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# Cerebral Microbleeds

## Prevalence and Associations With Cardiovascular Risk Factors in the Framingham Study

Tom Jeerakathil, MD; Philip A. Wolf, MD; Alexa Beiser, PhD; John K. Hald, MD; Rhoda Au, PhD; Carlos S. Kase, MD; Joseph M. Massaro, PhD; Charles DeCarli, MD

**Background and Purpose**—Cerebral microbleeds (CMBs) are areas of low signal intensity on gradient echo T2\*-weighted magnetic resonance imaging (T2\*MRI) corresponding to hemosiderin deposits in the perivascular space. Microangiopathy from atherosclerosis or amyloid angiopathy might lead to the formation of these lesions; therefore, there may be associations between CMBs and cardiovascular risk factors, APOE allele status, and brain morphology. We examined these relationships in the Framingham Study (FHS).

**Methods**—In 472 subjects from the FHS Offspring and Cohort, we related CMB status to age, sex, systolic blood pressure, total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels, smoking, diabetes, total hemispheric brain volume, white matter hyperintensity volume (WMHV), and APOE allele status.

**Results**—Overall prevalence of CMBs was 4.7%, but CMBs were more prevalent with advanced age and male sex. Blood pressure, brain volume, and WMHV were related to CMBs in crude analysis but not after adjustment for age and sex. There were no significant relationships demonstrated between CMBs and APOE allele status, cholesterol, smoking, or diabetes.

**Conclusions**—There is a low prevalence of CMBs in the community and a strong relationship with increasing age and male sex. We found no independent relationships with cardiovascular risk factors, APOE status, brain volumes, or WMH. (*Stroke*. 2004;35:1831-1835.)

**Key Words:** amyloid ■ angiopathy ■ intracerebral hemorrhage ■ risk factors ■ prevalence

Cerebral microbleeds (CMBs), visible on T2\*-weighted gradient echo magnetic resonance imaging (MRI) sequences, are rounded areas of signal loss, generally 2 to 5 mm in size, some of which represent deposits of hemosiderin.<sup>1-4</sup> CMBs are believed to be the consequence of microangiopathic processes, either from atherosclerosis and fibrohyalinosis or from cerebral amyloid angiopathy. The predominant contributors to the formation of these lesions might be cardiovascular risk factors, mechanisms underlying amyloid angiopathy, or perhaps the aging process itself.

Substantial evidence supports the association between CMBs and atherosclerotic or hypertensive vasculopathies. These lesions are present in up to 71% of individuals presenting with intracerebral hemorrhage and in 20% to 68% of those admitted with ischemic stroke.<sup>5-7</sup> In univariate analysis, CMBs increase in prevalence with age, hypertension, the presence of silent cerebral infarct, the presence of white matter hyperintensity (WMH), and a history of clinically apparent stroke.<sup>2,3,6</sup> More recently they have been

associated with hypertension, leukoaraiosis, low-serum total cholesterol and high-density lipoprotein cholesterol (HDL-C) in multivariate analysis in Korean patients with ischemic stroke, hemorrhagic stroke, or other neurological disorders.<sup>8</sup>

Although not yet proven, CMBs may be predictive of future risk of intracerebral hemorrhage in stroke-free individuals. Despite this possibility, there are insufficient data on CMB prevalence and risk factors in healthy subjects. Prevalence in healthy clinic-based subjects ranges from 3.1% to 7.7%.<sup>5,6,9</sup> In the only community-based study, the prevalence was 6.4% among 280 healthy elderly persons.<sup>2</sup> From these studies, age, hypertension, and smoking emerged as risk factors for CMBs in univariate analysis. These prevalence rates need to be confirmed in other community-based samples, and potential risk factors for CMBs need to be investigated with multivariate analyses.

A link between CMBs and amyloid angiopathy has also been suggested.<sup>1-10</sup> Cerebral amyloid angiopathy is associated with apolipoprotein E (APOE)  $\epsilon$ 4 and APOE  $\epsilon$ 2 alleles.<sup>11</sup>

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However, a relationship between CMBs and APOE status has not yet been demonstrated. Similarly, if these lesions represent sequelae of amyloid changes in the brain, they may be preclinical manifestations of dementing processes such as Alzheimer disease. If this is so, then asymptomatic subjects with CMBs might be expected to have smaller brain volumes than subjects without the lesions. These relationships may be particularly strong for subjects with CMBs in the cerebral cortex, where amyloid angiopathy is most active.

