Incidence of Symptomatic Hemorrhage in Patients With Lobar Microbleeds

Ellis S. van Etten, MD; Eitan Auriel, MD, MSc; Kellen E. Haley, BA; Alison M. Ayres, BA; Anastasia Vashkevich, BA; Kristin M. Schwab, BA; Jonathan Rosand, MD, MSc; Anand Viswanathan, MD, PhD; Steven M. Greenberg, MD, PhD; M. Edip Gurol, MD, MSc

Background and Purpose—Lobar microbleeds suggestive of cerebral amyloid angiopathy (CAA) are often identified on MRI in the absence of lobar intracerebral hemorrhage (ICH). We compared the baseline characteristics and risk of subsequent ICH among such patients to those presenting with CAA-related lobar ICH.

Methods—Clinical data (demographics, risk factors), apolipoprotein E genotype, neuroimaging markers of CAA severity (microbleed counts, leukoaraiosis volume), and clinical outcomes (incidence rates of ICH and death during a mean follow-up of 5.3±3.8 years) were compared between 63 patients enrolled because of incidentally found microbleeds and 316 with CAA-related ICH, in our prospectively enrolled cohort. Predictors of incident ICH were explored in the microbleed-only patients using multivariable Cox regression models.

Results—Microbleed-only patients shared similar demographic, apolipoprotein E, and vascular risk profiles with lobar ICH patients, but had more lobar microbleeds (median, 10 versus 2; P<0.001) and higher leukoaraiosis volumes (median, 31 versus 23 mL; P=0.02). Microbleed-only patients had a nontrivial incidence rate of ICH, not different from patients presenting with ICH (5 versus 8.9 per 100 person-years; adjusted hazard ratio, 0.58; 95% confidence interval, 0.31–1.06; P=0.08). 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

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 neurologic 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 for CAA.
Hospital with neurological symptoms and enrolled in a longitudinal cohort study of the natural history of CAA.18–20 Patients were enrolled with definite or probable CAA according to the previously validated Boston criteria,21 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 CAA22 or autosomal dominant hereditary CAA23 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.24 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.24 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, or APOE) did not differ from the longitudinal cohort (n=300; all P>0.2). Information on antithrombotic medication use, hypertension, WMH, and microbleeds. All 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.25

MRI Acquisition and Analysis
Images were obtained using a 1.5-T magnetic resonance scanner (GE Signa). 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.21 White matter hyper-intensity (WMH or leukoaraiosis) volume was quantified as previously validated24 using a computer-assisted algorithm that involves MRicron, a freely available tool.26 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 analysis 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 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 IHs 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>Lobar Microbleed-Only (n=63)</th>
<th>Lobar ICH (n=316)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Definite/probable CAA All</td>
<td>All</td>
<td></td>
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<tr>
<td>Clinical variables</td>
<td></td>
<td>Male sex (%) 40 (63) 162 (51)</td>
<td>0.1</td>
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<tr>
<td></td>
<td></td>
<td>Age, y 73.6±8.3 73.6±9</td>
<td>&gt;0.2</td>
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<td></td>
<td></td>
<td>Hypertension (%) 34 (54) 194 (61)</td>
<td>&gt;0.2</td>
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<tr>
<td></td>
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<td>Hypercholesterolemia (%) 26 (41) 136 (43)</td>
<td>&gt;0.2</td>
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<tr>
<td></td>
<td></td>
<td>Diabetes mellitus (%) 9 (14) 55 (17)</td>
<td>&gt;0.2</td>
<td></td>
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<tr>
<td>Genotype</td>
<td></td>
<td>APOE ε2 frequency 15.6% 12%</td>
<td>&gt;0.2</td>
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<tr>
<td></td>
<td></td>
<td>APOE ε4 frequency 25% 23%</td>
<td>&gt;0.2</td>
<td></td>
</tr>
<tr>
<td>Radiological markers</td>
<td></td>
<td>Lobar microbleed count 10 (4–30) 2 (1–9)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>WMH volume, mL 31 (18–46) 23 (12–40)</td>
<td>0.02</td>
<td></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>Lobar Microbleed-Only (n=60)</th>
<th>Lobar ICH (n=240)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event: occurrence of lobar ICH</td>
<td></td>
<td>Observed person-years 241 968</td>
<td>…</td>
<td>…</td>
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<tr>
<td></td>
<td></td>
<td>No. of occurrence (%) 12 (20) 86 (36)</td>
<td>…</td>
<td>…</td>
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<tr>
<td></td>
<td></td>
<td>Incidence of ICH per 100 person-years (95% CI) 5 (2.6–8.7) 8.9 (7.1–11)</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crude hazard ratio (95% CI) 0.57 (0.3–1.04) Ref</td>
<td>0.07</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted hazard ratio* (95% CI) 0.58 (0.31–1.06) Ref</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Event: occurrence of death</td>
<td></td>
<td>Observed person-years 261 1316</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of occurrence (%) 31 (52) 105 (44)</td>
<td>…</td>
<td>…</td>
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<tr>
<td></td>
<td></td>
<td>Incidence of death per 100 person-years (95% CI) 11.9 (8.6–16.8) 8 (6.5–9.7)</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crude hazard ratio (95% CI) 1.8 (1.2–2.8) Ref</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted hazard ratio* (95% CI) 1.67 (1.1–2.6) Ref</td>
<td>0.02</td>
<td></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.
risk of subsequent ICH, and an overall higher mortality than and Figure as previously observed in nontraumatic lobar ICH. There isolated lobar microbleeds were in the same age range and had compared with the lobar ICH CAA patients, the patients with vascular characteristics at presentation between individuals with In this study, we have identified similar genetic and radiologi- these patients. 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 (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. 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

