Differential Effect of White-Matter Lesions and Covert Brain Infarcts on the Risk of Ischemic Stroke and Intracerebral Hemorrhage

Sara Kaffashian, PhD; Christophe Tzourio, MD, PhD; Yi-Cheng Zhu, MD, PhD; Bernard Mazoyer, MD, PhD; Stéphanie Debette, MD, PhD

Background and Purpose—We examined the association of white-matter hyperintensity (WMH) volume and covert brain infarcts, which are the 2 major magnetic resonance imaging markers of covert cerebrovascular disease in older adults, with long-term risk of ischemic stroke and intracerebral hemorrhage (ICH) in the general population.

Methods—Participants were 1731 individuals aged ≥65 years from the Three-City Dijon study. We studied the association of WMH volume and brain infarct, with incident ischemic stroke overall, and by subtype, and with incident ICH.

Results—High total, periventricular, and deep WMHs were associated with increased risk of ischemic stroke (hazard ratio, 1.94; 95% confidence interval, 1.12–3.35), particularly cardioembolic stroke. Covert brain infarcts were associated with incident ICH but not with incident ischemic stroke or its subtypes.

Conclusions—Although of ischemic nature, both WMH volume and covert brain infarcts portend a major risk of ICH. If confirmed in independent studies, these findings could have important implications for the clinical management of covert vascular brain lesions. (Stroke. 2016;47:00-00. DOI: 10.1161/STROKEAHA.116.012734.)

Key Words: brain infarction ■ cerebral hemorrhage ■ cerebral small-vessel diseases ■ leukoaraiosis ■ stroke

Covert cerebrovascular disease detected on brain magnetic resonance imaging (MRI) is highly prevalent in older adults from the general population.1 White-matter hyperintensities (WMHs) and covert brain infarcts (BIs) are among the most studied MRI markers of vascular brain injury and have been shown to substantially increase the risk of stroke in the general population.2,3 However, although WMH and BI are thought to mostly reflect cerebral small-vessel disease, comparative association of WMH and BI with differential risk of stroke types and subtypes has not been examined in the general population.4,5

In a large population-based cohort of stroke-free older adults, we examined whether WMH burden and BI are prospectively associated with incident ischemic stroke (IS), overall and by subtype, and with incident intracerebral hemorrhage (ICH), and whether WMH and BI characteristics differentially impacted risk of incident stroke types and subtypes.

Materials and Methods
The Three-City (3C) Dijon study is a French population-based cohort study of 4931 community individuals.6 Our sample consists of 1731 stroke-free participants with MRI data followed up for ≤12 years. MRI acquisition was performed with a 1.5-T Magnetom Siemens scanner using T1-weighted, T2-weighted, and proton density-weighted sequences. Automated image processing software was developed to detect and localize WMH and measure WMH volume (WMHV).7,8 These were classified according to distance to the ventricle as periventricular (<10 mm, periventricular WMHV [PWMHV]) or deep (deep WMHV [DWMHV]). Covert BIs were defined as focal lesions ≥3 mm with the same signal characteristics as cerebrospinal fluid on all sequences. Lacunes of presumed vascular origin were defined as BI of 3 to 15 mm, located in basal ganglia, brain stem, or subcortical white matter.9

Incident stroke was defined as a new focal neurological deficit of sudden or rapid onset, of presumed vascular origin, that persisted for >24 hours, or leading to death. An expert panel adjudicated diagnosis of stroke and its types (ischemic, hemorrhagic, and unspecified) and subtypes (cardioembolic, large-artery, and small-artery occlusion IS).

WMHV was examined both as a continuous variable (expressed as a proportion of WM mask volume to account for differences in WM detection mask size) and dichotomized with the top quartile of total, periventricular, and deep WMHV representing extensive total WMHV, extensive DWMHV, and extensive PWMHV.

Associations of WMHV and BI with incident stroke were examined using multivariable Cox regression with age as the time scale, adjusted for sex, education, and the number of cardiovascular risk factors. We also examined modifying effects of hypertension. Analyses were performed using SAS version 9.3 (SAS Institute, Inc, Cary, NC).
Results
The mean age of participants at the time of MRI was 72±4 years; 61% were women. Risk factor distribution of the study sample is presented in Table I in the online-only Data Supplement. Of 1731 participants, 161 (9%) had ≥1 BI (130 lacunes). All individuals had some degree of WMHV. During 15 982 person-years of follow-up (mean, 9.6±2.4 years), there were 54 IS, 15 ICH, and 4 undetermined stroke events.

