Leukoaraiosis and Increased Cerebral Susceptibility to Ischemia: Lack of Confounding by Carotid Disease

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Background—Leukoaraiosis is associated with an increased risk of stroke, but the underlying mechanism remains uncertain, as do the associations with other risk factors, such as carotid disease. We aimed to determine the role of carotid disease and of other clinical variables in the development of leukoaraiosis and to define their contributions to the associated increased risk of stroke.

Methods and Results—We prospectively studied a large cohort of consecutive patients with transient ischemic attack (TIA) and minor stroke who attended a TIA clinic between 2002 and 2009. Detailed clinical data were obtained, and patients underwent magnetic resonance brain and vascular imaging. We assessed the severity of leukoaraiosis with use of the ARWMC (Age Related White Matter Changes) score: 671 patients (374 [56%] men; mean [SD] age 71 [11] years) were studied, of whom 415 (62%) had leukoaraiosis. In a multivariate analysis, leukoaraiosis was associated with increasing age ($P<0.0001$) and hypertension ($P=0.01$), as well as the presence of acute ($P<0.0001$) and chronic ($P=0.014$) infarction on magnetic resonance imaging. In the univariate analysis, a current and past diagnosis of stroke versus TIA also showed a strong association. Carotid disease was not associated with leukoaraiosis, even in the presence of a flow-limiting (>70%) stenosis or occlusion, and the risk factor profiles for leukoaraiosis and carotid disease differed.

Conclusions—The association with more severe ischemic events (stroke versus TIA) and infarction on imaging is consistent with leukoaraiosis being a marker of increased cerebral susceptibility to ischemia. In contrast, the presence, severity of, and risk factors for atheromatous disease showed no association with leukoaraiosis, suggesting that these are two unrelated disease processes. (J Am Heart Assoc. 2013;2:e000261 doi: 10.1161/JAHA.113.000261)

Key Words: leukoaraiosis • MRI • stroke

Leukoaraiosis is associated with an increased risk of stroke, and stroke outcome in patients with leukoaraiosis is poor. However, the pathophysiology of leukoaraiosis remains incompletely understood, and the mechanism of the increased stroke risk is uncertain.

Atheromatous disease of the carotid arteries is associated with a high risk of stroke, and it may also have a role in the development of leukoaraiosis, although this remains controversial. There are two ways in which carotid atheroma may be associated with leukoaraiosis. First, the presence of carotid atheroma may indicate more widespread atheromatous changes and increased arterial stiffness, both potentially affecting the small penetrating arteries and arterioles of the brain. Second, severe carotid disease may cause cerebral hypoperfusion. Chronic hypoperfusion is thought to be important in the aetiology of leukoaraiosis and, by reducing vascular reserve, may also increase the risk of stroke.

Our aim was to determine the role of carotid disease and of other clinical variables in the development of leukoaraiosis and to define their contribution to the associated increased risk of stroke. We prospectively studied a large cohort of consecutive patients with TIA and minor stroke, who had all undergone magnetic resonance (MR) imaging of the brain and related the presence and severity of leukoaraiosis to multiple clinical factors, in particular the presence of carotid stenosis.

Methods

We prospectively studied consecutive patients referred to a hospital-based neurovascular clinic between 2002 and 2009. All patients were assessed by a trained neurologist and diagnosed with a TIA or stroke defined according to World Health Organization criteria. All patients included in the
data were analyzed as categorical or continuous variables as appropriate. We tested categorical variables with the Pearson χ² test for heterogeneity across groups of different degrees of disease severity and with the χ² for trend (P trend) to detect a potential association with increasing disease severity. For continuous variables, we performed an ANOVA to test for heterogeneity and trend, respectively. For variables associated at the P<0.05 significance level in the univariate analysis across categories, we performed a stepwise backward multiple logistic regression analysis comparing patients with no disease (lowest quartile of the ARWMC score) versus patients with at least some leukoaraiosis (ie, the other 3 categories combined). To study the association between leukoaraiosis and flow-limiting carotid disease, we compared ARWMC scores between patients with and without carotid stenosis >70% or carotid occlusion with the independent-samples median test. We assessed interobserver agreement with the κ statistic for the category assignments for the ARWMC score by the 2 observers.

