Hyperlipidemia and Reduced White Matter Hyperintensity Volume in Patients With Ischemic Stroke

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Background and Purpose—White matter hyperintensity (WMH), or leukoaraiosis, is a radiologic finding generally assumed to reflect diseased small cerebral vasculature. WMH has significant functional impact through its relation to cognitive decline and risk of ischemic and hemorrhagic stroke. Accumulating evidence suggests that some manifestations of small-vessel disease such as intracerebral hemorrhage are associated with low levels of cholesterol. We sought to determine the relation between hyperlipidemia and WMH severity in patients with acute ischemic stroke (AIS).

Methods—We analyzed 2 independent, hospital-based AIS cohorts. Demographic and clinical data were collected prospectively. WMH was measured using semiautomated volumetric image analysis and a semiquantitative visual grading scale. Univariate and multivariable regression analyses were used to assess the relation between WMH severity and study variables.

Results—A total of 631 and 504 subjects in the first and second cohorts, respectively, were included. In univariate analyses, advancing age and hypertension were associated with severity of WMH (P<0.001) in both cohorts. In the multivariable analysis, after controlling for age, sex, and significant risk factors in the univariate and age-adjusted analyses, patients with a history of hyperlipidemia had less severe WMH in both cohorts (P<0.01).

Conclusions—Results from 2 independent cohorts demonstrate that AIS patients with a history of hyperlipidemia have less severe WMH at the time of stroke. These data support the hypothesis that hyperlipidemia may play a relatively protective role in cerebral small-vessel disease. (Stroke. 2010;41:437-442.)

Key Words: white matter disease ■ leukoaraiosis ■ hyperlipidemia ■ risk factors
AIS was more likely to be related to cerebral small-vessel disease and that they represent a subset of individuals in whom WMH has substantial clinical relevance, we used 2 independent cohorts of AIS to investigate this hypothesis.

Subjects and Methods

Study Population
The study included 2 independent cohorts of AIS patients from different institutions for whom prospectively collected data was analyzed retrospectively. Common inclusion criteria were as follows: (1) neuroimaging-confirmed AIS, (2) availability of brain MRI in the first 7 days, (3) complete data on vascular risk factors (VRFs) available, and (4) absence of ICH or nonvascular diseases that could interfere with the WMH interpretation, including neoplasms, demyelinating and autoimmune diseases, and vasculitides. All patients were assessed and classified by a neurologist.

MGH Cohort
All consecutive patients with AIS assessed in the Emergency Department of Massachusetts General Hospital (MGH, Boston, Mass) who provided informed consent were considered for inclusion. The subjects were recruited from 2003 to 2008 as part of an ongoing prospective, hospital-based study. A cohort-specific inclusion criterion was a T2 fluid-attenuated inversion recovery (FLAIR) axial MRI sequence available within the same study and in usable format for volumetric analysis of WMH.

HM Cohort
Consecutive consenting patients from 2005 to 2008 with a diagnosis of AIS fulfilling World Health Organization criteria were considered for inclusion. The subjects were enrolled in BasicMar (Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III; FIS No. PI051737), an ongoing prospective registry of AIS at the IMIM-Hospital Universitari del Mar (HM cohort; Barcelona, Spain).

Baseline Characteristics
In both cohorts, age, sex, and VRFs were recorded for every subject. Data were abstracted directly by patient and/or proxy interview and medical chart review. VRFs were coded according to the definitions of international guidelines as follows: arterial HTN (evidence of at least 2 raised blood pressure measurements, with systolic >140 mm Hg or diastolic >90 mm Hg recorded on different days before stroke onset; a physician diagnosis of HTN; or use of an antihypertensive medication), diabetes (a physician diagnosis or use of diabetes medication), HL (physician diagnosis, a presroke recorded serum cholesterol concentration >220 mg/dL or serum triglyceride concentration >150 mg/dL, and use of medication prescribed to control HL. Statin medication that was prescribed for an indication other than HL did not qualify patients for the diagnosis of HL), coronary artery disease (documented history of angina pectoris or myocardial infarction), atrial fibrillation (AF; documented history or diagnosis during hospitalization), and prior stroke (history of prior ischemic stroke). Alcohol and smoking habits were also recorded. In the MGH cohort, the threshold for alcohol abuse was “current alcohol intake >3 oz/d” and for smoking was “current smoker or quit smoking <7 years ago.” In the HM cohort, alcohol abuse was considered as “current or <1 year ago alcohol intake >60 g/d” and smoking habit was considered in “current smokers or quit <5 years ago.” For the purpose of the study, we focused exclusively on those VRFs collected in a comparable manner in both cohorts.

