Small Vessel Disease and General Cognitive Function in Nondisabled Elderly
The LADIS Study

Wiesje M. van der Flier, PhD; Elizabeth C.W. van Straaten, MD; Frederik Barkhof, MD, PhD; Ana Verdelho, MD; Sofia Madureira, PsyP; Leonardo Pantoni, MD, PhD; Domenico Inzitari, MD; Timo Erkinjuntti, MD, PhD; Militta Crisby, MD, PhD; Gunhild Waldemar, MD, DMSc; Reinhold Schmidt, MD; Franz Fazekas, MD; Philip Scheltens, MD, PhD; on behalf of the LADIS Study Group

Background and Purpose—On cerebral magnetic resonance imaging (MRI), white matter hyperintensities (WMH) and lacunes are generally viewed as evidence of small vessel disease. The clinical significance of small vessel disease in terms of global cognitive function has as yet not been completely clarified. We investigated the independent contribution of WMH and lacunes to general cognitive function in a group of independently living elderly with varying degrees of small vessel disease.

Methods—Data were drawn from the multicenter, multinational Leukokraurosis and Disability (LADIS) study. There were 633 independently living participants. General cognitive function was assessed using the Mini Mental State Examination (MMSE) and the modified Alzheimer Disease Assessment Scale (ADAS). On MRI, WMH was rated as mild, moderate, or severe. Lacunes were rated as none, few (1 to 3), or many (4 or more).

Results—In the basic analysis, increasing severity of both WMH and lacunes was related to deteriorating score on the MMSE and ADAS. When WMH and lacunes were entered simultaneously, both MRI measures remained significantly associated with MMSE score. Increasing severity of WMH remained associated with ADAS score, whereas the association with lacunes became less prominent. These associations were independent of other risk factors for dementia, like education, depression, vascular risk factors, or stroke.

Conclusion—We found WMH and lacunes to be independently associated with general cognitive function in a sample of independently living elderly. These results highlight the fact that WMH and lacunes should both be evaluated when assessing small vessel disease in relation to cognitive function. (Stroke. 2005;36:2116-2120.)

Key Words: cognition ■ elderly ■ lacunes ■ small vessel disease ■ white matter hyperintensities
Materials and Methods

Data were drawn from the multicenter, multinational Leukoaraiosis and Disability (LADIS) study. The LADIS project prospectively studies the role of WMH as an independent predictor of the transition to disability in nondisabled elderly. In short, 639 elderly subjects, who had no or only mild instrumental in their instrumental activities of daily living (IADLs), and were stratified for grade of WMH severity, were enrolled. Subjects presented for evaluation in the following settings: stroke units or stroke departments, cerebrovascular disease clinics, memory or dementia clinics, neurologic or geriatric wards/clinics, population studies on aging, and controls in other studies. Among the reasons for presentation were mild memory loss, minor motor disturbances, minor focal cerebrovascular events, or nonspecific reasons for undergoing a cranial neuroimaging study (WMH as incidental finding). To be included, subjects had to have: (1) age between 65 and 84 years; (2) WMH on MRI of any degree, according to the categorization into the 3 severity classes of the Fazekas scale; (3) no or only mild disability as defined by the IADL scale; (4) presence of a regularly contactable informant; and (5) agreement to sign an informed consent. Exclusion criteria were: (1) likely dropout because of the presence of severe illnesses (cardiac, hepatic, or renal failure, cancer or other relevant systemic diseases), (2) severe unrelated neurologic diseases, (3) leukoencephalopathy of nonvascular origin (immunologic–demyelinating, metabolic, toxic, infectious, other), (4) severe psychiatric disorders, (5) inability to give informed consent, and (6) inability or refusal to undergo cerebral MRI. Subjects are currently followed up for 3 years with repeated clinical and MRI studies. The present article is based on the baseline data of the LADIS project.

All subjects were assessed using clinical and functional tests, including global functioning, cognitive, motor, psychiatric, and quality-of-life measures. For the present study, general cognitive function was measured using the Mini Mental State Examination (MMSE) and a modified version of the Alzheimer Disease Assessment Scale (ADAS). The ADAS was slightly modified to include the item “delayed word recall.” A higher MMSE score indicates better performance, whereas a higher ADAS score corresponds to worse performance. ADAS score was missing in 6 subjects, so 633 subjects had available data for the present study. The following variables were evaluated as confounders: age, sex, education (years), depressive symptoms, motor function, hypertension, diabetes, smoking, and history of stroke.

