Leukoaraiosis
An Independent Risk Factor for Stroke?
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Background—Leukoaraiosis, a term that defines an abnormal appearance of the subcortical white matter of the brain on neuroimaging (bilateral patchy or diffuse areas of low attenuation on CT or hyperintense T2 MR areas), has gained evidence in retrospective studies to demonstrate its association with stroke and in prospective studies to demonstrate its prognostic value related to the occurrence of stroke, both ischemic and hemorrhagic, or the occurrence of vascular death.

Summary of Review—The subtype of ischemic stroke most strongly predicted by leukoaraiosis is lacunar infarct, which is likely caused by the same underlying small-vessel pathology. Leukoaraiosis has been shown to predispose to intracerebral hemorrhage at both the basal-ganglionic and lobar sites, primarily when leukoaraiosis is extensive and patients are treated with anticoagulants because of prior ischemic events.

Conclusions—Leukoaraiosis shares with stroke common pathophysiological mechanisms and, because it is likely an expression of the same disease, must be regarded as an intermediate surrogate of stroke rather than a true stroke risk factor. (Stroke. 2003;34:2067-2071.)

Key Words: leukoaraiosis ■ risk factors ■ stroke

In 1987, Hachinski and coworkers used the term leukoaraiosis (LA) (from the Greek: leuko=white; araiosis=rarefaction) to describe an abnormal CT appearance of the subcortical brain white matter, seen as bilateral patchy or diffuse areas of reduced x-ray attenuation with ill-defined margins, limited to the periventricular regions or extended to the centrum semiovale (Figure 1). On T2 or fluid-attenuated inversion recovery (FLAIR) MRI sequences, LA appears as hyperintense periventricular caps or rims or halos or subcortical multiple punctuate or patchy, partially confluent or confluent areas. The degree of these changes is variable. Examples of MRI-disclosed LA of increasing severity are shown in Figure 2. On the basis of multiple findings, including some recent observations using MRI perfusion, these changes are likely ischemic in nature and are caused by hypoperfusion in the distal deep arterial or arteriolar territories. Lipohyalinosis (arteriolosclerosis), produced by chronic hypertension with or without diabetes, also related to lacunar infarction (LI) and intracerebral hemorrhage (ICH), is thought to be the hallmark pathological process altering small vessels. Pontine hyperintense lesions, usually combined with hemispheric LA, have been reported as a LA subtype, possibly produced through the same mechanisms. LA may also be caused by cerebral amyloid angiopathy (CAA) or cerebral autosomal dominant arteriopathy stroke and ischemic leukoencephalopathy (CADASIL).

Evidence is being accumulated to document that the presence of LA is associated with a history of stroke and also predicts the future occurrence of either ischemic or hemorrhagic stroke. The aim of this article is to review the evidence on the risk of stroke among patients presenting with LA and to discuss whether LA should be considered more properly a stroke risk factor or an intermediate surrogate of stroke. Despite the controversy regarding whether the term LA, which was originally applied to CT changes, can be used to indicate the correspondent MRI changes, since the evidence about LA and stroke is derived primarily from CT studies, and because the studies based on MRI have predominantly utilized the term LA, I will use this term to indicate both CT and MRI changes.

LA as a Predictor of Ischemic Stroke or Vascular Death
Between the first anecdotal reports of such images in the late 1970s and the seminal articles accompanying the proposition of the term in the mid 1980s, LA was claimed to be the in vivo documentation of Binswanger’s disease, a rare form of dementia with a vascular basis linked to the pathological presentation termed subcortical arteriosclerotic encephalopathy. A few pathological studies had shown the main features to be similar to the following changes: myelin degeneration, proliferative astroglialosis, thickening with hyaline changes, and fibrosis of the wall of small deep vessels, with coexisting cavitated or noncavitated small deep infarcts. After the diffusion of CT imaging, cases with such changes began to be more frequently reported in the literature. In these early clinical-radiological reports, clinical
characteristics included arterial hypertension as the main risk factor, dementia, and focal signs possibly consequent to the ischemic events.

In 1985, within the framework of a dementia study assessing patients systematically for risk factors, clinical characteristics, and CT changes, 140 demented patients were compared retrospectively with 110 nondemented controls to identify vascular factors predicting LA. Arterial hypertension was expected to be the main factor associated with LA. In contrast, on analysis with the use of a regression model, history of stroke was found to be the most important single predictor of LA, independent of any other kind of stroke risk factor. Hypertension had a predictive effect on LA only when combined with the presence of an infarct on brain CT scan, which in two thirds of cases had the aspect of a LI. Dementia was not independently associated with LA; the higher prevalence of LA among demented patients was explained primarily by a previous history of stroke. This was the first study demonstrating a statistically valid association between stroke and LA. The additional information on the specific stroke type (especially LI) led to the hypothesis that the association was due to the small-vessel pathology likely inherent in both types of lesions.

