Cerebral amyloid angiopathy (CAA) represents amyloid β-peptide deposition in small- and medium-sized blood vessels in the brain, leading to hemorrhagic and ischemic injury.1–5 Classically, CAA patients are diagnosed when they develop lobar intracerebral hemorrhage (ICH), a severe type of stroke resulting in high rates of mortality and disability.6,7 Lobar microbleeds on T2*-weighted MRI have also been identified as a marker of CAA severity and constitute an important component of the Boston criteria, a validated set of clinical-radiological features that showed high accuracy in CAA diagnosis.8–10 The Boston criteria were originally validated in patients presenting with lobar ICH. With growing use of T2*-weighted MRI and increasing awareness of this condition, however, the diagnosis of CAA is now often considered in the setting of isolated lobar microbleeds in patients with neurological symptoms not related to ICH.11–13 Detection of lobar microbleeds in large proportions of stroke-free, community-dwelling older individuals13–15 also raises the question of whether many or most of them have advanced CAA or are at risk of future ICH. This issue is particularly important for individuals needing long-term anticoagulation, as there are few data about the risk of ICH in the setting of isolated lobar microbleeds.

We explored these questions in a prospective observational cohort of patients diagnosed with CAA in the absence or the presence of prior ICH. We hypothesized that patients without symptomatic lobar ICH but otherwise meeting Boston criteria for CAA (aged >55 years with strictly lobar microbleeds and no other cause of hemorrhage)8,16,17 would demonstrate similar vascular risk factors and genetic/radiological characteristics as lobar ICH patients diagnosed with definite/probable CAA and an appreciable risk of future ICH.

Methods

Study Population

We have analyzed prospectively collected baseline and follow-up data from consecutive patients presenting to Massachusetts General...
Hospital with neurological symptoms and enrolled in a longitudinal cohort study of the natural history of CAA. Patients were enrolled with definite or probable CAA according to the previously validated Boston criteria, by which individuals aged ≥55 years with multiple hemorrhagic lesions restricted to lobar, cortical, or cortico-subcortical regions (cerebellar hemorrhage allowed) and no other definite cause (trauma, ischemic stroke, tumor, vascular malformation, vasculitis, coagulopathy, anticoagulation with international normalized ratio ≥3.0) are diagnosed as probable CAA. For the current analysis, we grouped the patients into 2 categories: those presenting with (1) ≥2 lobar microbleeds in the absence of lobar ICH (microbleed-only patients) or (2) those presenting with a lobar ICH with ≥1 lobar microbleed (ICH patients). Patients with a diagnosis of inflammatory CAA or autosomal dominant hereditary CAA were not included into this analysis. A full history was obtained, a neurological examination was performed, and head computed tomography, brain MRI, and computed tomography angiography or magnetic resonance angiography of the brain were performed to exclude an underlying vascular abnormality or other structural causes of hemorrhage. Microbleed-only patients underwent neurological and cognitive testing including mini mental state examination as part of the research protocol on which they scored ≥27. For the survival analysis, day zero for the ICH group was taken as the date of ICH. For the microbleed-only subjects who entered the prospective study without a prior ICH, day zero for survival analyses was taken as the date of study enrollment.

Data Collection

Subject enrollment, baseline data collection, and MRI acquisition and analysis were performed as described previously. Baseline characteristics were compared between ICH patients and microbleed-only patients among all patients enrolled. Individuals who consented to longitudinal follow-up and ICH patients who survived the first 90 days after their index event were studied for incident lobar ICH or death as described. Forty-six patients who died within the first 3 months after their index ICH were not included into the longitudinal analyses. Thirty-three patients who did not consent for the longitudinal study, day zero for the ICH group was taken as the date of ICH. For the microbleed-only subjects who entered the prospective study without a prior ICH, day zero for survival analyses was taken as the date of study enrollment.

Clinical and Laboratory Data

Data on demographics (age, sex) and vascular risk factors (hypertension, diabetes mellitus, and hypercholesterolemia) were obtained by interviewing the patients (or their families or surrogates) at enrollment. APOE genotype was determined in a large subset of patients who provided research blood samples.