High total WMHV and PWMHV and extensive PWMHV were associated with the risk of both incident stroke types but particularly with ICH versus IS. DWMHV and extensive DWMHV were associated with ICH but not with IS (Table). When examining IS subtypes, extensive PWMHV was associated with the risk of cardioembolic IS.

Covert BIs were associated with incident ICH but not IS. Lacunes, a BI subtype thought to mostly reflect cerebral small-vessel disease, were associated with both IS and ICH, but the association was considerably stronger for ICH. When examining IS subtypes, lacunes were associated with the risk of small-artery occlusion IS.

There was no evidence of a modifying effect of hypertension in the observed associations between WMHV or BI and incident stroke.

Discussion
Our findings demonstrate that WMHV and lacunes, although associated with increased risk of both stroke types, are associated especially with the risk of ICH in the general population. DWMHV was associated only with increased risk of ICH. Although PWMHV and lacunes were associated with increased risk of both IS and ICH, the risk was twice greater for ICH. Lacunes were associated with small-artery occlusion IS and PWMHV with cardioembolic IS.

Although previous population-based and hospital-based cohorts had reported associations of WMHV and BI with increased risk of ICH, our simultaneous examination of both IS and ICH suggests a stronger association with ICH although confidence intervals overlap. Although we cannot exclude some misclassification bias, with hemorrhagic transformation of IS being classified as ICH, it is also well established that small-vessel disease can lead to both ICH and small-artery occlusion IS (with both showing similar signs of retinal microvascular dysfunction). Cerebral amyloid angiopathy, an important cause of ICH, and hypertension, a major risk factor for both IS and ICH, likely play important mediating roles in these associations. Antithrombotic medications may also contribute to these associations. Our findings emphasize the importance of formally evaluating, in randomized trials, the risk–benefit ratio of prescribing antithrombotic drugs to prevent stroke in patients with covert cerebrovascular disease.

The strongest association of PWMHV with incident cardioembolic IS is intriguing. Atrial fibrillation, the main cause of cardioembolic IS, may partly mediate this association; although mechanisms linking atrial fibrillation to PWMHV are unclear, they may include thromboemboli, chronic cerebral hypoperfusion in case of chronically altered cerebral perfusion, caused by beat-to-beat variation in stroke volume, and possibly shared risk factors, including genetic.

Table. Association of Magnetic Resonance Imaging–Defined White-Matter Hyperintensities and Covert Brain Infarcts With Incident Stroke Subtypes

<table>
<thead>
<tr>
<th></th>
<th>Incident Ischemic Stroke</th>
<th>Incident ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Lacunar</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>No. of events</td>
<td>54</td>
<td>11</td>
</tr>
<tr>
<td>WMHV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.50 (1.03–2.20)</td>
<td>0.03</td>
</tr>
<tr>
<td>Periventricular</td>
<td>1.47 (1.05–2.07)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Deep</td>
<td>1.21 (0.83–1.75)</td>
<td>0.31</td>
</tr>
<tr>
<td>Ext-WMHV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.60 (0.91–2.80)</td>
<td>0.10</td>
</tr>
<tr>
<td>Periventricular</td>
<td>1.94 (1.12–3.35)</td>
<td>0.01</td>
</tr>
<tr>
<td>Deep</td>
<td>1.38 (0.76–2.48)</td>
<td>0.27</td>
</tr>
<tr>
<td>BI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All BI</td>
<td>1.70 (0.82–3.52)</td>
<td>0.15</td>
</tr>
<tr>
<td>Lacunes</td>
<td>2.12 (1.01–4.42)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

BI indicates brain infarct; CI, confidence interval; ext-WMHV, extensive total white-matter hyperintensity volume; HR, hazard ratio; ICH, intracerebral hemorrhage; and WMHV, white-matter hyperintensity volume.

