Silent Brain Infarcts and White Matter Lesions Increase Stroke Risk in the General Population

The Rotterdam Scan Study

Sarah E. Vermeer, MD; Monika Hollander, MD; Ewoud J. van Dijk, MD; Albert Hofman, MD; Peter J. Koudstaal, MD; Monique M.B. Breteler, MD

Background and Purpose—Silent brain infarcts and white matter lesions are associated with an increased risk of subsequent stroke in minor stroke patients. In healthy elderly people, silent brain infarcts and white matter lesions are common, but little is known about their relevance. We examined the risk of stroke associated with these lesions in the general population.

Methods—The Rotterdam Scan Study is a population-based prospective cohort study among 1077 elderly people. The presence of silent brain infarcts and white matter lesions was scored on cerebral MRI scans obtained from 1995 to 1996. Participants were followed for stroke for on average 4.2 years. We estimated the risk of stroke in relation to presence of brain lesions with Cox proportional hazards regression analysis.

Results—Fifty-seven participants (6%) experienced a stroke during follow-up. Participants with silent brain infarcts had a 5 times higher stroke incidence than those without. The presence of silent brain infarcts increased the risk of stroke 3-fold, independently of other stroke risk factors (adjusted hazard ratio 3.9, 95% CI 2.3 to 6.8). People in the upper tertile of the white matter lesion distribution had an increased stroke risk compared with those in the lowest tertile (adjusted hazard ratio for periventricular lesions 4.7, 95% CI 2.0 to 11.2 and for subcortical lesions 3.6, 95% CI 1.4 to 9.2). Silent brain infarcts and severe white matter lesions increased the stroke risk independently of each other.

Conclusion—Elderly people with silent brain infarcts and white matter lesions are at a strongly increased risk of stroke, which could not be explained by the major stroke risk factors. (Stroke. 2003;34:1126-1129.)

Key Words: brain lesions ■ cerebral infarction ■ magnetic resonance imaging ■ population ■ stroke

Methods

Participants

The Rotterdam Scan Study was designed to study causes and consequences of brain changes in the elderly. In 1995 to 1996, we randomly selected participants aged 60 to 90 years in strata of age (5 years) and sex from two large ongoing population-based studies. A total of 1077 nondemented elderly people participated in our study (overall response 63%). The study design has been described in detail. The medical ethics committee of the Erasmus Medical Center approved the study and each participant gave informed consent.

Cerebral Infarcts and White Matter Lesions

All participants underwent MRI of the brain in 1995 to 1996. We made axial T1-, T2-weighted, and proton-density scans on 1.5 Tesla MRI scanners (MR Gyroscan, Philips, and MR VISION, Siemens). The slice thickness was 5 or 6 mm with an interslice gap of 20%. Infarcts were rated by a single rater (S.E.V.) and were defined as focal hyperintensities on T2-weighted images, 3 mm in size or larger. Proton-density scans were used to distinguish infarcts from dilated perivascular spaces. Lesions in the white matter also had to have a vascular origin and are frequently seen in neurologically asymptomatic elderly people. Little is known about the relevance of these lesions in the general population. Recently, a population-based study reported a 2-fold increased risk of stroke in elderly people with silent brain infarcts. We examined whether the presence of silent brain infarcts and white matter lesions increased the rate and risk of stroke in the general population. Furthermore, we quantified this relation and investigated if this was independent of the established stroke risk factors and of each other.
order to distinguish them from cerebral white matter lesions. Intrarater study (n=110) for detecting infarcts showed good agreement (κ=0.80). We obtained a history of stroke and transient ischemic attack (TIA) by self-report, and by checking medical records in all 1077 participants. An experienced neurologist (P.J.K.) subsequently reviewed the medical history and scans and categorized the infarcts as silent or symptomatic. We defined silent brain infarcts as evidence of 1 or more infarcts on MRI, without a history of a (corresponding) stroke or TIA. Participants with both symptomatic and silent infarcts were categorized in the symptomatic infarct group. Twenty participants with a confirmed history of stroke had no infarcts on MRI. Three of them experienced a hemorrhagic stroke; the 17 others with ischemic (n=12) or unspecified (n=5) stroke had minor symptoms. Participants with symptomatic infarcts on MRI (n=42, 16 of whose symptoms of a TIA corresponded to the infarct) and participants with a previous stroke without infarcts on MRI (n=20) were excluded from all analyses.