MRI Acquisition and Analysis

Images were obtained using a 1.5-T magnetic resonance scanner (GE Sigma). Whole-brain axial gradient-echo images (repetition time/echo time, 750/50 ms; 5 mm slice thickness; 1 mm interslice gap) and fluid-attenuated inversion recovery images (repetition time/echo time, 10000/140 ms; inversion time, 2200 ms; number of excitations, 1; 5 mm slice thickness; 1 mm interslice gap) were performed.

Lobar microbleeds were classified as punctate, hypointense foci (<5 mm in diameter) selectively involving the cortex and underlying white matter on gradient-echo images, distinct from vascular flow voids and leptomeningeal hemosiderosis. White matter hyperintensity (WMH or leukoaraiosis) volume was quantified as previously validated using a computer-assisted algorithm that involves MRicron, a freely available tool. All MRI analyses were performed and recorded by investigators blinded to clinical and genetic data.

Statistical Analysis

Univariate analyses were used to compare clinical characteristics, frequencies of the APOE ε2 and ε4 alleles, and radiological markers between the 2 groups. Subsequently, multivariate analyses were performed to look for independent associations between these predictors and diagnostic categories. For multivariate models, APOE genotype was analyzed as a categorical variable according to the presence or the absence of the ε2 and ε4 alleles. As blood samples for genotyping were not available in 28% of subjects, multivariate models were built with and without APOE; addition of this variable did not change the associations observed among other variables. In the follow-up cohort, the mean follow-up time was calculated and the incidence rates of ICH and death were determined using the incidence per 100 person-years of follow-up. We used multivariable Cox regression analyses to calculate the crude and adjusted hazard ratios for occurrence of ICH and death. For the adjusted Cox regression model, patient group (with ICH as the control group), age, sex, hypertension, WMH volume, and lobar microbleed counts were entered in the model. In the microbleed-only patients, a multivariable Cox regression model was built to test the association between anti-coagulant use and incident ICH after adjustment for demographics, hypertension, WMH, and microbleeds. All analyses were performed with SPSS 22.0 (released 2012, IBM SPSS Statistics for Windows, version 22.0, IBM Corp, Armonk, NY). All tests of significance were 2 tailed.

Results

We analyzed a total of 379 patients who were enrolled between January 1993 and January 2012, of whom 63 patients presented with lobar microbleeds only and 316 with lobar ICH. Of the 63 microbleed-only patients, 26 patients underwent their index MRI for evaluation of symptoms suggestive of an ischemic event, 27 because of mild cognitive symptoms, 4 because of a gait disorder, and 6 because of transient sensory spells. None of the microbleed-only patients was found to have ischemic stroke, dementia, mass lesion, or other neurodegenerative conditions after complete evaluation.

Demographics (age, sex), vascular risk factors, and APOE genotype did not differ significantly between microbleed-only and ICH groups (Table 1). The lobar microbleed count was significantly higher in microbleed-only patients (median, 10; interquartile range, 4–30) compared with the ICH patients (median, 2; interquartile range, 1–9; P < 0.001). This difference remained significant after adjusting for demographics and vascular risk factors (P < 0.001). Within the lobar microbleed-only group, no significant correlation was found between microbleed counts and other factors such as demographics, vascular risk factors, or APOE. Microbleed-only patients had a larger median WMH volume compared with the patients with ICH (31 versus 23 mL; P = 0.02; Table 1). Higher WMH volume remained independently associated with the microbleed-only category (P = 0.04) after correction for age, sex, and vascular risk factors.
Three hundred patients (240 ICH who survived the first 90 days after their index ICH and 60 microbleed-only) were followed longitudinally for 5.3±3.8 years after their index event. Twelve microbleed-only patients (20% of the microbleed-only group, 5 per 100 person-years) developed a lobar ICH during follow-up versus 86 patients (36%) presenting with ICH (8.9 per 100 person-years). Details of the incident event rates, hazard ratios, and confidence intervals are presented in Table 2. Cox regression analysis showed a mildly lower risk of incident ICH for the microbleed-only versus the lobar ICH patients, but this difference did not reach statistical significance (Figure 1A; hazard ratio, 0.58; 95% confidence interval, 0.31–1.06; P=0.08). The ICH rate observed in either group of CAA patients was orders of magnitude greater than that of the general elderly population (estimated at 0.015–0.05 incident ICHs per 100 people per year).16,17 Figure 2 shows the baseline and follow-up imaging of an microbleed-only patient who later developed a symptomatic ICH.