The objectives of this study were to: (1) determine the prevalence of CMBs in a community-based sample; (2) relate cardiovascular risk factors to presence of CMBs; (3) examine the relationships between CMBs and APOE allele status; and (4) relate the presence of CMBs to white matter hyperintensity volume (WMHV) and total brain volume measured quantitatively.

### Subjects and Methods

The sampling schemes for the Framingham Study Original Cohort (FSC) and Offspring Cohort (FSO) have been described in detail elsewhere.<sup>12,13</sup> Starting in 1999, all members of the FCS and FSO were invited to participate in a study of cognitive performance and MRI measures of brain structures. Subjects were scheduled in sequence based on the anniversary of the last cycle examination date.

Subjects were excluded from MRI scanning if they refused or if there was a contraindication, including certain implantable devices, intraorbital metallic foreign body, intracranial aneurysm clips, cardiac pacemaker, valvular prosthesis, and cochlear implants.

The current study group consists of all consecutive FSC and FSO subjects who underwent brain MRI from the date gradient echo sequences were added to the protocol on December 18, 2000 until August 30, 2001. A total of 509 MRIs were performed, with 28 excluded because data were not yet available, and 9 were excluded because of prevalent stroke, dementia, major head trauma, or other neurological diagnosis that might produce abnormal MRI or cognition, leaving a total of 472 subjects. All subjects provided informed consent in accordance with the requirements of the Boston Medical Center Institutional Review Board.

A 1.0-tesla MR machine (Siemens Magnetom) was used to obtain the following sequences: coronal T2-weighted 2420/20 to 90 (TR/TE), echo train length 8, field of view 22 cm, acquisition matrix 192×256 interpolated to 256×256 with 1 excitation, 4-mm slice thickness from nasion to occiput, sagittal T1-weighted 11.4/4.4, 3D FLASH, 192 mm slab, 128 slices of 1.5-mm thickness, 12-degree flip angle and axial gradient echo 760/26, 30-degree flip angle, 5-mm slice thickness, and 0.5 mm gap.

Imaging data were interpreted blindly to subject data and in random order using a custom-designed image analysis package, QUANTA 6.2, operating on a Sun Microsystems Ultra 5 workstation. Semiautomated analysis of pixel distributions, based on mathematical modeling of MRI pixel intensity histograms for cerebrospinal fluid and white and gray matter, was used to determine the optimal threshold of pixel intensity to best-distinguish cerebrospinal fluid from brain matter based on previously published methods with good interrater and intrarater reliabilities.<sup>14,15</sup>

The intracranial vault above the tentorium was outlined manually to determine the total cranial volume (TCV). After removal of skull and nonbrain tissues from the image, mathematical modeling was performed to determine total brain volume (TCB). The TCB measure consisted of supratentorial gray and white matter, excluding cerebrospinal fluid. A ratio was calculated of TCB over TCV and the resulting value was designated total cerebral brain volume (TCBV). TCBV is a measure of brain volume corrected for head size. Interrater reliability for TCV and TCB has been previously reported.<sup>14</sup>

The volume of WMH was determined quantitatively by segmentation of abnormal white matter from surrounding brain using

semiautomated computer algorithms according to previously published methods of high reliability.<sup>16,17</sup> WMHV was corrected for head size by expressing it as a ratio over TCV (WMH/TCV=WMHV). Because WMHV was not normally distributed, it was log-transformed for analysis as a continuous variable.

We defined CMBs as rounded areas of signal loss <10 mm in diameter. Symmetrical areas of physiological calcification in the globus pallidus were ignored. Sulcal flow voids from vessels were discounted, as were low-signal lesions thought to be signal averaging from adjacent bone. These criteria are similar to those used in previous studies.<sup>1-3</sup> All MRI scans were read by at least 2 (250 scans) or 3 (222 scans) independent raters blinded to clinical history who determined the presence, number, and location of CMBs. Given that other structures (blood vessels, calcifications, signal averaging of bone, small cavernous hemangiomas) can produce areas of signal loss similar in appearance to CMBs, all potential microbleeds were reviewed by a committee of 2 neurologists and a neuroradiologist. Generally there was agreement, but if not, the lesion was classified based on the majority opinion. Results of reliability testing are described.