White matter lesions were considered present if visible as hyperintense on proton-density and T2-weighted images, without prominent hypointensity on T1-weighted scans. Two raters scored periventricular and subcortical white matter lesions separately. Periventricular white matter lesions were rated semiquantitatively (grade range 0 to 9). A total volume of subcortical white matter lesions was approximated based on number and size of lesions (volume range 0 to 29.5 mL). Both intrarater and interrater studies (n=100) showed a good to excellent agreement (κ=0.79 to 0.90, r=0.88 to 0.95).

Cardiovascular Risk Factors
We obtained the cardiovascular risk factors by interview and physical examination from 1995 to 1996. Blood pressure was measured twice on the right arm with a random-zero sphygmomanometer. We used the average of these 2 measurements. Participants were asked to bring all prescribed drugs to the research center, where a physician checked the use. Hypertension was defined as a systolic blood pressure of 140 mm Hg or over, or a diastolic blood pressure of 90 mm Hg or over, and/or the use of blood pressure-lowering medication. We considered diabetes mellitus to be present if the random glucose level was 11.1 mmol/L or higher, or if a person used antidiabetic medication. Serum total cholesterol was determined using an automated enzymatic procedure (Hitachi analyzer, Roche Diagnostics). Plasma total homocysteine levels were determined by fluorescence polarization immun assay on an IMx analyzer (Abbott Laboratories). The presence of atrial fibrillation was assessed by 12-lead ECG (ACTA ECG, ESAOTE). In 4 participants, ECG was missing. The intima-media thickness was measured by longitudinal 2-dimensional ultrasound of the carotid artery. We calculated the mean common carotid artery intima-media thickness as the mean of 4 locations: the near and far wall of both the right and left common carotid artery. Nineteen participants lacked the measurement of the common carotid intima-media thickness. A physician assessed participants’ smoking habits using a structured questionnaire and classified smoking status as current or not.

Follow-Up for Incident Stroke
In 1999 to 2000, we reinterviewed 787 of the participants that were alive about symptoms of stroke and TIA using a structured questionnaire (response rate 81%). In addition, we continuously monitored the medical records of all 1077 participants at the general practitioner’s office to obtain information on the occurrence of stroke since the last visit until January 1st, 2001. For all reported strokes, we recorded information about signs and symptoms, date of onset, duration, and hospital stay. If participants had been hospitalized for a stroke, we retrieved discharge letters and radiology reports from the hospital where they had been treated. By reviewing all available information, an experienced neurologist assessed the exact day of onset and classified the stroke. Stroke was defined as an episode of relevant focal deficits with acute onset, documented by neurological examination, and lasting for >24 hours. On the basis of radiological findings strokes were further subdivided into hemorrhagic or ischemic stroke subtypes. Follow-up was complete.

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of all Participants Who Were Free of Stroke and Symptomatic Infarcts on MRI at Baseline</th>
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<tbody>
<tr>
<td>All Participants (n=1015)</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Women</td>
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<td>Hypertension</td>
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<td>Mean intima-media thickness, mm</td>
</tr>
<tr>
<td>Current smoking</td>
</tr>
<tr>
<td>History of TIA</td>
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<tr>
<td>Presence of silent brain infarcts</td>
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<td>Periventricular white matter lesions, grade</td>
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<td>Subcortical white matter lesions, mL</td>
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Values are unadjusted mean±SD or no. of participants (percentages).

Data Analysis
We used the Kaplan-Meier method to estimate the rates of stroke. The follow-up time was calculated from the date the MRI scan was made until the date of stroke, death, or end of follow-up, whichever came first. We did Cox proportional hazards regression analysis to determine whether the presence of brain lesions on MRI was predictive of subsequent stroke, by estimation of its hazard ratio (HR) and 95% CI. Adjustments were made for age and sex, and for the established stroke risk factors hypertension, diabetes mellitus, atrial fibrillation, common carotid intima-media thickness, smoking, and history of TIA. Separate models were used for presence of silent brain infarcts, periventricular, and subcortical white matter lesions. For silent brain infarcts, no distinction was made between participants with 1 or more infarcts on MRI. We did a subanalysis to examine whether the risk of stroke was different between participants with >1 silent infarct and those with only 1 infarct on MRI, by comparing them both to participants without infarcts. The association with periventricular and subcortical white matter lesions was analyzed in tertiles of their distribution, and continuously if the relation was linear. Furthermore, we investigated whether silent brain infarcts and white matter lesions predicted future stroke independently of each other, by including them in one model. In addition, we repeated the above analyses after exclusion of participants with previous TIA without infarcts on MRI (n=33).