We analyzed the predictors of incident ICH in the microbleed-only group. Warfarin use (P=0.02) and older age (P=0.04) were independently associated with time to incident ICH in a multivariable Cox regression model that also

### Table 1. Clinical and Radiological Characteristics of the 2 Patient Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients Presenting With</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lobar Microbleed-Only (n=63)</td>
</tr>
<tr>
<td>Definite/probable CAA All</td>
<td>All</td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>40 (63)</td>
</tr>
<tr>
<td>Age, y</td>
<td>73.6±8.3</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>34 (54)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>26 (41)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
</tr>
<tr>
<td>APOE ε2 frequency</td>
<td>15.6%</td>
</tr>
<tr>
<td>APOE ε4 frequency</td>
<td>25%</td>
</tr>
<tr>
<td>Radiological markers</td>
<td></td>
</tr>
<tr>
<td>Lobar microbleed count</td>
<td>10 (4–30)</td>
</tr>
<tr>
<td>WMH volume, mL</td>
<td>31 (18–46)</td>
</tr>
</tbody>
</table>

Values are displayed as mean±SD, median (25th–75th quartile), or n (%).

APOE genotypes were available in 48 subjects with microbleed-only and 224 with ICH. APOE indicates apolipoprotein E; CAA, cerebral amyloid angiopathy; ICH, intracerebral hemorrhage; and WMH, white matter hyperintensity.

### Table 2. Incidence Rates and Hazard Ratios for the Occurrence of ICH and Death in Both Groups During Follow-Up

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>No. of Patients Presenting With</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event: occurrence of lobar ICH</td>
<td></td>
</tr>
</tbody>
</table>
| Observed person-years               | 241                             | 968               | ...
| No. of occurrence (%)               | 12 (20)                         | 86 (36)          | ...
| Incidence of ICH per 100 person-years (95% CI) | 5 (2.6–8.7) | 8.9 (7.1–11) | ...
| Crude hazard ratio (95% CI)         | 0.57 (0.3–1.04)                 | Ref              | 0.07 |
| Adjusted hazard ratio* (95% CI)     | 0.58 (0.31–1.06)                | Ref              | 0.08 |
| Event: occurrence of death          |                                 |
| Observed person-years               | 261                             | 1316             | ...
| No. of occurrence (%)               | 31 (52)                         | 105 (44)         | ...
| Incidence of death per 100 person-years (95% CI) | 11.9 (8–16.8) | 8 (6.5–9.7) | ...
| Crude hazard ratio (95% CI)         | 1.8 (1.2–2.8)                   | Ref              | 0.005 |
| Adjusted hazard ratio* (95% CI)     | 1.67 (1.1–2.6)                  | Ref              | 0.02 |

CI indicates confidence interval; ICH, intracerebral hemorrhage; and ref, reference for hazard ratios.

*Adjusted for age, sex, hypertension, microbleed count, and white matter hyperintensity volume.
and Figure 2 as previously observed in nontraumatic lobar ICH.27 There were relatively high frequencies for the ε2 and ε4 alleles, similar vascular risk factors. APOE genotypes were also similar-to-severe CAA was pathologically confirmed in all of these patients.