Image Acquisition and Analysis
Brain MRI studies were performed with a 1.5-T whole-body scanner (GE Signa Excite II, GE Medical Systems) at both institutions on all subjects. Hypertense foci on diffusion-weighted imaging and chronic infarction lesions (reported or detected on T2) were excluded from quantification.

MGH Cohort
WMH volumetric analysis was performed on FLAIR sequences using a previously published semiautomated method. All raters displayed high interrater reliability for determination of WMH volume (WMHV) compared with “gold standard” WMHVs derived from scans analyzed in previous publications (intraclass correlation coefficient >0.92). To account for differences in head size, WMHVs were standardized by comparing the subject’s midline sagittal intracranial cross-sectional area with the study average midline sagittal intracranial cross-sectional area as in previous studies.

HM Cohort
WMH was evaluated on FLAIR sequences using a semiquantitative visual grading method and classified by a neurologist according to the Fazekas scale. LA scores were distributed in 4 groups: LA0, absence of WMH or minimal periventricular (PV) thin-lining; LA1, caps and thin-lining of the PV region and punctuate, deep, hypertense foci; LA2, early confluence foci or smooth halo in the PV region; and LA3, confluent foci or irregular hyperintensity in the PV region extending into the deep white matter.
Pearson's correlation for log_WMHV and age. In the HM cohort, WMH (log_WMHV or LA) with a value of by linear regression and ordinal logistic regression, depending on the division, all univariate analyses were also completed after adjusting for age the relation with LA, an ordinal variable. Given the potent and tests for dichotomous variables and ANOVA for age were used to assess dichotomous baseline variables were tested by Student's

Univariate analyses to evaluate the relation between log_WMHV and formed for all linear-regression analyses (log_WMHV; the Figure).

In the MGH cohort, the standardized WMHV was natural log–transformed for all linear-regression analyses (log_WMHV; the Figure). Univariate analyses to evaluate the relation between log_WMHV and dichotomous baseline variables were tested by Student’s t test and by Pearson’s correlation for log_WMHV and age. In the HM cohort, χ² tests for dichotomous variables and ANOVA for age were used to assess the relation with LA, an ordinal variable. Given the potent and well-established relation between advancing age and WMH progression, all univariate analyses were also completed after adjusting for age by linear regression and ordinal logistic regression, depending on the cohort.

Multivariable models included those variables associated with WMH (log_WMHV or LA) with a value of P<0.1 in at least 1 analysis (univariate or age adjusted) in either cohort. The variables were cross tabulated to assess for multicollinearity, thus confirming that the model fit was adequate. The model was tested in the MGH cohort with a multiple linear regression and in the HM cohort with an ordinal regression. Statistical significance was set at P<0.05. Tests were performed with SPSS package 13.0 for (SPSS Inc, Chicago, Ill).

**Results**

Of all patients with confirmed AIS who consented to participate in the study (MGH n=965, HM n=835), those with other diseases that could interfere with WMH interpretation (MGH n=59, HM n=43), absence of brain MRI data (MGH n=19, HM n=249), MRI formats that could not be used for volumetric analysis (MGH n=178), or incomplete VRF information (MGH n=78, HM n=39) were excluded. A total of 631 (65.39%) patients from the MGH and 504 (60.36%) from the HM cohort met all inclusion criteria. Characteristics and demographic data are shown in Table 1. The MGH cohort was younger (P<0.05). There were nonsignificant differences in nonmodifiable VRFs except for diabetes (19.2% vs 33.3%). The MGH cohort also showed a higher rate of smoking and alcohol abuse that was not explained by the different age of the cohorts (likely due to coding definition differences between centers).

In univariate analyses (Table 2), advancing age (P<0.001), HTN, and smoking (P<0.05) were correlated with WMH in both cohorts. There were associations that were not shared between the 2 samples. AF (P<0.001) and coronary artery disease (P=0.02) in the MGH cohort and prior stroke (P=0.003) and smoking (P<0.001) in the HM cohort were also significantly associated with WMH. HL was not associated in either cohort. After adjustment for age, however, HL emerged as protective in the MGH cohort (P=0.02), and a similar trend was noted in the HM cohort (P=0.06; Table 3).