The association of LA with stroke, particularly the LI type, was confirmed by several subsequent cross-sectional clinical-radiological studies (for a complete review, see Leys et al [1999]). One study, performed in a large series of patients admitted to a Danish stroke unit, denied any relationship between LA and stroke. This may be explained by the fact that in this study no discrimination was made between different infarct types, so that cortical infarct may have acted as a negative modifier of the association between LA and stroke. Retrospective studies that have not found any selective association with a specific stroke type are quite uncommon. Pontine LA, examined across groups of patients with symptomatic, differently located, atherosclerotic lesions, was shown to be associated more closely with stroke, especially LI, than with myocardial infarction or peripheral artery disease.

Prospective observations further corroborated the relationship between LA and stroke and the distinct role of LI. The presence of LA on CT scan predicted subsequent stroke in patients with first-ever lacunar stroke, in those with lacunar or cortical infarction, in elderly patients with gait problems and LA on CT scan, and in patients with lacunar stroke or trivial neurological symptoms. Recurrent stroke was predominantly of the lacunar type. When studies took into account the severity of LA, the risk of recurrence proved to be proportional to the extent of LA.

Since LA is often combined with images of symptomatic or silent LI, it was always difficult to separate the effect of these 2 abnormalities on the risk of subsequent stroke, even with adjustment by multivariate modeling. Lipohyalinosis, microatheroma, and, to a lesser extent, microembolism are considered the main causes of LI. At the occurrence of the first clinical lacunar stroke event, it has been observed that when multiple (silent) lacunes are seen on imaging, both arterial hypertension and LA are more frequent than when a single (the only symptomatic) lacunar lesion is identified, suggesting that lipohyalinosis in the former case and microatheroma in the latter case might be selectively involved. In a longitudinal observation of 333 patients with a first-ever lacunar stroke, mortality was >1.5-fold higher (odds ratio [OR], 1.74; 95% CI, 1.01 to 3.01) and the stroke recurrence rate was 2-fold higher (OR, 2.09; 95% CI, 1.08 to 4.06) among the 104 patients with multiple silent lesions than among the 229 patients with a single lesion. ICH occurred almost exclusively in the first group, in which the chance of hemorrhage was increased 7-fold. Compared with the patients with a single lacunar lesion, the 63 patients who, in addition to multiple silent lesions, also had LA had an even higher (OR, 3.17; 95% CI, 1.48 to 6.81) risk of stroke recurrence, showed greater disability after recurrent stroke, and had an increased risk of dying.

In all the studies hitherto described, cortical territorial infarct was largely less probable than lacunar or hemorrhagic stroke as recurrent stroke. The main causes of cortical infarcts are large-artery disease and cardioembolism. In regard to the first mechanism, while cross-sectional data from the patients randomized in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) showed an inverse relationship between the degree of carotid stenosis and presence
of LA, a few population studies have consistently reported an association between intima-media thickness or the presence of carotid plaques and white matter hyperintensities on MRI, even after adjustment for other vascular risk factors.\textsuperscript{23-25} Atrial fibrillation, a major cause of cardioembolic stroke, was found to be negatively associated with LA in 1 study\textsuperscript{12} and positively associated in 2 other studies.\textsuperscript{26,27} These conflicting results are likely justified by the variable impact of age and other age-related vascular risk factors as confounders for these associations.