Results
The baseline characteristics of the study population are shown in Table 1. Fifty-seven participants (6%) experienced at least 1 stroke during 4260 person-years (mean follow-up 4.2 years). Six of these strokes were hemorrhagic, 42 ischemic, and in 9 the stroke subtype was unspecified. Thirty-one of these 57 participants (54%) had 1 or more silent brain infarcts present on MRI. They had more severe periventricular and subcortical white matter lesions.

The 4-year mortality was 7% (95% CI 6% to 9%). The overall stroke rate was 11 per 1000 person years (95% CI 8 to 15). Thirty-one of the 217 participants (14.3%) with silent brain infarcts developed a stroke during an average follow-up of 4.2 years. The absolute risk of developing stroke within 4 years was 11.7% for participants with silent brain infarcts and 2.3% for those without. This absolute risk was 5.0 times higher (95% CI 2.7 to 9.2) for participants with 1 or more silent brain infarcts on MRI compared with the ones without, both for participants younger and older than 75 years of age (Figure 1). There were no
statistically significant differences in stroke risk between men and women (absolute risk of developing stroke within 4 years: 4.9% for men and 3.7% for women).

The presence of silent brain infarcts more than tripled the risk of stroke after adjustment for the established stroke risk factors (Table 2). Participants with >1 silent infarct (n=76) had a higher stroke risk than those with only 1 infarct on MRI (n=141), although these risk estimates were not significantly different (age- and sex-adjusted HR 4.9, 95% CI 2.5 to 9.4, and 2.8, 95% CI 1.5 to 5.3, respectively). Both participants in the upper tertile of the distribution of periventricular white matter lesions (n=291) and subcortical white matter lesions (n=336) had an increased stroke risk, independent of other stroke risk factors (Table 2). Additional adjustment for blood pressure levels did not change the results (HR for silent brain infarcts 3.5, 95% CI 2.0 to 6.0; for the upper tertile of periventricular white matter lesions 4.5, 95% CI 1.9 to 10.7, and for the upper tertile of subcortical white matter lesions 3.5, 95% CI 1.4 to 8.6), nor did adjustment for the duration of hypertension or diabetes mellitus (data not shown). There was no interaction between hypertension and silent brain infarcts for the risk of stroke. When silent brain infarcts, tertiles of periventricular, and subcortical white matter lesions were all included in the same model, the associations with stroke risk remained for silent brain infarcts, but diminished for periventricular and especially subcortical white matter lesions. For subcortical white matter lesions, the risk of stroke did not increase linearly. The largest risk difference was between no and very small volumes of subcortical white matter lesions (0.05 mL). With larger volumes the stroke risk only marginally increased further. The relationship between periventricular white matter lesions and the risk of stroke was linear, and remained after adjustment for stroke risk factors (adjusted HR per grade increase of periventricular lesions 1.36, 95% CI 1.20 to 1.54) and after additional adjustment for silent brain infarcts and subcortical white matter lesions (adjusted HR 1.27, 95% CI 1.10 to 1.47). Results of above analyses were similar after exclusion of participants with previous TIA (data not shown). Additional adjustment for the less established stroke risk factors homocysteine and cholesterol levels did not change any of the associations (data not shown).

Discussion

We found that elderly people with silent brain infarcts have a >3-fold–increased risk of stroke, compared with those without infarcts on MRI in the general population. The presence of more severe white matter lesions also increased stroke risk. This was independent of other established stroke risk factors and of each other.