All subjects were studied by MRI following a standard protocol on the same day as the clinical investigation. Scans were made on a 0.5-T (one center) or 1.5-T scanner (10 centers) and were collected centrally at the Image Analysis Centre (IAC) of the Vrije Universiteit Medical Center, Amsterdam. Imaging guidelines were distributed that center of origin acts as a confounder in the association between general cognitive function and lacunes. The number of lacunes was recoded into none, few (1 to 3 lacunes), and many (4 lacunes or more). The intrarater reliability of rating of WMH was determined on 18 randomly selected scans that were scored twice (weighted Cohen’s k = 0.84). Interrater reliabilities and intrarater reliability of lacunes were not determined.

Statistical analysis was performed using SPSS for windows (release 11.5). Spearman’s correlation was used to assess the association between WMH and lacunes. The strength of the associations between small vessel disease and general cognitive measures was assessed using partial correlations, correcting for age and sex. Associations between small vessel disease and general cognitive function were assessed using general linear models for MMSE and ADAS separately. WMH and lacunes were entered as continuous variables. Age and sex were entered as covariates in all models. First, basic associations between general cognitive function and WMH and between general cognitive function and lacunes were assessed. Subsequently, WMH and lacunes were entered simultaneously to assess their independent contribution to cognitive function. The interaction between WMH and lacunes was tested. Because 11 different centers participate in the LADIS project, it is conceivable that center of origin acts as a confounder in the association between small vessel disease and cognition. Therefore, center of origin was entered as a factor in the GLM. Additional corrections were made for education, depressive symptoms, motor function, hypertension, diabetes, smoking, and a history of stroke.

Results

Characteristics of the participants are presented in Table 1. The number of lacunes increased with the severity of WMH (Spearman r = 0.25, P < 0.001; Figure 1).

General linear models were performed for WMH and lacunes separately, correcting for age and sex and with the MMSE and the ADAS as dependent variable. In these basic models, WMH and lacunes each were associated with score on the MMSE and ADAS (MMSE-WMH: β[se] = −0.48 [0.12], P < 0.001; MMSE-lacunes: β[se] = −0.62 [0.14]),
To assess the independent effect of WMH and lacunes on general cognitive function, both variables were entered simultaneously into general linear models (Table 2). Increasing WMH and lacunes were independently associated with a lower score on the MMSE. With increasing severity of WMH, the performance on the ADAS deteriorated. In the multivariate model, increasing severity of lacunes tended to be associated with worse performance on the ADAS, but this association was less prominent. There was no interaction between lacunes and WMH. The interaction term was therefore left out of subsequent analyses. Correction for possible confounders left results largely unaltered. Results did not change after exclusion of subjects with an infarct other than a lacune on MRI.

Discussion

The main finding of the current study is that WMH and lacunes are independently associated with general cognitive function in a large sample of nondisabled elderly subjects.

Small vessel disease is prevalent among the elderly. Several population-based studies have shown before that, small vessel disease may cause subtle cognitive deficits in nondemented subjects. In the present study, we demonstrated that both WMH and lacunes independently influence cognitive function. We found only a moderate correlation between WMH and lacunes, supporting the view that they are 2 distinct expressions of small vessel disease. Lacunar infarcts are produced when the ischemic damage is focal and of sufficient severity to result in a small area of necrosis. They are largely confined to the cerebral white matter and subcortical structures, including the basal ganglia, thalamus, and brain stem. In contrast, diffuse WMH, considered to be a form of rarefaction or incomplete infarction, are usually widespread.

In the present study, we defined small vessel disease as WMH and lacunes on MRI. Although these MRI abnormalities are generally considered as measures of small vessel disease, they have in fact variable pathologic correlates. Arteriolosclerosis has been reported to be the primary factor in the pathogenesis of WMH in the elderly. Alternatively, WMH may have as diverse pathologic correlates as loss of myelin, axons, and oligodendroglial cells, dilatation of perivascular spaces, and mild reactive astrocytic gliosis.

There have been a few studies evaluating the simultaneous effect of WMH and lacunes in a sample of subjects with a broad range of cognitive impairment. In these studies, WMH were found to be related to cognitive impairment, but there were no independent associations between lacunes and cognitive dysfunction. In addition, there has been a large population-based study assessing risk factors and functional consequence of lacunes that showed associations between lacunes and cognitive function, even after correction for WMH. In the present study, we demonstrated both lacunes and WMH to be associated with general cognitive function as measured using the MMSE. Scores on the ADAS were related to WMH and lacunes in the basic analysis. However, the association between ADAS score and lacunes was not independent of WMH, although associations remained borderline significant. Insufficient power may be partly responsible for the disappearance of the significant association, because the variability in ADAS is larger than the variability in MMSE. Furthermore, ADAS and MMSE are both widely used tests of general cognitive function. The fact that even with these relatively crude measures, clear associations with WMH, the performance on the ADAS deteriorated. In the multivariate model, increasing severity of lacunes tended to be associated with worse performance on the ADAS, but this association was less prominent. There was no interaction between lacunes and WMH. The interaction term was therefore left out of subsequent analyses. Correction for possible confounders left results largely unaltered. Results did not change after exclusion of subjects with an infarct other than a lacune on MRI.
small vessel disease were observed, underlining the clinical relevance of both WMH and lacunes. However, it is conceivable that tests of cognitive functions specifically associated with small vessel disease such as mental speed and executive function may yield even stronger associations with WMH and lacunes.