In the multivariable analyses (Table 4), only advancing age and absence of HL were independently associated with increasing severity of WMH in both cohorts (P<0.01). HTN appeared associated with WMH severity with robust signifi

**Table 1. Characteristics and Demographic Data: Comparison Between Cohorts**

<table>
<thead>
<tr>
<th></th>
<th>MGH n=631</th>
<th>HM n=504</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (SD)</td>
<td>64.8 (15.63)*</td>
<td>69.1 (12.82)*</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>58.3</td>
<td>61.4</td>
</tr>
<tr>
<td>HTN, %</td>
<td>62.3</td>
<td>67.3</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>19.2*</td>
<td>33.3*</td>
</tr>
<tr>
<td>HL, %</td>
<td>38.7</td>
<td>39.8</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>17.7</td>
<td>14.3</td>
</tr>
<tr>
<td>AF, %</td>
<td>14.1</td>
<td>17.2</td>
</tr>
<tr>
<td>Prior stroke, %</td>
<td>15.3</td>
<td>19.2</td>
</tr>
<tr>
<td>Smoking habit, %</td>
<td>54.3*</td>
<td>34.9*</td>
</tr>
<tr>
<td>Alcohol abuse, %</td>
<td>55.0*</td>
<td>14.9*</td>
</tr>
<tr>
<td>WMHV, cm³, median (IQR)</td>
<td>7.99 (3.89–16.24)</td>
<td>...</td>
</tr>
<tr>
<td>LA, % (LA0, LA1, LA2, LA3)</td>
<td>...</td>
<td>(33.3, 37.7, 20.2, 8.7)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.

*Variables significantly different (P<0.05) between cohorts.

**Ethical Considerations**

All study aspects were approved by the local institutional review board/institutional ethics committee for each cohort. All participants or their approved proxy provided informed consent for participation.

**Statistical Analysis**

In the MGH cohort, the standardized WMHV was natural log–transformed for all linear-regression analyses (log_WMHV; the Figure). Univariate analyses to evaluate the relation between log_WMHV and dichotomous baseline variables were tested by Student’s t test and by Pearson’s correlation for log_WMHV and age. In the HM cohort, χ² tests for dichotomous variables and ANOVA for age were used to assess the relation with LA, an ordinal variable. Given the potent and well-established relation between advancing age and WMH progression, all univariate analyses were also completed after adjusting for age by linear regression and ordinal logistic regression, depending on the cohort.

Multivariable models included those variables associated with WMH (log_WMHV or LA) with a value of P<0.1 in at least 1 analysis (univariate or age adjusted) in either cohort. The variables appeared associated with WMH severity with robust signifi
These data, from 2 independent cohorts, demonstrate that HL significance among HM patients (P=0.001) and with borderline with WMH only in the HM but not in the MGH cohort, whereas smoking showed a risk effect in the MGH cohort only.

We performed an additional analysis of prior statin treatment. It was not associated with WMH in the univariate or age-adjusted analyses in either cohort. Forcing its inclusion into the multivariate model again gave a nonsignificant result with opposite directions of effect between cohorts (odds ratio=1.142, \( P=0.123 \) in MGH; odds ratio=0.678, \( P=0.006 \) in HM). Although inclusion of prior statin treatment did not change the HL effect direction on WMH severity, it rendered the association nonsignificant. Exposure to statin treatment and HL also demonstrated a high degree of colinearity in both cohorts (\( P<0.01 \)).

### Discussion

These data, from 2 independent cohorts, demonstrate that HL may, in fact, be associated with reduced WMH severity in individuals with AIS. This observation is consistent with prior studies that have demonstrated an inverse relation between HL and ICH risk. Together they suggest that patients with a history of HL appear to be at reduced risk of cerebral small-vessel disease.

In this study, the approach to WMH measurement differed between cohorts. Whereas the Fazekas scale for LA used in the HM cohort is widely validated and well established, the semiautomated volumetric measurement performed in the MGH cohort may add accuracy and reliability.

HTN has been reported as a main risk factor for small-vessel diseases and also related to WMH. We found that HTN increased the risk of severe WMH in the univariate analyses, but after adjustment for age and the multivariable analysis, it did not achieve statistical significance in the MGH cohort. This might be explained by the cohort-specific age differences (ie, the older the individual, the stronger its effect on WMH). Given that MGH individuals were younger, the effect size of HTN may still be not sufficiently strong to withstand the adjustment. That might suggest that depending on the age distribution of the cohort, the strength of the HTN effect could vary.

The associations of prior stroke, AF, smoking habit, or alcohol abuse with WMH burden were found in 1 cohort but were not replicated in the other. Smoking and alcohol abuse had different rates between cohorts (likely due to coding differences between centers), and this might explain possible differences. However, this is not applicable to prior stroke and AF. Whether these discrepancies are the result of between-study variability or unpredictable relations between these variables and WMH severity is unclear.