*Adjusted for sex.
†Adjusted for sex, education, and the number of cardiovascular risk factors (diabetes, hypertension, hypercholesterolemia, history of cardiovascular disease, and current smoking).
may be especially prone to ischemia related to vascular risk factors also predisposing to coronary artery disease.\textsuperscript{14} If confirmed in independent studies, our observation may raise the question whether screening for atrial fibrillation should be performed in patients with extensive WMH.

The different association of PWMHV and DWMHV with IS and ICH may point to distinct lesion subtypes as also suggested by differential association with dementia risk.\textsuperscript{15} The association of DWMHV with ICH could potentially be attributed to a more prominent distribution of cerebral amyloid angiopathy–related WMH in the deep white matter although this is speculative.

Strengths of this study include the large population-based cohort and long follow-up with prospective ascertainment of stroke, including detailed subtyping. The relatively small number of stroke events remains a limitation.

In conclusion, WMH burden and covert BI are important risk factors for the risk of both incident IS (especially the small-vessel occlusion and cardioembolic) and ICH. In addition to justifying further examination of underlying mechanisms, this may have implications for the clinical management of covert vascular brain lesions.

Acknowledgments

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Disclosures
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http://stroke.ahajournals.org/content/suppl/2016/06/27/STROKEAHA.116.012734.DC1
http://stroke.ahajournals.org/content/suppl/2017/07/10/STROKEAHA.116.012734.DC2

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Supplemental Table. Baseline characteristics

<table>
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<tr>
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<th>No ext-WMH</th>
<th>ext-WMH</th>
<th>P</th>
<th>No BI</th>
<th>BI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1299</td>
<td>432</td>
<td></td>
<td>1570</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td>Age at MRI exam, years</td>
<td>72±4</td>
<td>73±4</td>
<td>&lt;0.001</td>
<td>72±4</td>
<td>74±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>819(63)</td>
<td>235(54)</td>
<td>0.002</td>
<td>985(62)</td>
<td>69(42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low education levela</td>
<td>516(39)</td>
<td>174(40)</td>
<td>0.92</td>
<td>628(40)</td>
<td>62(38)</td>
<td>0.96</td>
</tr>
<tr>
<td>Hypertensionb</td>
<td>955(73)</td>
<td>371(85)</td>
<td>&lt;0.001</td>
<td>1182(75)</td>
<td>144(89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemiac</td>
<td>746(57)</td>
<td>237(55)</td>
<td>0.38</td>
<td>897(57)</td>
<td>86(53)</td>
<td>0.30</td>
</tr>
<tr>
<td>Diabetesd</td>
<td>90(6)</td>
<td>48(11)</td>
<td>0.01</td>
<td>123(7)</td>
<td>15(9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Current smoker</td>
<td>64(4)</td>
<td>32(7)</td>
<td>0.07</td>
<td>86(5)</td>
<td>10(6)</td>
<td>0.75</td>
</tr>
<tr>
<td>Prior CVDe</td>
<td>47(3)</td>
<td>25(5)</td>
<td>0.06</td>
<td>56(3)</td>
<td>16(9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of CVD risk factors</td>
<td>1.4±0.7</td>
<td>1.6±0.8</td>
<td>&lt;0.001</td>
<td>1.4±0.7</td>
<td>1.6±0.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Use of antithrombotics</td>
<td>150(11)</td>
<td>76(17)</td>
<td>0.001</td>
<td>183(12)</td>
<td>43(27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>20(1)</td>
<td>11(2)</td>
<td>0.15</td>
<td>23(1)</td>
<td>8(5)</td>
<td>0.001</td>
</tr>
<tr>
<td>WMHV (ml)</td>
<td>3.5±1.3</td>
<td>11.7±6.6</td>
<td>&lt;0.001</td>
<td>5.3±5.5</td>
<td>7.8±5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WMHV (ratio of mask volume)</td>
<td>0.01±0.005</td>
<td>0.04±0.02</td>
<td>&lt;0.001</td>
<td>0.02±0.01</td>
<td>0.03±0.02</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD or number (%)

a High-school or less. b Systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of blood pressure lowering medications. c Total cholesterol ≥ 6.2 mmol/L, or use of lipid lowering medications. d Fasting blood glucose ≥ 7 mmol/L or use of antidiabetic drugs. e History of myocardial infarction, angina pectoris, heart failure, or peripheral vascular disease.
虚血性脳卒中および脳内出血のリスクに及ぼす白質病変と無症候性脳梗塞の異なる影響

