Long-Term Clinical Impact of Vascular Brain Lesions on Magnetic Resonance Imaging in Older Adults in the Population

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

Background and Purpose—White matter hyperintensity (WMH) volume and covert brain infarcts are highly prevalent in older adults and are often asymptomatic. We compared the impact of WMH volume and brain infarcts on risk of clinical stroke and dementia in older adults in the population.

Methods—Participants were 1677 individuals aged ≥65 years from the 3-City Dijon study, who were free of stroke and dementia at baseline, followed-up for ≤12 years.

Results—Both lesion types were comparably associated with an increased risk of stroke (adjusted hazard ratio, 1.72; 95% confidence interval, 1.24–2.40 for WMH volume and hazard ratio, 2.15; 95% confidence interval, 1.18–3.93 for brain infarcts), but only WMH volume was associated with an increased risk of dementia (hazard ratio, 1.41; 95% confidence interval, 1.09–1.83).

Conclusions—The differential impact of WMH and brain infarcts on clinical stroke and dementia suggests relatively different prognostic value of the 2 lesions. WMHs may represent a particularly pertinent magnetic resonance imaging intermediate marker that can be utilized in optimizing prevention strategies for both stroke and dementia in primary care and in trials. (Stroke. 2016;47:2865-2869. DOI: 10.1161/STROKEAHA.116.014695.)

Key Words: cerebral small vessel disease ■ dementia ■ epidemiology ■ magnetic resonance imaging ■ stroke

White matter hyperintensities (WMHs) and covert brain infarcts (BIs) are often asymptomatic and are commonly observed on brain magnetic resonance imaging performed in the general population. They have been independently shown to substantially increase risk of stroke and dementia in the general population. However, the relative prognostic importance of these magnetic resonance imaging markers with respect to risk of stroke and dementia, and whether they result from the same pathological processes, remain unclear. WMHs are mostly believed to reflect chronic hypoperfusion (other mechanisms have been suggested as well, such as impaired blood–brain barrier) and are commonly considered as less severe than BIs. To date, no studies have simultaneously examined the impact of both WMH and BI on risk of stroke and dementia in the older population.

In a large population-based sample of older adults with ≤12 years of follow-up, we investigated the relationship of WMH and BI with risk of incident stroke and dementia.

Materials and Methods

The 3-City (3C) Dijon study is a French population-based cohort study of 4931 community individuals. Our study sample consisted of 1677 individuals who were free of stroke and dementia followed-up for ≤12 years (see Methods section in the online-only Data Supplement).

Magnetic resonance imaging acquisition was performed with a 1.5-T Magneton 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 total WMH volume (WMHV). 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 BIs of 3 to 15 mm, located in the basal ganglia or subcortical white matter. They were distinguished from dilated perivascular spaces using multiplanar reformattting. Lesions with a typical vascular shape following the orientation of perforating vessels were regarded as perivascular spaces.

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 of neurologists adjudicated diagnosis of stroke based on criteria of the World Health Organization, and dementia, based on criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (See Methods section in the online-only Data Supplement).

WMHV was examined both as a continuous variable (expressed as a proportion of WM mask volume to account for differences in

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.014695/-/DC1.

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Results

Mean age of participants at baseline was 72±4 years, 61% were women. Detailed characteristics of the study sample are shown in the online-only Data Supplement Table. During follow-up, 68 participants were diagnosed with stroke (10 fatal), and 124 participants were diagnosed with dementia (89 AD).

Larger WMHV, PWMHV, and DWMHV were associated with increased risk of incident stroke; BI and lacunes were also associated with increased risk of incident stroke, all independently of vascular risk factors (Table). Finally, to test whether the association of WMHV with dementia was mediated by incident stroke, we further adjusted these analyses for interim stroke events.

Discussion

In this population-based study, WMHV (in all locations) and BI equally conferred an increased risk of clinical stroke, but only WMHV, overall and in the periventricular location were associated with an increased risk of dementia. This differential association raises important points about the relative prognostic value and potentially distinct underlying mechanisms of the 2 lesion types.