**Results**

Over the study period, 1191 patients attended the clinic. Of those, 469 were excluded because they were considered not to have had a cerebrovascular event, and 51 were excluded because of refusal, or because of contraindications to MR imaging. Of the 671 remaining patients [374 (56%) men; mean [SD] age 71 [11] years), 301 (45%) were diagnosed with a transient ischemic attack (TIA) and 370 (55%) with a stroke. Leukoaraiosis of at least a mild degree was present in 415 (62%) patients. Interobserver agreement for assessing the severity of leukoaraiosis was very good with a κ value of 0.82 (95% CI 0.78 to 0.85, P<0.0001). Eighty-five (12.6%) patients did not undergo carotid imaging (possible vascular intervention not felt to be appropriate or refused). Mean age (71 [11] versus 73 [12] years, P=0.08) and the presence of leukoaraiosis (61% versus 68%, P=0.2) did not differ significantly between patients who had or had not undergone carotid imaging, respectively. Otherwise, data collection was near complete, with <1% missing data for vascular risk factors, and complete clinical and brain imaging data.

Table 1 shows the prevalence of clinical baseline variables, vascular risk factors, and their association with leukoaraiosis in the univariate analysis. We confirmed the well-known association of leukoaraiosis with increasing age (P=0.0001) and with a history of hypertension (P=0.003). Women were more likely to have severe leukoaraiosis than were men, but this may have been due to confounding by age, as women in this cohort were older than men (mean [SD] age=72.5 [11.3] versus 70.1 [11.5] years, P=0.008). Furthermore, increasing severity of leukoaraiosis was associated with a current diagnosis of stroke versus TIA (P=0.008), a history of previous
stroke ($P=0.03$) but not previous TIA ($P=0.56$), and imaging markers of focal ischemic damage, such as acute infarction on DWI ($P<0.0001$) and chronic infarction on T2-weighted imaging ($P<0.0001$). In the multivariate analysis, only age, hypertension, acute and chronic infarction, and the presence of lacunar infarction on MR imaging remained associated with the presence of leukoaraiosis (Table 2). While the association with stroke versus TIA was no longer significant in the multivariate analysis, the clinical presentation was strongly correlated with infarct presence on imaging. Presence of acute infarction on DWI was much more common in patients with stroke versus TIA (OR 5.43, 95% CI 3.90 to 7.58, $P<0.0001$) and presence of chronic infarction was associated with a history of previous stroke (OR 5.92, 95% CI 2.67 to 13.16, $P<0.0001$) but not previous TIA (OR 1.20, 95% CI 0.72 to 2.01, $P=0.49$). Hypertension was associated with a diagnosis of previous ($P<0.0001$) and current stroke ($P=0.02$) and with chronic ($P=0.04$) infarction on MR imaging, as well as showing a borderline association with lesion presence on DWI ($P=0.07$). There was no significant age

| Characteristic | OR (95% CI) | $P$ Value |
|----------------|------------|-----------|
| Age (per decade) | 2.34 (1.95 to 2.81) | $<0.0001$ |
| History of hypertension | 1.74 (1.20 to 2.52) | 0.006 |
| Acute infarct on DWI | 2.72 (1.80 to 4.12) | $<0.0001$ |
| Chronic infarct on T2 | 1.93 (1.12 to 3.31) | 0.03 |
| Any lacunar infarction | 3.27 (1.68 to 6.38) | 0.001 |

Variables included were those showing an association at the 0.05 significance level in the univariate analyses: age, sex, hypertension, diagnosis stroke, previous stroke, acute infarct on DWI, chronic infarct on T2, lacunar infarct on DWI and peripheral vascular disease. DWI indicates diffusion-weighted sequence; ARWMC, Age Related White Matter Changes.
difference between patients with and without a history of hypertension (mean [SD] age=71.7 [10.9] versus 70.3 [12.2] years, \( P=0.12 \)), with and without a past history of stroke (mean [SD] age=71.6 [11.8] versus 71.1 [11.4] years, \( P=0.76 \)) or a current diagnosis of stroke versus TIA (mean [SD] age=71.6 [11.4] versus 70.6 [11.6] years, \( P=0.28 \)). However, patients with acute and chronic infarction on MR imaging were significantly older than those without any infarcts (mean [SD] age=73.0 [10.8] versus 69.3 [11.8] years, \( P<0.0001 \)) and (mean [SD] age=72.6 [10.7] versus 68.8 [12.1] years, \( P<0.0001 \)), respectively.

