarct was defined as a cerebral infarct (by the above criteria) with maximum diameter <2 cm located in the brain stem, basal ganglia, internal capsule, thalamus, or deep cerebral white matter. All MRI scans were reviewed by a second reader, and disagreements were adjudicated by consensus. A total of 144 randomly selected cases were reread for the purpose of analyzing lesion detection reproducibility. Inter-reader and in-trader reader \( \kappa \) ranged from 0.52 and 0.78, respectively.15

Retinal Photographic Grading and Definitions
Retinal photography and the grading procedure have been described in detail previously.4,16 After 5 minutes of dark adaptation, a 45° retinal photograph was taken in 1 randomly selected eye, centered on the region of the optic disc and the macula, using an auto-focus camera. The photographic slides were evaluated by trained graders, masked to subject identity, using an established grading system.16 Focal microvascular abnormalities analyzed in this report include arteriovenous nicking, focal arteriolar narrowing, blot hemorrhages, soft exudates (cotton wool spots), and microaneurysms; other lesions were too infrequent for analysis.4 Quality control measures have been reported previously.17 In general, intragrader and intergrader \( \kappa \) statistics ranged from 0.61 to 1.00.

In addition to focal grading, a semiquantitative method estimated generalized arteriolar narrowing, expressed as arteriole-to-venule...
ratio (AVR). A smaller AVR represents narrower arterioles relative to venular caliber and is associated with higher blood pressure. This measurement has been shown to be reproducible and sensitive to modest blood pressure elevations and to reflect the effect of previous pressure elevations independent of the currently measured blood pressure. All statistical procedures were based on SAS software. Focal retinal signs independent of measure blood pressure.

 Definitions of Stroke Risk Factors
Participants underwent standardized evaluations of cardiovascular risk factors at all 3 examinations. Blood pressure was measured with a random-zero sphygmomanometer, and the average of the second and third readings of the measurements was used in this analysis. The mean arterial blood pressure was computed as two thirds of the diastolic plus one third of the systolic value, and the average of this over all 3 examinations (ie, 6-year mean arterial blood pressure) was used in all multivariate analyses to assess the effects of the retinal signs independent of measure blood pressure. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medication during the previous 2 weeks. Diabetes mellitus was defined as a fasting glucose ≥ 7.0 mmol/L (≥ 126 mg/dL), a nonfasting glucose ≥ 11.1 mmol/L (≥ 200 mg/dL), or a self-reported history of treatment for diabetes. A person was considered to have hypertension or diabetes if these criteria were met at any of the 3 examinations.

Values from the third examination, if available, were used for other variables. Cigarette smoking status was characterized as never, former, or current cigarette smoker. Methods used for measurements of total cholesterol and triglycerides, high-density lipoprotein cholesterol, and serum fibrinogen are based on techniques described previously.

Statistical Analysis
All statistical procedures were based on SAS software. Focal retinal variables were dichotomized as present versus absent for analysis. Because the relationship between AVR and cerebral infarction was nonlinear, AVR was divided into quintiles for analysis, with the fifth or highest quintile (interpreted as no generalized arteriolar narrowing) serving as reference. χ² and t test were used to compare categorical and continuous variables, respectively, whereas test of trend for infarct prevalence across AVR quintiles was based on the Mantel–Haenszel χ² statistic. Multivariable odds ratios (ORs) for presence of MRI cerebral infarct as a function of retinal abnormalities were calculated using logistic regression analysis.

Table 2 shows the association of retinal microvascular signs and MRI infarcts in the total population and in persons with and without hypertension. After adjustment for age,