Our findings about the risk of stroke are consistent with previous population-based studies, reporting a 3- to 4-fold increase in risk associated with extensive WMH burden and BI in the general population.27–29 The similar effect of these distinct lesion types on stroke risk, as we highlight here in the same data set, suggests WMHV and BI to be comparable independent markers of cerebrovascular burden and risk.

Table. Association of WMHV and Brain Infarcts With Incident Stroke and Dementia

<table>
<thead>
<tr>
<th></th>
<th>Incident Stroke</th>
<th>Incidence Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>68</td>
<td>124</td>
</tr>
<tr>
<td>WMHV (ratio of TIV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.72 (1.24–2.40)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>1.41 (1.09–1.83)</td>
<td>0.008</td>
</tr>
<tr>
<td>Periventricular</td>
<td>1.62 (1.20–2.18)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>1.37 (1.09–1.73)</td>
<td>0.007</td>
</tr>
<tr>
<td>Deep</td>
<td>1.53 (1.08–2.15)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>1.09 (0.85–1.39)</td>
<td>0.41</td>
</tr>
<tr>
<td>Ext-WMHV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.88 (1.16–3.07)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>1.73 (1.24–2.59)</td>
<td>0.001</td>
</tr>
<tr>
<td>Periventricular</td>
<td>2.04 (1.26–3.31)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>1.78 (1.24–2.57)</td>
<td>0.001</td>
</tr>
<tr>
<td>Deep</td>
<td>1.85 (1.13–3.04)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>1.27 (0.85–1.89)</td>
<td>0.23</td>
</tr>
<tr>
<td>BI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All BI</td>
<td>2.15 (1.18–3.93)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>1.07 (0.60–1.92)</td>
<td>0.79</td>
</tr>
<tr>
<td>Lacunes</td>
<td>2.69 (1.46–4.95)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>1.13 (0.60–2.13)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

WM detection mask size) and dichotomized with the top quartile of WMHV, PWMHV, and DWMHV representing extensive total WMHV, extensive DWMHV, and extensive PWMHV. Covert BI and lacunes were defined as the presence of at least one infarct/lacune versus none. Participants with at least 1 magnetic resonance imaging-defined nonlacunar BI were not included in analyses of lacunes (n=31).

We examined the association of WMHV and BI with incident stroke and incident dementia using Cox proportional-hazards regression analysis with age as the time scale, adjusted for sex, education, diabetes mellitus, hypertension, hypercholesterolemia, history of cardiovascular disease, current smoking, and APOE-ε4 genotype. In addition, we used linear mixed effects models to examine the association of WMHV and BI with longitudinal change in IST scores (Isaacs Set Test; semantic fluency), using 5 assessments over 12 years. Finally, to test whether the association of WMHV with dementia was mediated by incident stroke, we further adjusted these analyses for interim stroke events.

Results

These results were independent of vascular risk factors (Table). PWMHV was associated with incident dementia (Table). TIA (Table; Figure 1).
Figure 1. Age- and sex-adjusted cumulative incidence of stroke. BI indicates covert brain infarct; Ext-WMH, extensive white matter hyperintensity; and MRI, magnetic resonance imaging.
Figure 2. Age- and sex-adjusted cumulative incidence of dementia. BI indicates covert brain infarct; Ext-WMH, extensive white matter hyperintensity; and MRI, magnetic resonance imaging.
Similarly, the association of WMHV with increased risk of dementia is consistent with previous population-based studies.\textsuperscript{2,7,10} One previous study had also described a more prominent association of PWMHV than DWMHV with dementia.\textsuperscript{10} The exclusive association of PWMHV (not DWMHV) with accelerated decline in IST scores supports findings of a similar association with increased risk of dementia in our study and may suggest an early impact of PWMHV on cognitive decline during the preclinical phase of dementia. These observations may point to differential mechanisms underlying PWMHV and DWMHV. Periventricular WM may be more vulnerable to hypoperfusion; in individuals with WMH, reduced cerebral blood flow in normal appearing periventricular (but not deep) WM has been observed.\textsuperscript{11}