Discussion

In this study, we have identified similar genetic and radiological characteristics at presentation between individuals with nonspecific symptoms who had lobar microbleeds on T2* MRI and patients with CAA diagnosed after a lobar ICH. Compared with the lobar ICH CAA patients, the patients with isolated lobar microbleeds were in the same age range and had similar vascular risk factors. APOE genotypes were also similar, with relatively high frequencies for the ε2 and ε4 alleles as previously observed in nontraumatic lobar ICH.27 There also seemed to be notable differences between the 2 groups. The microbleed-only group demonstrated higher microbleed counts, a finding that might in part reflect a higher likelihood that patients with large numbers of microbleeds would be identified and referred to our longitudinal research study. Patients with lobar microbleed-only in this study demonstrated increased WMH volume, a previously identified consequence of severe CAA pathology,28 as well as a substantial risk of subsequent ICH, and an overall higher mortality than CAA patients presenting with ICH.

The Boston criteria for diagnosis of CAA during life originally assumed the presence of ≥1 lobar hemorrhage, the presence of lobar microbleeds strengthening the diagnosis. The ongoing question in the field has been the diagnostic and prognostic importance of finding multiple lobar microbleeds on MRI of an older adult without any symptomatic ICH and without other causes for microbleeds. The results of our baseline comparisons that show similar demographic, genetic, and vascular risk profiles between the groups support the view that the lobar microbleed-only pattern can reliably be considered as probable CAA. The finding of a more severe marker of CAA-related cerebral damage (high WMH volume) also suggests vascular amyloid-related small vessel dysfunction as the principal pathological mechanism in these cases.

The current data bear on the important question of which patients should receive anticoagulant therapy. Individuals with isolated lobar microbleeds are being increasingly detected by more frequent use of sensitive MRI techniques, with prevalences in the range of 11% to 24% of the community-dwelling elderly.13,14 As the risk of ICH in these patients is largely unknown, however, there has been insufficient evidence to conclude that the presence of lobar microbleeds alone should preclude anticoagulant therapy.29 A neuropathologic study also suggested that CAA patients with multiple microbleeds might have different vessel pathology (with thicker amyloid-positive vessel walls) compared with CAA patients with few lobar microbleeds, suggesting that the ICH risk might be different across these groups.30 For these reasons, it has not been possible to extrapolate ICH risk estimates in a population with isolated lobar microbleeds based on prior studies of patients with past ICH.1,24 The current study suggests that microbleed-only CAA patients, though at mildly lower risk for future ICH than those with past ICH, are nonetheless at substantial risk.

Despite our relatively small sample size, we have also found that coumadin use was independently associated with the risk of incident symptomatic lobar ICH. An important area for future research will therefore be to determine, either by observational analysis or by randomized clinical trial, whether this risk of future ICH is sufficient to tip the risk versus benefit calculation away from anticoagulant treatment in specific clinical situations. Such a study will need to be powered to analyze the contribution of multiple ICH risk factors.31 A previous decision analysis suggested that the particularly high risk of future ICH among CAA patients with past ICH weighed strongly against anticoagulation, even in patients with nonvalvular atrial fibrillation.32

In light of the substantial risk for future ICH observed among the microbleed-only subjects, it is reasonable to consider this condition as a potential precursor or early form of CAA-related ICH. In other respects, however, the microbleed-only patients in the current study demonstrate markers of CAA equal to or greater than those in the ICH group. Among these markers were increased microbleed counts (possibly a reflection of referral preferences as noted above), higher WMH burden, and earlier mortality. We were unable to determine the potential causes of increased mortality in patients with microbleed-only CAA, but this finding is in line with
recent studies that show higher mortality in older adults with microbleeds. Despite these findings, the current data suggest that microbleed-only CAA may represent an alternative pathway by which this pathology can cause progressive neurological damage, even in the absence of major hemorrhagic stroke. Pathological confirmation of the CAA diagnosis in all 11 patients who underwent autopsy also supports the view that Boston criteria can accurately establish this diagnosis during life.