Apart from advancing age, the only risk factor clearly related to WMH in our study was HL. This inverse association was strong, consistently significant in both cohorts, and independent after multivariable adjustment. HL is widely recognized as a risk factor for stroke, and lipid-lowering therapies have demonstrated benefits in stroke prevention and prognosis. However, there is also evidence of higher cholesterol levels being related to better outcomes and decreased mortality after AIS or ICH and a lower risk of

### Table 3. Age-Adjusted Analyses for Natural Logarithm of Standardized WMH (Log_WMHV) in the MGH Cohort and LA in the HM Cohort

<table>
<thead>
<tr>
<th></th>
<th>MGH</th>
<th>HM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>( \beta )</td>
<td>( P )</td>
</tr>
<tr>
<td>Sex, female</td>
<td>-0.03</td>
<td>0.344</td>
</tr>
<tr>
<td>HTN</td>
<td>0.04</td>
<td>0.264</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.01</td>
<td>0.725</td>
</tr>
<tr>
<td>HL</td>
<td>-0.08</td>
<td>0.026</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>-0.01</td>
<td>0.871</td>
</tr>
<tr>
<td>AF</td>
<td>0.01</td>
<td>0.752</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>0.05</td>
<td>0.210</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>0.10</td>
<td>0.004</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>0.06</td>
<td>0.128</td>
</tr>
</tbody>
</table>

### Table 4. Multivariate Analyses for Natural Logarithm of Standardized WMH (Log_WMHV) in the MGH Cohort and LA in the HM Cohort

<table>
<thead>
<tr>
<th></th>
<th>MGH</th>
<th>HM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95% CI for B</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.038</td>
<td>0.032</td>
</tr>
<tr>
<td>Sex, male</td>
<td>-0.051</td>
<td>-0.209</td>
</tr>
<tr>
<td>HTN</td>
<td>0.162</td>
<td>-0.006</td>
</tr>
<tr>
<td>HL</td>
<td>-0.215</td>
<td>-0.375</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>-0.055</td>
<td>-0.256</td>
</tr>
<tr>
<td>AF</td>
<td>0.056</td>
<td>-0.163</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>0.148</td>
<td>-0.057</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>0.204</td>
<td>0.048</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>0.054</td>
<td>-0.100</td>
</tr>
</tbody>
</table>
ICH and microbleeds. Although this issue was not addressed directly in prior studies, the data suggest an association between higher cholesterol levels and less severe WMH. Whereas hypercholesterolemia appears to impair endothelial reparative processes, it is also known that cholesterol plays a fundamental role in the development of the central nervous system and in the creation and maintenance of new synapses. This could explain the role of elevated cholesterol levels in a better response to an acute injury such as stroke, as well as a better response to chronic cerebral injury (such as the processes involved in WMH development). Other possible explanations might be based on some shared genetic burden, given that both HL and severity of WMH have a significant heritability component. Future studies may unveil novel clues in this field.

In our study, we used the HL variable instead of serum lipid measurements because the time of blood draw was not equivalent between cohorts and lipid values might have been altered by lipid-lowering treatment (as well as different intensities of such treatment). A history of HL may represent a more uniform way to measure an altered lipid profile between different cohorts and might have been more informative with regard to long-term conditions such as WMH. However, HL is still subject to measurement heterogeneity and should be further investigated to confirm the specific lipid level implications and to reveal the underlying mechanisms that might be involved in this phenomenon.

Similarly, the wide use of statin treatment makes its effect difficult to analyze. In the case of WMH burden, statins have not demonstrated any consistent role; moreover, considering that this study did not have enough power to address the interaction between HL, statin treatment, and WMH burden, especially because of its high collinearity, the inclusion of statin treatment in the model is unwarranted. However, whether statin treatment has any true effect on WMH severity or might partially contribute to the beneficial effect of HL is uncertain. A specifically designed, randomized, controlled trial would best be suited to address this issue.

The limitations of the study relate first to its retrospective design. Second, the characteristics of the study did not permit us to clearly separate the contribution of statin treatment to the HL effect. Third, although the AIS population characteristics allowed us to powerfully test our hypothesis, the results may warrant future study in population-based cohorts before reaching full generalizability. Fourth, the observed differences in baseline characteristics between the 2 cohorts, especially age and rates of alcohol abuse and smoking, may have reduced the power to find the same results in both. Fifth, the nonharmonized WMH measurement between cohorts, with the consequent use of different statistical tests in each, may also reduce the capability of finding reproducible associations. However, these limitations would have led, if anything, to null results. Thus, it is reassuring that our observations are unlikely to be the result of biases introduced through limitations of the study design.

Summary
This study describes for the first time that a history of HL independently relates to decreased severity of WMH in patients with AIS. Together with previous studies linking HL to a lower ICH risk, our data suggest a protective role of HL in cerebral small-vessel disease. Data also confirmed that advancing age was strongly correlated to WMH severity in these patients. Consistency in the results from independent cohorts reinforces these findings.

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Disclosures
None.

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