At each cycle examination, extensive risk factor information was gathered, including systolic and diastolic blood pressure, smoking status, diabetes status, and cholesterol levels, and this information was available from the most recent examination cycle for 87% (410/472) of subjects. Risk factor data from examination cycle 24 (1995-1998) were used for FSC and risk factor data from examination cycle 6 (1995-1999) were used for FSO. Hypertension was defined as a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg or the need for antihypertensive medical therapy.

APOE genotype determination was performed using standard techniques of DNA amplification and restriction isotyping. For the purposes of analysis, subjects were classified as having an APOE  $\epsilon$ 2 allele if their allele status was 2,2 or 2,3 or 2,4 and as having an APOE  $\epsilon$ 4 allele if their status was 4,4 or 4,3 or 4,2.

For comparison of risk factors between subjects with and without CMBs, we used 2 sample *t* tests for continuous variables and either  $\chi^2$  tests or Fisher exact test for categorical variables. We then performed logistic regression with systolic blood pressure, total cholesterol level, HDL-C, age, smoking status, diabetes, APOE allele status, and sex as independent variables and CMB status as the dependent variable. We performed crude analyses and analyses adjusted for age and sex. In addition we compared allele frequency for each APOE allele between subjects with and without CMBs using  $\chi^2$  tests. We used analysis of covariance to compare TCBV between those with and without CMBs in crude analysis and adjusted for age and sex. Similarly, we compared log WMHV between those with and without CMBs in crude analysis and adjusted for age and sex with analysis of covariance.

### Results

The kappa statistics for the classification of microbleeds for the 3 raters based on 222 scans read independently by all raters ranged from 0.33 to 0.57. This corresponds to fair to moderate agreement according to Landis and Koch.<sup>18</sup> Compared with those FSC and FSO not included in the current study, those included were younger with a higher HDL and a lower prevalence of diabetes and hypertension (Table 1).

The mean age (SD) of the study sample at the time of MRI was 64.4 (12.4) with 213 men (45.0%). The prevalence of CMBs in the entire sample was 4.7% (22/472), but prevalence differed by age and gender. Subjects 75 years of age or older had a prevalence of 12.6% compared with 2.2% in those younger than 75. CMBs were present in 7.0% (15/213) of men and 2.7% (7/259) of women. Sixteen patients (73%) had lesions in the cerebral cortex or subcortical white matter, 5 (23%) had lesions in the basal ganglia or thalamus, and 3

**TABLE 1. Comparison of FSC and FSO Subjects Included in Current Study Versus Not Included**

	With CMB Data	Without CMB Data
N	472	3953
Age at examination 6 or 24 (y)	60.5	64.3‡
Male (%)	45	44
SBP (mm Hg)	128.6	130.6
TChol (mg/dL)	205.3	204.5
HDL (mg/dL)	53.3	50.5†
Current smoker (%)	12.7	13.6
Diabetes (%)	7.8	13.4†
Hypertension (%)	28.9	38.2‡

SBP indicates systolic blood pressure; Tchol, total cholesterol; HDL, high-density lipoprotein.

\* $P < 0.05$ .

† $P < 0.01$ .

‡ $P < 0.001$ .

(14%) had posterior fossa lesions. Only 4 subjects had multiple CMBs with counts ranging from 3 to 7.

Subjects with lesions had a significantly higher mean age, systolic blood pressure, and proportion of men in univariate comparisons (Table 2). In logistic regression age and male sex remained significantly related to CMBs after adjustment for each other but systolic blood pressure was no longer significant after age and sex adjustment (Table 3). There were no significant relationships demonstrated between lesions and the other risk factors.

APOE status was available for 78% (368/472) of subjects. For subjects with an  $\epsilon 2$  allele, the odds ratio for CMBs was 1.59 ( $P = 0.438$ ) and for subjects with an  $\epsilon 4$  allele the odds ratio was 0.52 ( $P = 0.316$ ). The frequency of the APOE  $\epsilon 2$  allele was higher in those with lesions (0.095) compared with those without (0.074), but the difference was not significant ( $P = 0.55$ ). The frequency of APOE  $\epsilon 4$  allele was lower in those with CMBs (0.071) compared with those without

**TABLE 2. Comparison of Cardiovascular Risk Factors in Subjects With and Without CMBs**

	Without CMB	With CMB
N	450‡	22‡
Mean age at MRI (SD)	63.9 (12.0)	74.4 (14.1)†
Mean SBP mm Hg (SD)	128.9 (18.5)	140.1 (19.6)†
Mean TChol mg/dL (SD)	205.3 (36.3)	206.5 (35.1)
Mean HDL-C mg/dL (SD)	53.5 (18.0)	50.1 (17.2)
Male (%)	44	68†
Current smoker (%)	12.6	15.0
Hypertension (%)	28.8	30.0
Diabetes (%)	8.0	5.0

SBP indicates systolic blood pressure; Tchol, total cholesterol.