Our study has limitations. It is indeed likely that many of the microbleed-only patients were referred to our clinic because of finding relatively high number of lobar microbleeds, an issue that might be related to higher WMH load and mortality in this particular cohort. We do note, however, that the number of lobar microbleeds was not related to the risk of incident ICH in subjects, suggesting that this possible referral bias did not account for the relatively high incidence of future hemorrhage in microbleed-only patients. The question of CAA diagnosis is typically raised when a brain MRI obtained for neurological complaints in an older adult shows lobar microbleeds. In that sense, our study population is similar to patients seen in clinical practice. None of our microbleed-only patients had dementia, stroke, or other neurodegenerative conditions at enrollment, limiting the contribution of potential confounders to the outcomes observed. A second limitation was our sample size, which limited our ability to assess the risk of antithrombotic use in better multivariate models. A larger study would be necessary to address the risk of ICH with or without antithrombotic use, in patients with isolated lobar microbleeds who are at high risk of ischemic events because of the presence of arterial fibrillation, deep venous thrombosis, or pulmonary embolism. Data from randomized clinical trials are unlikely to be forthcoming, however, as such trials to rule out harmful medication effects in high-risk subjects are difficult to justify and perform.

Conclusions

The vascular risk factors as well as genetic and radiological characteristics of patients with isolated lobar microbleeds are similar to patients with CAA diagnosed after a lobar ICH, therefore suggestive of substantial CAA pathology. In this sense, lobar microbleeds on MRI, a common finding in otherwise healthy elderly individuals with or without nonspecific symptoms, seem to be a promising diagnostic marker of advanced CAA. We also find that patients presenting with isolated lobar microbleeds are at considerable risk of future lobar ICH, a risk made worse by the use of warfarin. Given the high prevalence of isolated lobar microbleeds in the elderly, our findings support the importance of developing early detection markers for CAA in asymptomatic individuals, studying its impact in this population, and determining the feasibility of treating CAA before it becomes symptomatic.

Sources of Funding

Research reported in this publication was supported by the National Institute of Neurological Disorders and Stroke (K23 NS083711, T32 NS048005, R01 NS070834), the National Institute on Aging (R01 AG26484), the Department of Radiology at Leiden University, and Dutch Alzheimer Foundation.

Disclosures

Dr Rosand serves as a consultant for Boehringer Ingelheim. Drs Rosand, Greenberg, and Gurrol receive research support from National Institutes of Health. The other authors report no conflicts.

References

Incidence of Symptomatic Hemorrhage in Patients With Lobar Microbleeds

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Stroke. published online June 19, 2014;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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脑叶出血组(n=316) P值