The presence of carotid stenosis \( \geq 50\% \) showed no association with leukoaraiosis. Table 3 shows the risk factor associations for carotid disease, defined as the presence of at least one carotid artery stenosis of \( \geq 50\% \) and compares them with the risk factor associations for leukoaraiosis. Risk factor associations differed. Whereas smoking and ischemic heart disease were associated with carotid disease, they showed no association with leukoaraiosis, and the risk factor associations for leukoaraiosis (female sex, increasing age, hypertension, and current stroke) showed no association with carotid atheroma.

To determine if leukoaraiosis was more severe distal to a flow-limiting stenosis, we compared ARWMC scores in both hemispheres in patients who had unilateral \( \geq 70\% \) stenosis or occlusion and no significant contralateral disease (stenosis <50%), and we also compared patients with bilateral carotid stenosis \( \geq 70\% \) with patients with no significant stenosis (Table 4). ARWMC scores did not differ significantly distal to a flow-limiting stenosis compared with patients with no or mild disease only.

### Table 3. Risk Factors for Carotid Disease (Presence of Carotid Stenosis \( \geq 50\% \)) and for Leukoaraiosis

| Risk Factor            | Carotid Disease | Leukoaraiosis |
|------------------------|-----------------|---------------|
|                        | OR (95% CI)     | \( P \) Value | \( P \) Value |
| Female sex             | 0.68 (0.42 to 1.07) | 0.10          | 0.002         |
| Mean (SD) age, y       |                 |               |
| Absent: 70.9 (11.5)    | 0.83            | <0.0001       |
| Present: 70.6 (11.9)   |                 |               |
| Hypertension           | 1.27 (0.80 to 2.03) | 0.31          | 0.002         |
| Current diagnosis of stroke | 1.13 (0.72 to 1.77) | 0.60          | 0.004         |
| Lesion on DWI          | 1.27 (0.81 to 2.00) | 0.30          | <0.0001       |
| Previous stroke        | 1.81 (0.95 to 3.45) | 0.07          | 0.12          |
| Smoking                | 1.87 (1.13 to 3.10) | 0.015         | 0.09          |
| Ischemic Heart Disease | 2.21 (1.32 to 3.68) | 0.002         | 0.50          |
| Peripheral Vascular Disease | 2.11 (0.86 to 5.16) | 0.10          | 0.06          |
| High cholesterol       | 0.93 (0.55 to 1.54) | 0.77          | 0.60          |
| Previous TIA           | 1.48 (0.79 to 2.80) | 0.23          | 0.64          |
| Diabetes               | 0.84 (0.44 to 1.61) | 0.71          | 0.40          |

For categorical variables, the unadjusted ORs (95% CIs) for a risk factor being present vs absent in patients with \( \geq 50\% \) stenosis vs <50% stenosis are shown. Mean (SD) age did not differ significantly between patients with and without carotid disease. For leukoaraiosis, the \( P \) values for trend across the quartiles of increasing disease severity are shown. The same analyses as shown in Table 1 were performed, but only including the patients in whom carotid imaging was available. DWI indicates diffusion-weighted sequence; TIA, transient ischemic attack. Numbers in italics show associations significant at the \( P<0.05 \) level.
vulnerability to ischemia may be due to reduced vascular reserve. However, if chronic hypoperfusion was the sole contributing factor, we would expect leukoaraiosis to be more severe distal to flow-limiting arterial occlusive disease. In our cohort, severe carotid atheroma was unrelated to the presence of leukoaraiosis. While these data are limited by lack of information about the presence of collateral flow, several other recent studies also found no association of leukoaraiosis with carotid disease.6,8,21 and with collateral supply.22 Hypoperfusion alone, at least when caused by large vessel occlusion, does not appear to contribute to leukoaraiosis. Alternatively, any damaging effect of hypoperfusion might be offset by an opposite effect of the stenosis protecting the small vessels from the damaging effects of hypertension, with no overall change.