An important piece of evidence about LA as a determinant of ischemic stroke was provided by a few randomized clinical trials. Among the 3017 patients with transient ischemic attack (TIA) or minor stroke entered into the Dutch TIA Trial,\textsuperscript{28,29} the 337 patients with LA on entry CT scan compared with the 2680 patients without LA had a 2-fold (15\% versus 8\%; hazard ratio [HR], 2.0; 95\% CI, 1.4 to 2.7) higher risk of subsequent fatal or nonfatal stroke (lacunar or cortical infarction, ICH), independent of age and other vascular risk factors. In another study in which the data from NASCET were used,\textsuperscript{30} of the 2618 patients with TIA or minor stroke randomized, 493 had LA, which was restricted in 354 and widespread in 139. Across these 3 groups of patients, the Kaplan-Meier 3-year risks of any stroke for medically treated patients were 20\%, 27\%, and 37\% (\(P=0.01\), log-rank test). For surgically treated patients, the differences were even greater: 14\%, 25\%, and 34\%, respectively (\(P<0.001\), log-rank test). Although deep small infarcts on CT scan were >2-fold more prevalent among patients with LA at baseline, no difference was observed in the follow-up related to the occurrence of any specific stroke type. Independent of surgery, surgically treated patients who had widespread LA had a greater chance of dying from vascular death (10.1\%, 6.8\%, 3.6\%; \(P=0.02\), log-rank test, for comparison of the 3 subgroups). Three prospective hospital-based studies\textsuperscript{31-33} had already focused on survival and causes of death among elderly patients with LA. In all 3 studies, LA predicted death (particularly vascular death in 1 study)\textsuperscript{32} independently of other death predictors in aged patients.

**LA and ICH**

In 1989 and 1990, 2 cross-sectional studies of hospitalized stroke patients\textsuperscript{34,35} reported for the first time the association between LA and ICH. The latter of the 2 studies\textsuperscript{35} also examined the possible confounders for this association. In this study extensive LA was over twice more prevalent among 116 patients with ICH than among 155 control patients without ICH (18.1\% versus 7.7\%; OR, 2.34; 95\% CI, 1.05 to 5.28). In an analysis with a multivariate adjustment for other vascular risk factors, the association was almost fully explained by the higher prevalence of arterial hypertension and lacunar infarcts on CT scan. In patients with LA, hemorrhage was more frequently seated in the deep basal ganglia, confirming the hypothesis that the association was due to the common underlying pathology, ie, small-artery disease on a hypertensive basis. A more direct pathological confirmation of this hypothesis has now become possible with the use of gradient-echo T2-weighted MRI sequences, which are able to disclose silent cerebral microbleeds. In 1 study\textsuperscript{36} the number of deep microbleeds was significantly correlated with the severity of periventricular hyperintensities on MRI. Microbleeds also proved to be related to both LI and ICH.

The Stroke Prevention in Reversible Ischemia Trial (SPIRIT),\textsuperscript{37} a trial of secondary prevention with anticoagulation and target international normalized ratio (INR) values of 3.0 to 4.5 in patients with cerebral ischemia of presumed arterial origin, pointed to a definite, prospectively assessed, independent role of LA as a risk factor for major bleeding during anticoagulation after cerebral ischemia. The adjusted HR for ICH was 2.7 (95\% CI, 1.4 to 5.3) when patients with and without LA were compared. ICHs were equally frequent in deep hemisphere compared with lobar locations. On the basis of the experience of SPIRIT, the ongoing European/Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT),\textsuperscript{38} despite the lower target INR range (INR, 2 to 3), decided to exclude patients with LA from the study candidates. A case-control study\textsuperscript{39} was recently performed to investigate radiographic and clinical characteristic of patients with warfarin-related ICH after ischemic stroke (cases) compared with patients treated with warfarin and without ICH (controls). At any INR value, the presence and severity of LA on CT scan were strongly correlated with the occurrence of ICH. LA was present in 24 of 26 ICH cases and in 27 of 56 controls (OR, 12.9; 95\% CI, 2.8 to 59.8), an association that persisted after controlling for other risk factors. The fact that in the last 2 studies LA patients had an increased risk not only of basal ganglionic but also of lobar ICH, a site typical of CAA-related hemorrhage, suggests that reexamining the relationship of LA with CAA, supported by a few pathological observations,\textsuperscript{40,41} may be worthwhile. The information regarding LA and ICH raises the question of reconsidering the risk-to-benefit ratio evidenced by the major anticoagulation trials in atrial fibrillation, particularly for patients with extensive LA.

**LA and Stroke: Risk Factor or Intermediate Surrogate?**

LA is a neuroimaging finding caused by several pathological changes (demyelination, gliosis, cavitated and noncavitated small deep infarcts) and etiologies (hypoperfusion, vessel lipohyalinosis, disturbed blood-brain exchanges). The term stroke has clinical and pathological significance and also regroups heterogeneous conditions (eg, ischemia, hemorrhage, embolism, lacunar, silent stroke) and finally etiologies (large- and small-vessel disease, heart disease) and risk factors. Stroke and LA are likely 2 related diseases. In many aspects, LA is an ischemic disease, as is ischemic stroke; ICH and LA share a common cause, that of arterial hypertension. If LA shares with stroke common mechanisms, and the appearance of LA on imaging predicts stroke, then, according to current terminology, LA can be regarded as an intermediate surrogate of stroke.