因症状性脑出血在患者中发生率较高

本研究比较了单纯脑叶微出血患者和CAA相关的脑叶ICH患者的基线特征及随后ICH的风险。

随访5.3±3.8年期间ICH和死亡的发生率)。通过多因素Cox回归模型探索单纯脑微出血患者发生ICH的预测因子。

具体资料,危险因素),载脂蛋白E(APOE)基因型,CAA严重程度的神经影像学标志物(微出血的数量,白质高信号的体积)和临床结局(平均

由病历回顾来判断新的ICH,死亡或2012年6月随访结束。

临床和影像学数据

分配IICH的患者基因、神经影像及脑出血危险因素等方面提示有重度CAA的病理机制参与,这类患者发生ICH的风险很大,

表2 两组患者在随访过程中脑出血和死亡的发生率和风险比

<table>
<thead>
<tr>
<th>变量</th>
<th>全部</th>
<th>死亡</th>
<th>脑出血</th>
<th>背景资料</th>
<th>原始风险比(95% CI)</th>
<th>校正风险比*(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄(岁)</td>
<td>73.6±8.3</td>
<td>73.6±8.3</td>
<td>74.9±8.3</td>
<td>56.5±18.2</td>
<td>0.57 (0.3–1.04)</td>
<td>0.57 (0.3–1.04)</td>
</tr>
<tr>
<td>性别(%)</td>
<td>35 (40)</td>
<td>35 (40)</td>
<td>36 (41)</td>
<td>29 (45)</td>
<td>1.2 (0.7–2.0)</td>
<td>1.2 (0.7–2.0)</td>
</tr>
<tr>
<td>高血压(%)</td>
<td>9 (10)</td>
<td>9 (10)</td>
<td>9 (10)</td>
<td>36 (50)</td>
<td>1.6 (1.1–2.6)</td>
<td>1.6 (1.1–2.6)</td>
</tr>
<tr>
<td>高胆固醇血症(%)</td>
<td>22 (25)</td>
<td>22 (25)</td>
<td>22 (25)</td>
<td>36 (50)</td>
<td>1.6 (1.1–2.6)</td>
<td>1.6 (1.1–2.6)</td>
</tr>
<tr>
<td>糖尿病(%)</td>
<td>16 (18)</td>
<td>16 (18)</td>
<td>16 (18)</td>
<td>36 (50)</td>
<td>1.6 (1.1–2.6)</td>
<td>1.6 (1.1–2.6)</td>
</tr>
<tr>
<td>老年(%)</td>
<td>241 (282)</td>
<td>241 (282)</td>
<td>241 (282)</td>
<td>36 (50)</td>
<td>1.6 (1.1–2.6)</td>
<td>1.6 (1.1–2.6)</td>
</tr>
<tr>
<td>神经影像学特征</td>
<td>105 (44)</td>
<td>105 (44)</td>
<td>105 (44)</td>
<td>36 (50)</td>
<td>1.6 (1.1–2.6)</td>
<td>1.6 (1.1–2.6)</td>
</tr>
<tr>
<td>脑叶微出血数量</td>
<td>23%</td>
<td>23%</td>
<td>23%</td>
<td>36 (50)</td>
<td>1.6 (1.1–2.6)</td>
<td>1.6 (1.1–2.6)</td>
</tr>
<tr>
<td>白质高信号体积,mL</td>
<td>102 (88)</td>
<td>102 (88)</td>
<td>102 (88)</td>
<td>36 (50)</td>
<td>1.6 (1.1–2.6)</td>
<td>1.6 (1.1–2.6)</td>
</tr>
</tbody>
</table>
| MRI的采集和分析

单纯脑叶微出血组(n=60)

单纯脑叶微出血组(n=63)和ICH组(n=240)的基线资料和人口统计学资料的P值

Hovsepian et al             Postpartum Acute Cerebrovascular Disease

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脑出血发生率之间的关系。所有分析均用 SPSS 20.0 软件完成。所有图 1. 两组患者发生脑内出血 (ICH; A) 和死亡 (B) 的生存曲线。

在单纯脑叶微出血组和患者发生脑出血(占该组的 20%,5 例/100 人 - 年)中,在随访过程中,单纯微出血组有 31 例死亡(11.9/100 人 - 年),平均高于一般的老年人(估计每年每 100 人发生 0.015–0.05 例脑出血事件/100 人 - 年)。事件发生率、风险比和可信区间详见表 2。Cox 回归分析显示了单纯微出血组较脑叶出血组患者脑出血风险轻微降低,虽然这种差异未达到统计学差异(图 1A;HR 0.58;95%CI 0.31–1.06; P=0.032)。但这种差异未达到统计学差异可能导致单纯脑叶微出血组在临床上被视为一种安全的治疗选择。尽管这种差异未达到统计学差异,但这一发现与最近的研究结果均一致,即年龄大的微出血患者的血管病理改变可能有所不同(血管壁淀粉样病变更厚),这也可能是由偏倚引起,即微出血病灶多的患者更容易发现并转诊纳入研究。在进行完整的评估后,单纯微出血的患者中无一例发现有缺血症状。前非外伤性脑叶 ICH 患者的研究中已经发现同样现象。在进行完整的评估后,单纯微出血的患者中无一例发现有缺血症状。因此,我们无法证明单纯微出血患者不能接受抗凝治疗。32

在进行完整的评估后,单纯微出血的患者中无一例发现有缺血症状。前非外伤性脑叶 ICH 患者的研究中已经发现同样现象。在进行完整的评估后,单纯微出血的患者中无一例发现有缺血症状。因此,我们无法证明单纯微出血患者不能接受抗凝治疗。32

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