However, BIIs were not associated with incident dementia in our study, contrary to previous population-based studies.\textsuperscript{2,7,12} although some only showed borderline associations of BI after adjustment for vascular risk factors.\textsuperscript{12} Population characteristics, vascular profiles, and methodological differences (especially distinction of BI from dilated perivascular spaces) may partly explain these differences. We speculate that most single small covert BI may not, in isolation, predispose to greater risk of dementia, but may reflect underlying cerebrovascular pathology that may in some instances escalate over time and later contribute to dementia risk. In contrast, WMHV may be a marker of more widespread cerebrovascular pathology or may be more interactive with dementia-related neurodegenerative processes.\textsuperscript{13,14} Nonvascular mechanisms including reverse causation with Wallerian degeneration secondary to cortical atrophy, possibly induced by preexisting neurodegenerative mechanisms, may also contribute to the relationship between WMH and dementia.\textsuperscript{15}

The strong association of WMH with both stroke and dementia makes it a potentially valuable surrogate end point in trials of preventive or potentially disease modifying interventions for stroke and dementia. In clinical practice, presence of extensive WMH should lead to cognitive evaluation and follow-up. To this end, there is an urgent need for recommendations on optimal management of individuals with covert cerebrovascular disease, especially WMH burden.

Acknowledgments

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Materials and Methods

Study Population

The Three-City (3C) Dijon study is a French population-based cohort study of 4,931 community individuals, enrolled between March 1999 and March 2001. Baseline examination consisted of a face-to-face interview conducted at the participant’s home, to obtain socio-demographic health-related information, and medical history, and a cognitive and physical examination conducted at the study examination center. Those who refused or were unable to attend the study center had a second visit at home. Five examinations have been performed over a 12-year follow-up period (at 2, 4, 7-8, 10, and 12 years). Between June 1999 and September 2000 a random sample of 2,763 individuals (<80 years of age) was invited to undergo brain MRI. Participation rate was high (82.7%, 2,285 individuals) but due to financial restrictions, only 1,924 MRI scans were performed. Exclusion criteria for the examination were: presence of an internal electrical or magnetic device, presence of metal fragments in the eyes, brain or spinal cord, history of neurosurgery or aneurysm, and claustrophobia. Subsequently, 247 participants were excluded due to: MRI scans with poor technical quality (n=146), participants with a clinical diagnosis of dementia (n=7), stroke (n=39), or brain tumor (n=6) at baseline, or with no follow-up for dementia or stroke (n=49). Our final study sample consisted of 1,677 individuals with MRI data (both WMH and covert brain infarcts) who had at least one examination over the 12-year follow-up. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre. All participants provided written informed consent to participate in the study.
Outcomes

Stroke

At baseline individuals with reported hospitalization for stroke were excluded from the analysis. During follow-up participants were asked about the occurrence of interim stroke since baseline or since the last follow-up visit. Information on stroke symptoms and hospitalization was also obtained. For participants who reported a stroke or stroke symptoms, further medical reports from family physicians, specialists, emergency medical services, hospitalizations, and neuroimaging examinations were obtained. In case of fatal events, emergency medical services and hospital records were used and if unavailable, family physicians and family members were consulted. An incident stroke was defined as a new focal neurological deficit of sudden or rapid onset, of presumed vascular origin, that lasted 24 hours or more, or leading to death. An expert committee reviewed all available medical records and adjudicated diagnosis of stroke according to the criteria of the World Health Organization. A stroke event was regarded as fatal if the patient died within 28 days of onset of the stroke. Both fatal and non-fatal strokes were included.

Dementia

At baseline, participants were screened for incident dementia using criteria based on the Mini-Mental State Examination (MMSE), and the Isaacs’ Set Test of category/verbal fluency (IST). The IST is a test of verbal fluency and response rapidity and consists of generating words belonging to given semantic categories (e.g. animal names) in 15 seconds. This test has been reported to show the earliest decline in the decade preceding dementia diagnosis. Cut off scores were defined according to education level as previously described. Further data on cognitive functioning and daily activities, severity of cognitive disorders (Clinical Dementia Rating Scale), and where possible, hospitalization records and magnetic resonance
images were obtained and a provisional diagnosis was established.\textsuperscript{1} Functional assessment included questions about impairment of vision, hearing and movement. The Katz (activities of daily living),\textsuperscript{6} Lawton (instrumental activities of daily living)\textsuperscript{7} and Rosow and Breslau scales were used to assess disabilities.\textsuperscript{1,8} A final diagnosis of dementia was made based on all available information, by an independent panel of neurologists who reached a consensus on the diagnosis of dementia according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4\textsuperscript{th} Edition. Dementia classification as Alzheimer’s disease (AD) was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association.\textsuperscript{9} At follow-up, the cognitive examination included additional tests: a modified version of the Hachinski score,\textsuperscript{10} the Pasquier-Lebert\textsuperscript{11} and McKeith Scales,\textsuperscript{12} and the Clock Drawing test.\textsuperscript{1,13}

