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 ICH. Microbleed-only patients had a higher mortality rate (hazard ratio, 1.67; 95% confidence interval, 1.1–2.6) compared with ICH survivors. Warfarin use and increasing age were independent predictors of future ICH among microbleed-only patients after correction for other covariates.

Conclusions—Patients presenting with isolated lobar microbleeds on MRI have a genetic, neuroimaging, and hemorrhagic risk profile suggestive of severe CAA pathology. They have a substantial risk of incident ICH, potentially affecting decisions regarding anticoagulation in clinical situations. (Stroke. 2014;45:2280-2285.)

Key Words: cerebral amyloid angiopathy ▪ cerebral hemorrhage ▪ cerebral microbleeds ▪ magnetic resonance imaging

Received February 12, 2014; final revision received May 20, 2014; accepted May 20, 2014.
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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.114.005151
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 were older (P=0.003), but other baseline characteristics (sex, vascular risk factors, apolipoprotein E [APOE], number of microbleeds, and leukoaraiosis volume) did not differ from the longitudinal cohort (n=300; all P>0.2). Information on antithrombotic medication use, incident lobar ICH, and occurrence and cause of death was obtained by follow-up phone calls at 3 months after enrollment and every 6 months thereafter. Chart review was performed when needed to adjudicate the nature of an event reported as a new lobar ICH. We accrued the date of death by consulting the Social Security Death Index as described previously. All patients were followed from their date of enrollment until the occurrence of ICH, death, or the end of follow-up in June 2012.

This study was performed with the approval of and in accordance with the guidelines of the institutional review board of Massachusetts General Hospital and with informed consent of all subjects or authorized family members. Radiological and genetic analyses were performed by separate study personnel and the results recorded without the knowledge of the subjects’ clinical information.

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 MIRcron, 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 into 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 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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lobar Microbleed-Only (n=63)</td>
<td>Lobar ICH (n=316)</td>
</tr>
<tr>
<td>Definite/probable CAA</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>40 (63)</td>
<td>162 (51)</td>
</tr>
<tr>
<td>Age, y</td>
<td>73.6±8.3</td>
<td>73.6±9</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>34 (54)</td>
<td>194 (61)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>26 (41)</td>
<td>136 (43)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>9 (14)</td>
<td>55 (17)</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE ε2 frequency</td>
<td>15.6%</td>
<td>12%</td>
</tr>
<tr>
<td>APOE ε4 frequency</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>Radiological markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar microbleed count</td>
<td>10 (4–30)</td>
<td>2 (1–9)</td>
</tr>
<tr>
<td>WMH volume, mL</td>
<td>31 (18–46)</td>
<td>23 (12–40)</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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Event: occurrence of lobar ICH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed person-years</td>
<td>241</td>
<td>968</td>
</tr>
<tr>
<td>No. of occurrence (%)</td>
<td>12 (20)</td>
<td>86 (36)</td>
</tr>
<tr>
<td>Incidence of ICH per 100 person-years (95% CI)</td>
<td>5 (2.6–8.7)</td>
<td>8.9 (7.1–11)</td>
</tr>
<tr>
<td>Crude hazard ratio (95% CI)</td>
<td>0.57 (0.3–1.04)</td>
<td>Ref</td>
</tr>
<tr>
<td>Adjusted hazard ratio* (95% CI)</td>
<td>0.58 (0.31–1.06)</td>
<td>Ref</td>
</tr>
<tr>
<td>Event: occurrence of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed person-years</td>
<td>261</td>
<td>1316</td>
</tr>
<tr>
<td>No. of occurrence (%)</td>
<td>31 (52)</td>
<td>105 (44)</td>
</tr>
<tr>
<td>Incidence of death per 100 person-years (95% CI)</td>
<td>11.9 (6.5–16.8)</td>
<td>8 (6.5–9.7)</td>
</tr>
<tr>
<td>Crude hazard ratio (95% CI)</td>
<td>1.8 (1.2–2.8)</td>
<td>Ref</td>
</tr>
<tr>
<td>Adjusted hazard ratio* (95% CI)</td>
<td>1.67 (1.1–2.6)</td>
<td>Ref</td>
</tr>
</tbody>
</table>

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.

Figure 1. Survival curves of the 2 groups for occurrence of intracerebral hemorrhage (ICH; A) and death (B). MB indicates microbleed.
Hemorrhage Risk in Patients With Lobar Microbleeds

van Etten et al

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. 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, 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. 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. A neuropathologic study also suggested that CAA patients with multiple microbleeds might have different vessel pathology (thicker amyloid-positive vessel walls) compared with CAA patients with few lobar microbleeds, suggesting that the ICH risk might be different across these groups. 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. 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. 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.

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

Figure 2. Baseline and follow-up imaging of a lobar microbleed-only patient who later developed intracerebral hemorrhage (ICH). An 85-year-old woman with no prior stroke, who presented with cognitive symptoms, was enrolled after finding of multiple isolated lobar microbleeds on MRI (white arrows, A). Four months later, the patient presented to the emergency department with acutely altered mental status. Her head computed tomography showed a right-sided posterior lobar ICH with ventricular extension (black arrow, B).
recent studies that show higher mortality in older adults with microbleeds.33-34 Although clearly requiring further analysis, 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 these 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 atrial 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 Gurol 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*. 2014;45:2280-2285; originally published online June 19, 2014; doi: 10.1161/STROKEAHA.114.005151

*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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Incidence of Symptomatic Hemorrhage in Patients With Lobar Microbleeds

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Background and purpose: Cerebral amyloid angiopathy (CAA) is a dominant cause of spontaneous lobar and deep lobar hemorrhages. The diagnosis is usually made post mortem, and it is not clear whether patients who have a recent hemorrhage are likely to have CAA.