<table>
<thead>
<tr>
<th>Retinal Abnormalities</th>
<th>All Persons</th>
<th>Persons With Hypertension</th>
<th>Persons Without Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. At Risk</td>
<td>% MRI Infarct</td>
<td>P</td>
</tr>
<tr>
<td>Arteriovenous nicking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1401</td>
<td>9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>234</td>
<td>17.5</td>
<td></td>
</tr>
<tr>
<td>Focal arteriolar narrowing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1354</td>
<td>9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>238</td>
<td>17.2</td>
<td></td>
</tr>
<tr>
<td>Blot retinal hemorrhages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1536</td>
<td>9.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>55</td>
<td>32.7</td>
<td></td>
</tr>
<tr>
<td>Soft exudates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1597</td>
<td>10.1</td>
<td>0.0013</td>
</tr>
<tr>
<td>Yes</td>
<td>33</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td>Microaneurysms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1416</td>
<td>9.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>46</td>
<td>30.4</td>
<td></td>
</tr>
<tr>
<td>AVR Quintiles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>300</td>
<td>16.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2nd</td>
<td>300</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>301</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>300</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>5th</td>
<td>300</td>
<td>7.7</td>
<td></td>
</tr>
</tbody>
</table>
gender and race/center, all retinal variables were significantly associated with MRI cerebral infarction, with OR ranging from 1.89 for arteriovenous nicking to 4.04 for blot hemorrhages. Additional adjustment for 6-year mean blood pressure, diabetes, and other risk factors attenuated some of these associations (OR ranging from 1.74 to 3.17). Among hypertensive persons, the presence of all retinal microvascular signs was associated with MRI infarcts (multivariable OR ranging from 2.30 to 4.24). Among normotensive persons, none of the retinal signs were associated with retinal microvascular signs.

Table 4 shows further analyses confined to persons with hypertension. The associations of the 3 most common retinal abnormalities (arteriovenous nicking, focal arteriolar narrowing, and AVR) were entered simultaneously in models adjusting for stroke risk factors. After multivariable adjustment, arteriovenous nicking (OR, 2.47), focal arteriolar narrowing (OR, 1.78), and smaller AVR (OR, 4.76 for first versus fifth quintile) were significantly associated with MRI cerebral infarction. Excluding persons with diabetes, with previous transient ischemic attacks, and diabetes and previous transient ischemic attacks had little impact on the results shown.

Results were overall similar when persons with ≥1 non-lacunar infarct were excluded, in persons older and younger than 65 years of age, and for past and current nonsmokers (data not shown).

**Discussion**

These population-based data show that in middle-aged persons, retinal microvascular signs are associated with MRI-defined cerebral infarction, even after adjustment for blood pressure and other stroke risk factors. In stratified analyses, these associations were confined to persons with hypertension.

The retinal microvascular signs assessed here are thought to largely reflect arteriolar damage from hypertension, and possibly inflammation and endothelial dysfunction. The association of these retinal signs with MRI-defined cerebral infarcts, most of which is lacunar, may therefore reflect similar arteriolar processes in the cerebral microvasculature.

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**TABLE 3. Association of Retinal Microvascular Abnormalities and MRI Cerebral Infarct**

<table>
<thead>
<tr>
<th>Retinal Abnormalities</th>
<th>All Persons</th>
<th>Persons With Hypertension</th>
<th>Persons Without Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-gender-race OR (95% CI)*</td>
<td>Multivariable Age-gender-race OR (95% CI)*</td>
<td>Multivariable Age-gender-race OR (95% CI)*</td>
</tr>
<tr>
<td>Arteriovenous nicking</td>
<td>1.89 (1.28, 2.80)</td>
<td>1.90 (1.25, 2.88)</td>
<td>2.40 (1.52, 3.79)</td>
</tr>
<tr>
<td>Focal arteriolar narrowing</td>
<td>2.03 (1.37, 3.02)</td>
<td>1.89 (1.22, 2.92)</td>
<td>2.27 (1.40, 3.66)</td>
</tr>
<tr>
<td>Blot retinal hemorrhages</td>
<td>4.04 (2.21, 7.41)</td>
<td>2.93 (1.30, 6.71)</td>
<td>4.23 (2.14, 8.38)</td>
</tr>
<tr>
<td>Soft exudates</td>
<td>2.99 (1.36, 6.59)</td>
<td>2.08 (0.69, 6.31)</td>
<td>3.65 (1.48, 8.99)</td>
</tr>
<tr>
<td>Microaneurysms</td>
<td>3.82 (1.94, 7.51)</td>
<td>3.17 (1.05, 9.64)</td>
<td>3.24 (1.49, 7.06)</td>
</tr>
</tbody>
</table>

*OR of MRI cerebral infarct associated with retinal abnormalities (presence vs absence, except for AVR, each quintile relative to fifth quintile), adjusted for age, gender, race, 6-year mean arterial blood pressure, antihypertensive medication use, fasting blood glucose, diabetes, smoking status, plasma total and high-density lipoprotein cholesterol, plasma triglycerides, and serum fibrinogen.