According to the traditional concepts of epidemiology, a risk factor is defined as such when its presence in a person, compared with a person with similar characteristics but without that factor, increases the risk of incurring a definite disease. The nature of risk factors is heterogeneous because
they include the following: (1) susceptibility factors (for stroke, examples are demographic factors and genetic polymorphisms predisposing to stroke); (2) acquired factors, linked with lifestyle or behavioral habits (for stroke, examples are dietary habits and smoking); (3) function or organ abnormalities that are directly involved in causing the disease event (eg, atrial fibrillation); and (4) function or organ abnormalities that are not involved in the pathogenesis of the disease and for which the association can be explained by the effect of shared risk factors (for stroke, an example is left ventricular hypertrophy, which is usually included in the list of conventional stroke risk factors). In a manner similar to that for ECG or other instrumental measures of cardiac hypertrophy, LA can be seen as an indicator of organ damage (brain) that, although consequent to the effect of vascular risk factors (eg, arterial hypertension) shared with stroke, carries an independent amount of risk for stroke. Consistent with this concept, LA may be considered an intermediate surrogate of stroke, as well as ECG hypertrophy.

Conclusive evidence of the role of a factor as a risk factor must be obtained by prospectively estimating the incidence of the disease among people exposed to the factor compared with those not exposed to the factor, obtaining statistically valid risk increases among the exposed persons, possibly with a dose-response effect. Retrospective studies are less informative because they are unable to establish the sequential, cause-effect relationship between the factor and the disease. Cohorts must be free of the target disease when the longitudinal observation is begun. The effect of the factor must be definitely independent from other factors that may behave as confounders or modifiers of the association. Finally, treating the factor must favorably alter the natural history of the disease.

The aforementioned evidence does not fulfill the requirement for defining LA as a stroke risk factor for the following reasons: (1) The evidence comes almost exclusively from studies examining patients already affected by stroke or stroke-related diseases (eg, dementia); in both cross-sectional and longitudinal studies, the outcome was stroke recurrence, and therefore the only possible inference is that LA is a risk factor for stroke recurrence. (2) It was achieved by examining patients selected on a hospital basis; a few population studies have been conducted that sought to identify subjects with LA in the unselected general population. None of these studies has yet supplied data about the risk of stroke among these subjects, whether or not they are affected by previous stroke or stroke-related abnormalities. (3) While the confounding effect of other conventional stroke risk factors seems to have been ruled out by the majority of studies evidencing the association between LA and stroke, it remains to be conclusively elucidated whether silent stroke, usually of the lacunar type, commonly combined with LA on imaging, is the true determinant of the stroke risk. This applies to either the ischemic or the hemorrhagic stroke type. In the Cardiovascular Health Study, stroke-free subjects with silent infarcts on MRI had a risk of stroke that was double that of subjects without silent stroke (18.7 versus 9.5 per 1000 person-years; HR, 1.80; 95% CI, 1.31 to 2.47). Unfortunately, this study did not consider the effect of LA. An ongoing study in Europe (LADIS [LeukoaraisiOn And DISability]) supported by the European Union is prospectively following up a large multicenter cohort of subjects with MRI-detected LA, including those without previous cardiovascular events, to compare the effect of LA as an independent predictor of different outcomes, including death, stroke, and dementia, across groups of patients with different degrees of LA severity. It is hoped that this study will provide information on the risk of stroke in asymptomatic free-dwelling subjects with LA and will also contribute data regarding whether the risk is proportional to the degree of changes on imaging. (4) Since no intervention is known to be capable of controlling LA, there is no proof that treating LA prevents stroke.

In conclusion, there is substantial evidence that LA is associated with stroke, independent of other stroke risk factors. Even though the most common stroke type predicted by LA is LI, in patients with LA the risk of cortical infarct is also increased, as is that of vascular death. The presence of extensive LA predisposes to ICH, especially in patients treated with anticoagulants for secondary prevention after an ischemic stroke. Both specialists and family physicians should be educated to recognize the importance of LA as an intermediate surrogate of stroke; surveillance and accurate management of conventional risk factors are suggested, even in subjects without prior events. LA should be assessed at entry and taken into account as a potential confounder of stroke in any trial that seeks to investigate stroke prevention and should be considered a potential cofactor of hemorrhage in trials investigating antithrombotic agents.

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