Methods: The incidence of symptomatic hemorrhage in patients with lobar microbleeds was examined in the Baseline-MR Imaging Follow-Up of High-Risk Patients (BUPH) study. Patients with lobar microbleeds were identified in a database of patients recruited to study the clinical significance of microbleeds. Baseline and follow-up MRIs were obtained on 316 patients with lobar microbleeds (mean age 63 years, 137 men); 240 patients had symptomatic hemorrhage at follow-up. Clinical and laboratory data were available for 204 patients at baseline and at follow-up.

Results: Patients with lobar microbleeds who experienced a hemorrhage were significantly older at baseline and at follow-up and were more likely to be male than those without hemorrhages. Generalized linear models showed that older age, male gender, and prior microbleeds increased the risk of symptomatic hemorrhage. The risk of symptomatic hemorrhage was 11% (95% CI 5%–19%) in patients with lobar microbleeds compared with 5% (95% CI 2%–9%) in patients with deep microbleeds (P = 0.01), after controlling for age and gender.

Conclusion: Our results show that patients with lobar microbleeds who experience a symptomatic hemorrhage are significantly older at baseline and at follow-up than those without hemorrhages.

Stroke. 2014;45:2280-2285.
检验均是双侧检验。所有分析均用 SPSS 20.0 软件完成。所有平高于一般的老年人（估计每年每 100 人发生 0.015–0.05 例脑出血）但这种差异未达到统计学差异（图 1A；HR 0.58；95%CI 0.31–1.06；P = 0.06）。

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，但这种差异未达到统计学差异。在随访过程中，单纯微出血组有 31 例死亡（11.9/100 人 - 年），而脑出血组有 105 例（8/100 人 - 年）。校正年龄、性别、高血压、白质高信号体积和微出血数量等因素后，脑出血组的事件致死率高于单纯微出血组（每 100 人 - 年）。

结果

脑叶出血患者基线和随访影像资料。

29 例是轻度认知症状，4 例步态异常，6 例因为短暂的感觉障碍而入院治疗。30 例患者发生症状性 ICH，8 例患者发生 ICH 并未接受抗凝治疗。31

与脑叶 ICH 相比，单纯脑微出血组存在等同甚至更强的 CAA 病理学改变。研究显示单纯脑叶微出血患者及以脑叶 ICH 起病的 CAA 患者有相似的遗传学及影像学特征。两组患者有相对较高的整体 ICH 发生率这一结果。对于因神经系统相关的症状而行 MRI 检查的老年患者，如果发现脑叶微出血灶，一般情况下会怀疑是否患 CAA。本研究人群也存在类似问题。研究纳入的单纯微出血患者在年龄和血管危险因素方面均无差异。在 APOE 基因型上，两者也无显著差异。单纯脑微出血组较脑叶出血组的事件数致死率高。33,34

我们分析了单纯脑叶微出血组继发脑出血的预测因素。在包括性别、年龄、血管危险因素和载脂蛋白 E 等其他因素之后，更大的白质高信号体积和微出血数量作为协变量的多因素 Cox 回归模型中，华法林的使用 (P = 0.02) 和高龄 (P = 0.04) 是和继发脑出血时间独立相关的因素。当把阿司匹林的使用引入模型之后，这种关联仍然和继发性脑出血相关 (P = 0.04)。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性卒中、痴呆、大面积损伤或其他的神经退行性改变。

我们探讨了单纯脑微出血患者发生 ICH 的风险，尤其是 CAA 相关 ICH。虽然单纯脑微出血的 CAA 患者较既往有 ICH 者发生新 ICH 的风险更高，但这种差异未达到统计学差异（表 2 和图 1B；校正 HR1.67；95% CI 为 1.1-2.6；P = 0.01）。这提示他们发生 ICH 的风险可能不同。30

同时该组患者存在较高的 ICH 风险，整体死亡率亦较以脑叶 ICH 起病的 CAA 患者高。33,34

脑出血的患者的基线和随访影像资料。

我们分析了单纯脑叶微出血组继发脑出血的预测因素。在包括性别、年龄、血管危险因素和载脂蛋白 E 等其他因素之后，更大的白质高信号体积和微出血数量作为协变量的多因素 Cox 回归模型中，华法林的使用 (P = 0.02) 和高龄 (P = 0.04) 是和继发脑出血时间独立相关的因素。当把阿司匹林的使用引入模型之后，这种关联仍然和继发性脑出血相关 (P = 0.04)。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性卒中、痴呆、大面积损伤或其他的神经退行性改变。

我们探讨了单纯脑微出血患者发生 ICH 的风险，尤其是 CAA 相关 ICH。虽然单纯脑微出血的 CAA 患者较既往有 ICH 者发生新 ICH 的风险更高，但这种差异未达到统计学差异（表 2 和图 1B；校正 HR1.67；95% CI 为 1.1-2.6；P = 0.01）。这提示他们发生 ICH 的风险可能不同。30

同时该组患者存在较高的 ICH 风险，整体死亡率亦较以脑叶 ICH 起病的 CAA 患者高。33,34

脑出血的患者的基线和随访影像资料。患者发生症状性脑叶 ICH 的风险并无相关性，提示上述选择偏倚并不影响单纯微出血组

结论

回

我们分析了单纯脑叶微出血组继发脑出血的预测因素。在包括性别、年龄、血管危险因素和载脂蛋白 E 等其他因素之后，更大的白质高信号体积和微出血数量作为协变量的多因素 Cox 回归模型中，华法林的使用 (P = 0.02) 和高龄 (P = 0.04) 是和继发脑出血时间独立相关的因素。当把阿司匹林的使用引入模型之后，这种关联仍然和继发性脑出血相关 (P = 0.04)。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性卒中、痴呆、大面积损伤或其他的神经退行性改变。

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