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.
recent studies that show higher mortality in older adults with microbleeds.\textsuperscript{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

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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


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脑叶出血组(n=316) P值

因进行了前瞻性分析18-20且不具有其它可能引起脑出血的因素

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>事件:脑叶出血</th>
<th>患者组别及例数</th>
<th>每100人-年的脑出血发生率(95% CI)</th>
<th>事件数,人-年</th>
<th>校正风险比*(95% CI)</th>
<th>原始风险比(95% CI)</th>
<th>每100人-年的死亡发生率(95% CI)</th>
<th>事件数,人-年</th>
<th>校正风险比*(95% CI)</th>
<th>原始风险比(95% CI)</th>
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<tr>
<td></td>
<td>仅有脑叶微出血组(n=63)</td>
<td>5 (2.6–8.7)</td>
<td>241</td>
<td>12 (20)</td>
<td>261</td>
<td>13 (23%)</td>
<td>23 (1–9)</td>
<td>6 (3.6–5.8)</td>
<td>22 (4–39)</td>
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统计分析

单因素分析用于比较两组间的临床特征、载脂蛋白 ε4 和载脂蛋白 ε2 等基因型的差异。对不同的危险因素,包括性别、年龄、高血压、高同型半胱氨酸血症、糖尿病、脑出血和死亡,在研究假设下进行分析性分析。对除载脂蛋白 E 外的基因型,我们在校正分析中通过应用其他基因型,进行单因素分析。单因素分析用于比较两组间的临床特征、载脂蛋白 ε4 和载脂蛋白 ε2 等基因型的差异。对不同的危险因素,包括性别、年龄、高血压、高同型半胱氨酸血症、糖尿病、脑出血和死亡,在研究假设下进行分析性分析。对除载脂蛋白 E 外的基因型,我们在校正分析中通过应用其他基因型,进行单因素分析。单因素分析用于比较两组间的临床特征、载脂蛋白 ε4 和载脂蛋白 ε2 等基因型的差异。对不同的危险因素,包括性别、年龄、高血压、高同型半胱氨酸血症、糖尿病、脑出血和死亡,在研究假设下进行分析性分析。对除载脂蛋白 E 外的基因型,我们在校正分析中通过应用其他基因型,进行单因素分析。
脑出血及 9 例脑叶出血患者进行了尸检。均经病理证实存在中到重度的
脑损伤严重程度的标记物, 这表明在这些病例中经典的血管淀粉样
病可能就导致在本队列研究中, 纯微出血组患者表现为高 WMH 负荷及
形体标志物, 这些标志物包括微出血病灶数目多(可能存在上述偏倚)、
和 ε4 等位基因频率相对较高, 这在以
CAA 患者再次出现 ICH 风险高, 即使伴有心房纤颤, 也不宜应用抗凝
治疗。32

目前的数据将影响抗凝治疗的抉择。随着 MRI 技术的广泛应用,
经病理学研究发现, 与微出血灶数目较少的 CAA 患者相比, 多发性脑
叶微出血发生率高, 本研究结果进一步支持在无症状个体中检测 CAA
的 ICH 风险, 从而推断出风险的低限。其在脑叶微出血的患者中, 也
显示有脑叶 ICH 风险增高, 然而, 华法林并不应作为 CAA 患者的首
选抗凝药物。33

尽管需要进一步的研究分析, 但目前数据提示, 对于存在这类偏
倚的患者, 无论单因素分析还是多因素分析中, 单纯脑叶微出血的
患者均无痴呆、卒中或其他神经退行性疾病, 从而减少了可能影响
推测是否患 CAA。本研究结果也存在类似问题。研究纳入的单纯微出
血患者均无痴呆、卒中或其他神经退行性疾病, 这可能使偏倚影响更
为明显。

我们选择了单独脑叶微出血作为研究对象, 因为其较少有临床
症状评估, 27 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, 4 例是由于脑卒中或脑肿瘤, 其他 24 例是由于其他原因
入院。

因此, 我们目前仍不能根据
CAA 患者再次出现 ICH 的风险来推断这些病灶的临床意义。34

多项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
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
没有显著差异。唯一具有统计显著性
差异的 ICH 风险稍低, 但整体来说仍然有较高的出血风险。35

关于脑损伤严重程度的标记物, 这表明在这些病例中经典的血管淀粉样
病可能就导致在本队列研究中, 纯微出血组患者表现为高 WMH 负荷及
形体标志物, 这些标志物包括微出血病灶数目多(可能存在上述偏倚)、
和 ε4 等位基因频率相对较高, 这在以
CAA 患者再次出现 ICH 风险高, 即使伴有心房纤颤, 也不宜应用抗凝
治疗。32

目前的数据将影响抗凝治疗的抉择。随着 MRI 技术的广泛应用,
经病理学研究发现, 与微出血灶数目较少的 CAA 患者相比, 多发性脑
叶微出血发生率高, 本研究结果进一步支持在无症状个体中检测 CAA
的 ICH 风险, 从而推断出风险的低限。其在脑叶微出血的患者中, 也
显示有脑叶 ICH 风险增高, 然而, 华法林并不应作为 CAA 患者的首
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