In this study, leukoaraiosis was unrelated to atheromatous disease in the carotid and other circulations, and the risk factor profiles for leukoaraiosis and carotid disease differed. While it has been suggested that leukoaraiosis may at least partly be caused by atheroma of the small penetrating arteries, the complete lack of association between leukoaraiosis and the presence of atheroma and its risk factors in our study and others21 suggest that atheroma plays little role in the pathogenesis of leukoaraiosis. In contrast, two big population-based studies found an association between leukoaraiosis, carotid intima-media thickness, and carotid plaque, although the findings of the studies differed to some extent, in that in the Rotterdam Scan Study,9 carotid plaque was associated with periventricular white matter lesions and not with subcortical white matter lesions, whereas in the Cardiovascular Health Study (CHS),10 these associations were reversed. As these studies were population based, the prevalence of carotid stenosis >50% was low (5.4% in the CHS and 1.4% in the Rotterdam Study), and the studies concentrated much more on the early stages of atheroma, whereas our cohort consisted of patients with already established cerebrovascular disease. Some risk factors, such as increasing age or hypertension, will contribute to large and to small vessel damage and may explain the association between early atheroma and leukoaraiosis described in these two studies. Additional risk factors, such as smoking or genetic factors, may be required to lead to more severe atheromatous disease, explaining the differences in risk factor profiles between patients with ≥50% carotid stenosis and leukoaraiosis in our study.

In this study and others,23–26 there was a strong association of leukoaraiosis with lacunar infarction, which suggests that these are two manifestations of a shared underlying aetiology. Most commonly, this is likely to be due to small vessel changes associated with hypertension and increasing age, as further discussed later. However, there are also other disease processes that cause leukoaraiosis and lacunar infarcts,24 such as cerebral amyloid angiopathy25 and CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukencephalopathy).26 There are several explanations why a small vessel vasculopathy may cause both leukoaraiosis and focal infarction. They may be different degrees of severity of the same process; leukoaraiosis may increase the susceptibility to developing infarction; or infarcts may contribute to the appearance of leukoaraiosis, with the distinction between leukoaraiosis and infarction being less clear than previously thought.24

Hypertension is the most consistently reported modifiable risk factor for leukoaraiosis1 and showed a strong association in our cohort. Similar to leukoaraiosis, it was associated with a past and current diagnosis of stroke versus TIA and with infarction on MR imaging. Indeed, adjusting for hypertension in the multivariate analysis reduced the strength of the association of leukoaraiosis with past and current stroke. Our

| Table 4. Lack of Association Between Flow-limiting Carotid Stenosis and Severity of Leukoaraiosis |
|-----------------------------------------------|
| **Within Patient Comparison**                  |
| Right ICA | Left ICA | Right ARWMC | Left ARWMC | No. of Patients | P-het         |
| ≥70%      | No stenosis | 1 [0 to 2] | 1 [0 to 2] | 20             | 0.99          |
| 100%      | No stenosis | 1 [0 to 3.5] | 1 [0 to 3.5] | 4             | 0.99          |
| <50%      | ≥70%      | 1 [0 to 3] | 1 [0 to 2] | 33             | 0.36          |
| <50%      | 100>      | 0 [0 to 1.75] | 0 [0 to 1.75] | 8             | 0.99          |

| Between Patient Comparison                     |
|-----------------------------------------------|
| Bilateral ≥70% stenosis | No. of Patients | Total ARWMC | P-het |
| Bilateral <50% stenosis | 6         | 6 [Q1R 0 to 18; range 0 to 18] | 0.15   |
| Bilateral <50% stenosis | 496       | 2 [Q1R 0 to 6; range 0 to 18] | 0.15   |