Among the strengths of the present study is the large sample size. Each subject underwent MRI scanning. All scans were analyzed centrally, which guaranteed reliability of MRI measures. Patients were selected to represent a broad range of WMH, enabling us to assess the subtle associations of small vessel disease and cognitive function. Among the limitations of the study may be the subject selection. Subjects were identified mainly in a hospital or secondary/tertiary referral setting. The study sample was selected to represent the full range of severity of WMH. Although stratification by WMH may hamper the generalizability of the results to the general population, the reasons for referral were those commonly leading to discover WMH in elderly persons, so that the LADIS sample likely reflects the assorted patient population, the reasons for referral were those commonly leading to discover WMH in elderly persons, so that the LADIS sample likely reflects the assorted patient population. Consequently, other potentially confounding variables were entered into the model. The number of missing values varied but was less than 2% of the total number of participants in a particular model.

Because 11 different centers participate in the LADIS project, center of origin may act as a confounder. Therefore, center of origin was entered as a factor in the GLM. In conclusion, we found WMH and lacunes to be independently associated with cognitive function in a sample of independently living elderly. These results provide further evidence for the importance of small vessel disease in cognitive impairment at old age, and they highlight the fact that WMH and lacunes should both be evaluated when assessing small vessel disease in relation to cognitive function.

### Appendix

**List of Participating Centers and Personnel**

Helsinki, Finland (Memory Research Unit, Department of Clinical Neurosciences, Helsinki University): Timo Erkinjuntti, MD, PhD, Tarja Poljusvaara, MD, PhD, Pia Pihlanen, MD, Raija Ylikoski, PhD, Hanna Jokinen, LPsyCh, Meija-Marijut Somerokskis, Mpsych, Riitta Mätylä, MD, PhD; Graz, Austria (Department of Neurology and MRI Institute, Medical University): Franz Fazekas, MD, Reinhold Schmidt, MD, Stefan Ropele, PhD, Alexandra Seewann, MD, Katja Petrovic, MagPsychol, Ulrike Garmehi; Lisboa, Portugal (Serviço de Neurologia, Centro de Estudos Egas Moniz, Hospital de Santa Maria): José M. Ferro, MD, PhD, Ana Verdelho, MD, Sofia Madureira, PsDy; Amsterdam, The Netherlands (Department of Neurology, VU Medical Center): Philip Scheltens, MD, PhD, Ilse van Straaten, MD, Wiesje van der Flier, PhD, Alida Gouw, MD, Frederik Barkhof, MD, PhD; Göteborg, Sweden (Institute of Clinical Neuroscience, Göteborg University): Anders Wallin, MD, PhD, Michael Jonsson, MD, Karin Lind, MD, Arto Nordlund, PsyD, Sindre Rolstad, PsyD, Kerstin Gustavsson, RN; Huddinge, Sweden (Neurotec Department, Section of Clinical Geriatrics, Karolinska Universitetssjukhuset): Lars-Olof Wahlund, MD, PhD, Militta Crisby, MD, PhD, Anna Pettersson, physiotherapist, Kaarina Amberla, PsyD, Paris, France (Department of Neurology, Hopital Lariboisière): Hugues Chabriat, MD, PhD, Ludovic Benoit, MD, Karen Hernandez, Solene Pointeau, Annie Kurtz, Daniel Retzine, MD; Mannheim, Germany (Department of Neurology, University of Heidelberg, Klinikum Mannheim): Michael Hennerici, MD, Christian Blahak, MD, Hansjörg Baenzler, MD, Martin Wiarda, PsyD, Susanne Seip, RN; Copenhagen, Denmark (Copenhagen University Hospital: Memory Disorders Research Unit, Department of Neurology, Rigshospitalet, and the Danish Magnetic Resonance Research Center, Hvidovre Hospital): Gunhild Waldemar, MD, DMSc, Egill Rostrup, MD, MSc, Charlotte Ryberg, Tim Dyrb, Newcastle-upon-Tyne, U.K. (Institute for Ageing and Health, University of Newcastle): John O’Brien, DM, Sanjeet Pakrasi, MRC Psych, Thuis
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