The screening method used in the 3C-Dijon study was derived from the previously validated PAQUID study.\textsuperscript{5} The sensitivity and specificity of the dementia diagnostic criteria used in the 3C-Dijon Study were estimated to be 87.5\% (95\% CI=86.5-88.5\%), and 78.8\% (95\% CI=77.9-19.7\%) respectively.\textsuperscript{1}
References


## Results

**Table.** Baseline characteristics of the study sample

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>No ext-WMHV</th>
<th>ext-WMHV</th>
<th>P</th>
<th>No BI</th>
<th>BI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1677</td>
<td>1257</td>
<td>420</td>
<td></td>
<td>1525</td>
<td>152</td>
<td></td>
</tr>
<tr>
<td>Age at MRI exam, years</td>
<td>72±4</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>1024 (61)</td>
<td>794 (63)</td>
<td>230 (54)</td>
<td>0.002</td>
<td>959 (62)</td>
<td>65 (42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low education level*</td>
<td>665 (39)</td>
<td>498 (39)</td>
<td>167 (39)</td>
<td>0.95</td>
<td>605 (39)</td>
<td>60 (39)</td>
<td>0.96</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>1281 (76)</td>
<td>922 (73)</td>
<td>359 (85)</td>
<td>&lt;0.001</td>
<td>1146 (75)</td>
<td>135 (89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia‡</td>
<td>948 (56)</td>
<td>721 (57)</td>
<td>227 (54)</td>
<td>0.30</td>
<td>868 (58)</td>
<td>80 (53)</td>
<td>0.31</td>
</tr>
<tr>
<td>Diabetes§</td>
<td>135 (8)</td>
<td>88 (7)</td>
<td>47 (11)</td>
<td>0.01</td>
<td>120 (8)</td>
<td>15 (10)</td>
<td>0.43</td>
</tr>
<tr>
<td>Current smoker</td>
<td>91 (5)</td>
<td>61 (4)</td>
<td>30 (7)</td>
<td>0.08</td>
<td>82 (5)</td>
<td>9 (6)</td>
<td>0.77</td>
</tr>
<tr>
<td>Prior CVDǁ</td>
<td>68 (4)</td>
<td>45 (3)</td>
<td>23 (5)</td>
<td>0.08</td>
<td>53 (3)</td>
<td>15 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APOE-ε4 carrier</td>
<td>334 (20)</td>
<td>261 (20)</td>
<td>73 (17)</td>
<td>0.16</td>
<td>307 (20)</td>
<td>27 (18)</td>
<td>0.44</td>
</tr>
<tr>
<td>WMHV(cm³)</td>
<td>5.5±5.1</td>
<td>3.4±1.3</td>
<td>11.5±6.8</td>
<td>&lt;0.001</td>
<td>5.2±4.8</td>
<td>7.9±6.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WMHV(ratio of TIV)</td>
<td>0.02±0.02</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>
<tr>
<td>Ext-WMHV</td>
<td>420(25)</td>
<td>-</td>
<td>-</td>
<td></td>
<td>344 (22)</td>
<td>76 (50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BI#</td>
<td>152 (9)</td>
<td>76 (6)</td>
<td>76 (18)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD or number (%)

*High school or less. †Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or use of blood pressure lowering medication. ‡Total cholesterol ≥6.2 mmol/L or use of lipid lowering medication. §Fasting blood glucose ≥7 mmol/L or use of antidiabetic medication. ¶History of myocardial infarction, angina pectoris, heart failure, or peripheral vascular disease. *121 lacunes. WMHV=white matter hyperintensity volume; Ext-WMHV=extensive white matter hyperintensity volume; TIV=total intracranial volume; BI=covert brain infarct.