The within-patient comparison shows the median (interquartile range [IQR]) ARWMC (Age Related White Matter Changes) score for each hemisphere in patients with unilateral ≥70% carotid stenosis or occlusion, and no significant disease (<50%) in the contralateral artery. Between-patient comparison shows total ARWMC scores for patients with bilateral ≥70% carotid stenosis vs patients with no carotid atheroma. P-het indicates P for heterogeneity, the comparison was performed with the independent samples median test; ICA, internal carotid artery.
findings indicate that hypertension plays an important role in increasing cerebral susceptibility to ischemia. This is further supported by animal studies, in which the same ischemic stimulus led to bigger infarcts in hypertensive versus normotensive rats, and human studies, in which acute infarct growth was bigger in hypertensive patients. Possible mechanisms by which hypertension may increase susceptibility to ischemia include the release of vasoactive substances, which lead to changes in vascular tone, reduced cerebral autoregulation, and subsequently increased vulnerability to reductions in perfusion pressure. Furthermore, cytokine release may render the endothelium more procoagulant, and hypertension may cause longer-term changes in arteriolar wall thickness and reduction in lumen, with subsequently reduced blood flow. Of course, the latter mechanism is also thought to cause leukoaraiosis.

Increasing age is widely accepted as the most important risk factor for leukoaraiosis, and was strongly associated in our cohort. While it showed no association with past and current stroke, patients with infarction on imaging were significantly older than those without, perhaps indicating that increasing age also increases cerebral susceptibility to ischemia. This has been suggested previously by a study that found greater conversion of “tissue at risk” to infarction in older patients with acute stroke. Older age leads to a number of changes that could increase cerebral susceptibility to ischemia, such as reduced capillary lumen diameter, increased vascular tortuosity, thickening of vessel walls, and impairment in cerebral autoregulation. Some of these changes appear to be very similar to those caused by hypertension.

While we believe our findings to be valid, this study has several potential limitations. First, we used the ARWMC score rather than volumetric analysis to grade the severity of leukoaraiosis. Visual rating scales can make comparison between studies difficult if different scales are used; they depend on the expertise of the rater, and they may not detect small changes in disease severity in follow-up studies. In contrast, volumetric analysis may be more sensitive to detecting small changes in lesion load. By using the now well-established ARWMC score we aimed to make our study comparable to others. Interrater agreement was high, supporting the validity of the readings, and it is uncertain if a volumetric analysis would have been more accurate or meaningful, in particular as it is also subject to rater experience. We believe that the visual semiquantitative ARWMC score helped to identify relevant differences between scans and offered the most robust analysis. Second, our imaging sequence did not include any T1-weighted imaging, which can help to differentiate focal infarction from the lesions of leukoaraiosis. However, most studies of leukoaraiosis are based on T2-weighted imaging alone, and differentiating a focal infarct from leukoaraiosis may not always be possible even with T1-weighted imaging. Third, not all patients had carotid imaging, as this was only done when thought to be of therapeutic consequence. However, risk factors and severity of leukoaraiosis did not differ significantly between patients with and without carotid imaging, and we do not think that this introduced any bias to the results. Fourth, the proportion of patients with severe carotid disease in this cohort was low, perhaps making it difficult to detect any association between leukoaraiosis and carotid stenosis. We therefore performed multiple different analyses, which all consistently showed no association. While this does not eliminate the low patient numbers, we believe that the consistent results, and previous similar reports in other studies, support the validity of our findings.

Conclusion
In this large cohort of patients with established cerebrovascular disease, neither the presence or severity of atheromatous disease, nor the presence of risk factors for atheroma were associated with leukoaraiosis, suggesting that these are two unrelated disease processes. In contrast, increasing age and hypertension were strongly associated, as were past and current stroke, and infarct presence on imaging. Our findings suggest that leukoaraiosis represents the visible structural damage caused by age, hypertension, and potentially other factors and that these changes indicate that the brain is more vulnerable to ischemic damage. Leukoaraiosis is not a classic risk factor for stroke. However, it is a marker of increased cerebral susceptibility to ischemia, and this makes it more likely that, if the brain is exposed an acute ischemic challenge, infarction will develop and clinically the patient will have a stroke.

Sources of Funding
Dr Schulz was funded by a National Institute for Health Research (NIHR) Clinician Scientist Fellowship.

Disclosures
None.

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