**TABLE 4. Association of Common Retinal Microvascular Abnormalities and MRI Cerebral Infarct, Persons with Hypertension**

<table>
<thead>
<tr>
<th>Retinal Abnormalities</th>
<th>All n=682</th>
<th>No Diabetes n=523</th>
<th>No Previous Transient Ischemic Attack n=658</th>
<th>No Diabetes or Previous Transient Ischemic Attack n=504</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriovenous nicking</td>
<td>2.47 (1.43, 4.29)</td>
<td>2.39 (1.30, 4.41)</td>
<td>2.53 (1.44, 4.45)</td>
<td>2.36 (1.26, 4.43)</td>
</tr>
<tr>
<td>Focal arteriolar narrowing</td>
<td>1.78 (1.00, 3.19)</td>
<td>1.93 (1.01, 3.67)</td>
<td>1.75 (0.96, 3.18)</td>
<td>1.88 (0.96, 3.67)</td>
</tr>
</tbody>
</table>

AVR

First quintile 4.76 (1.68, 13.47) 3.11 (1.05, 9.22) 4.43 (1.54, 12.69) 2.69 (0.89, 8.14)
Second quintile 2.50 (0.85, 7.30) 2.13 (0.71, 6.39) 2.35 (0.80, 6.93) 1.95 (0.64, 5.93)
Third quintile 4.09 (1.43, 11.65) 2.66 (0.88, 8.10) 3.79 (1.32, 10.87) 2.51 (0.82, 7.65)
Fourth quintile 2.23 (0.72, 6.91) 1.37 (0.41, 4.57) 1.95 (0.62, 6.16) 1.11 (0.32, 3.84)
Fifth quintile 1.00 1.00 1.00 1.00

Data show OR (95% CI) of MRI cerebral infarct associated with retinal abnormalities (presence vs absence, except for AVR, each quintile relative to fifth quintile), adjusted for age, gender, race/center, and other stroke risk factors.
These findings are supported by data from epidemiological studies using less quantitative clinical assessment of retinal microvascular signs.\textsuperscript{19,20} In a Japanese study in the 1970s, retinal microvascular abnormalities diagnosed by ophthalmoscopy were associated with hemorrhagic and thrombotic stroke.\textsuperscript{19} A more recent study describes associations “retinal arterial sclerosis” and small infarcts detected by cerebral CT or MRI.\textsuperscript{20} The current findings are also consistent with our previous analyses of retinal microvascular signs, with clinical stroke\textsuperscript{6} cognitive impairment,\textsuperscript{21} and MRI white matter lesions,\textsuperscript{14} in the ARIC population.

Anatomical, histopathological, and functional studies provide further biological basis for our observations.\textsuperscript{3} In an autopsy study of stroke decedents, retinal arteriolar fibrous thickening were seen in all 19 stroke cases but only 12 of 21 disease-free controls.\textsuperscript{22} Another study demonstrated functional alterations in the retinal vasculature (eg, a slow retinal arteriolar-venule passage time) in persons with lacunar stroke.\textsuperscript{23} Strengths of this study include applicability to contemporary populations with low prevalence of severe hypertension, standardized retinal and cerebral examinations, and the inclusion of blacks. Limitations include the following. First, because of the cross-sectional design, it is possible that some of the cerebral infarctions detected by MRI may have preceded the retinal lesions. However, prospective studies suggest that retinal findings precede clinical stroke.\textsuperscript{66} Second, possible selection biases should be considered because a significant proportion of participants did not have MRI or retinal data. Those excluded tended to be older and to have a higher prevalence of cardiovascular risk factors (Table 1). If these people were also more likely to have retinopathy signs and MRI infarcts, the associations could have been attenuated.

In summary, we demonstrate a strong association between retinal microvascular signs and MRI-defined cerebral infarction. These associations were seen only in persons with hypertension. The data suggest that a careful examination of retinal vessels and their changes by retinal photography may be useful for investigating the contribution of small vessel disease to the pathogenesis of cerebrovascular\textsuperscript{24} and perhaps other cardiovascular diseases.\textsuperscript{25}

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References

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