The strengths of this study are the large number of participating elderly people and its population-based design. Furthermore, we had no losses to follow-up, and therefore no selection bias. A potential methodological limitation of our study is misclassification. Despite good agreement, we may have systematically over- or underrated infarcts or white matter lesions on MRI. We do not have pathological verification of the lesions seen on MRI. Furthermore, infarcts may have been erroneously classified as

| TABLE 2. Relationship Between the Presence of Silent Brain Infarcts, Tertiles of Periventricular, and Subcortical White Matter Lesions (WML) on MRI and the Risk of Stroke |
|-----------------|-----------------|-----------------|-----------------|
|                  | Risk of Stroke (Hazard Ratio [95% CI]) | Adjusted for Age and Sex | Adjusted for Stroke Risk Factors* | Adjusted for MRI Lesions† |
| Silent brain infarcts |                  |                  |                  |
| Absent           | 1 (reference)   | 1 (reference)   | 1 (reference)   |
| Present          | 3.6 (2.1–6.1)   | 3.9 (2.3–6.8)   | 3.3 (1.8–5.9)   |
| Periventricular WML |                 |                  |                  |
| 1st tertile (grade 0–1.0) | 1 (reference) | 1 (reference) | 1 (reference) |
| 2nd tertile (grade 1.5–3.0) | 2.5 (1.0–6.3)  | 2.5 (1.0–6.2)  | 2.0 (0.8–5.3)  |
| 3rd tertile (grade 3.5–9.0) | 4.7 (2.0–11.2) | 4.7 (2.0–11.2) | 2.8 (1.0–7.6) |
| Subcortical WML |                 |                  |                  |
| 1st tertile (0.0–0.05 mL) | 1 (reference) | 1 (reference) | 1 (reference) |
| 2nd tertile (0.05–0.6 mL) | 2.2 (0.8–5.7)  | 2.3 (0.9–6.1)  | 1.4 (0.5–4.0)  |
| 3rd tertile (0.6–29.5 mL) | 3.7 (1.5–9.1)  | 3.6 (1.4–9.2)  | 1.4 (0.5–4.0) |

*Age, sex, hypertension, diabetes mellitus, atrial fibrillation, mean intima-media thickness, smoking, and history of TIA; †Adjusted for stroke risk factors and additionally for the presence of silent brain infarcts and tertiles of periventricular and subcortical white matter lesions.
silent or symptomatic. Both the readers who identified white matter lesions and infarcts and the neurologist who classified infarcts into silent or symptomatic were blinded to all other data. Misclassification may also have occurred in the identification of strokes during follow-up. People probably underreport symptoms of TIA and minor stroke, which will have resulted in an underestimation of the true number of events. But because we obtained information about these events both by self-report and from medical records, without knowledge of baseline MRI findings, it is unlikely that this has introduced a major bias in our study. If anything, this nondifferential misclassification will have resulted in an attenuation of the relation.

We report a >3-fold–increased risk of stroke in elderly people with silent brain infarcts on MRI in the general population. This is in line with the finding of the Cardiovascular Health Study, the only other population-based study that examined this relationship.\textsuperscript{10} This study also observed that people defined as having white matter lesions by cluster analysis had a higher risk of stroke.\textsuperscript{17} We extended this finding and found that more severe white matter lesions, both periventricular and subcortical located, also increased the risk of stroke. A Japanese study of healthy volunteers found an increased stroke risk when silent brain infarcts and white matter lesions were present on MRI, but this study was based on adults who wished to receive health screening at their own expense and it obtained information about 19 incident strokes by self-report only.\textsuperscript{18} Unfortunately, numbers were too small in our study to do separate analyses for stroke subtypes.

Both silent brain infarcts, of which the majority are lacunar infarcts,\textsuperscript{6,9} and white matter lesions reflect mainly small-vessel disease. We showed however that the increased stroke risk with the presence of silent infarcts and white matter lesions remained after adjustment for cardiovascular risk factors. These risk factors did not explain the effect of silent brain infarcts and white matter lesions on stroke risk. There may be residual confounding by the way we adjusted for these stroke risk factors, because we could not account totally for duration and severity of exposure. However, we do not think it will dispel the strong risk increase of stroke by the presence of silent brain infarcts and white matter lesions. This suggests that silent brain infarcts and white matter lesions are not just intermediates in the relation of vascular risk factors and the risk of stroke, but that these lesions might be markers for other, yet unknown, factors that lead to symptomatic stroke.

In conclusion, we found that elderly people with silent brain infarcts and white matter lesions from the general population are at a high risk of stroke. The major stroke risk factors seemed to account for only part of this increased stroke risk. Because the clinical relevance of these lesions was long unknown, no special treatment regimen has been developed for these people. The stroke risk for people with silent brain infarcts is comparable with the risk of TIA patients, of whom approximately 20% develop stroke within 4 years. Further research will have to show if treatment of these people, comparable to the treatment regimen for people with TIA, effectively prevents stroke.

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