Differential Effect of White-Matter Lesions and Covert Brain Infarcts on the Risk of Ischemic Stroke and Intracerebral Hemorrhage

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背景および目的: 本研究では、高齢者の潜在性脳血管障害の2つの主要なMRIマーカーである白質高信号病変（white-matter hyperintensity: WMH）容積と無症候性脳梗塞の関連を一般集団における虚血性脳卒中および脳内出血（ICH）の長期リスクによって検討した。

方法: 本研究の参加者はThree-City Dijon研究に登録した65歳以上の1,731人であった。全虚血性脳卒中の発症、各サブタイプ別の発症、ICHの発症についてWMH容積と脳梗塞の関連を検討した。

結果: 総容積が大きなWMH、脳室周囲のWMH、深部のWMHはICHの発症に関連した。脳室周囲のWMH容積が広範囲に及ぶと虚血性脳卒中のリスクが増大し[ハザード比 1.94, 95%信頼区間 (CI): 1.12 ~ 3.35], 特に心原性脳塞栓症との関連が顕著であった。無症候性脳梗塞はICHの発症と関連したが、虚血性脳卒中およびそのサブタイプとの関連はみられなかった。

結論: 虚血性であってもWMH容積と無症候性脳梗塞はいずれも重要なICHリスクの候補となる。本研究の結果が独立した複数の研究で確認されれば、潜在性脳血管病変の臨床管理に大きな意味を持つであろう。

表 脳卒中サブタイプの発症によるMRIで定義した白質高信号病変と無症候性脳梗塞の関連

<table>
<thead>
<tr>
<th></th>
<th>全虚血性脳卒中</th>
<th>ラクナ梗塞</th>
<th>心原性脳梗塞</th>
<th>ICH の発症</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P値*</td>
<td>P値†</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>イベント数</td>
<td>54</td>
<td>11</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

WMHV

合計 1.50 (1.03-2.20) 0.03 0.02 1.15 (0.45-2.92) 0.75 0.70 1.15 (0.45-2.92) 0.08 0.07 3.54 (1.65-7.60) 0.001 0.001
脳室周囲 1.47 (1.05-2.07) 0.0002 0.01 1.11 (0.49-2.53) 0.79 0.69 1.13 (0.49-2.53) 0.06 0.05 2.88 (1.43-5.78) 0.002 0.003
深部 1.21 (0.83-1.75) 0.31 0.26 1.23 (0.50-3.00) 0.64 0.63 1.41 (0.70-2.86) 0.33 0.30 4.95 (2.10-11.65) 0.0002 0.0003
Ext-WMHV

合計 1.60 (0.91-2.80) 0.10 0.07 0.66 (0.14-3.09) 0.60 0.56 1.91 (0.67-5.38) 0.22 0.19 4.92 (1.43-16.88) 0.01 0.01
脳室周囲 1.94 (1.12-3.35) 0.01 0.01 1.13 (0.29-4.30) 0.60 0.62 3.10 (1.11-8.62) 0.02 0.02 4.68 (1.36-16.08) 0.01 0.01
深部 1.38 (0.76-2.48) 0.27 0.22 1.09 (0.28-4.16) 0.89 0.87 1.20 (0.38-3.77) 0.75 0.72 8.78 (2.32-33.22) 0.001 0.001

BI

合計 1.70 (0.82-3.52) 0.15 0.13 3.64 (0.94-14.11) 0.06 0.05 0.55 (0.07-4.31) 0.57 0.52 6.78 (2.00-23.04) 0.002 0.002
脳室周囲 2.12 (1.01-4.42) 0.04 0.03 4.49 (1.14-17.59) 0.03 0.02 0.68 (0.08-5.36) 0.72 0.68 8.65 (2.49-30.05) 0.0009 0.0009

BI：脳梗塞, CI：信頼区間, ext-WMHV：広範囲の白質高信号病変の総量, HR：ハザード比, ICH：脳内出血, WMHV：白質高信号病変容積。
*性別について調整。
†性別、教育、心血管リスク因子（糖尿病、高血圧、高コレステロール血症、心血管疾患の既往、現在の喫煙状況）の数について調整。