\* $P < 0.05$ .

† $P < 0.01$ .

‡Age and sex were available for all 472 subjects.

Other risk factor information was available for 410 of 472 subjects.

(0.127), but the difference was not significant ( $P = 0.47$ ). The frequency of APOE  $\epsilon 3$  allele was similar in those with (0.83) and without (0.80) lesions ( $P = 0.69$ ). We repeated the logistic regression analyses including only subjects with lesions in a cortical/subcortical location ( $n = 16$ ) and those without CMBs ( $n = 450$ ) but still found no significant associations.

The mean TCBV was 0.73 (SD 0.04) for those with lesions and 0.77 (SD 0.04) for those without lesions. This difference was significant in crude ( $P < 0.001$ ) analysis but not after adjustment for age and sex ( $P = 0.130$ ). For subjects with cortical/subcortical CMBs the mean TCBV was 0.74 (SD 0.05), and this was significantly lower than the TCBV of subjects without CMBs in crude ( $P = 0.006$ ) but not adjusted analysis ( $P = 0.163$ ).

The quantity of WMH expressed as a percentage of total cranial volume (WMHV) was higher in subjects with CMBs (mean 0.24%; SD 0.27%) compared with subjects without CMBs (mean 0.10%; SD 0.17%). After log transformation and analysis of covariance, this difference was significant in crude analysis ( $P = 0.001$ ) but not after adjustment for age and sex ( $P = 0.279$ ). These analyses were repeated comparing only the 16 subjects with cortical/subcortical CMBs to those without any CMBs and there were no significant differences in crude ( $P = 0.178$ ) or adjusted analysis ( $P = 0.926$ ).

## Discussion

The prevalence of CMBs in the current study was similar to that found in the healthy community-based sample from the Austrian Stroke Prevention Study and lower than that found in hospitalized subjects with intracerebral hemorrhage or ischemic stroke.<sup>1-3,6,8,10</sup> We confirmed previous associations of these lesions with age.<sup>2,7</sup> Our results also demonstrate a striking increase in prevalence after the age of 75, which has not previously been reported.<sup>2</sup> Even after adjustment for age, men had a much higher risk of CMBs than women. Given observed relationships between CMBs and intracerebral hematoma, our findings are in keeping with the observation that the rate of intracerebral hematoma is higher in men than women.<sup>19</sup> Our results are not consistent with some autopsy series of patients with cerebral amyloid angiopathy that reported a higher proportion of women, and with some studies of Alzheimer disease, another cerebral amyloidopathy, which suggest greater risk for women.<sup>20,21</sup> Two other studies of healthy subjects reported a higher proportion of males in subjects with CMBs compared with those without, but the differences were not significant.<sup>2,9</sup>

Similar to previous studies in community-based subjects and healthy controls, we found a positive association between CMBs and blood pressure in crude analysis.<sup>2,3,9</sup> Unlike previous studies, we adjusted our analysis for age and sex, after which the odds ratio was smaller and the relationship was no longer significant. Therefore, age appears to be a positive confounder of the relationship between blood pressure and CMBs because systolic blood pressure and lesion prevalence increase with age. Another reason for the lack of a relationship with hypertension in our sample could be the low proportion of basal ganglionic and thalamic CMBs. Lesions in the basal ganglia or thalamus might be more likely to be related to hypertension, analogous to the situation with

**TABLE 3. Crude and Adjusted Logistic Regression of Cardiovascular Risk Factors to Predict CMB Status**

		Probability of CMB (%)	Odds Ratio for CMB	Odds Ratio for CMB*
Male	Y	7.0	2.73† (1.09–6.82)	3.06† (1.20–7.83)
	N	2.7		
Smoker	Y	5.8	1.23 (0.35–4.33)	2.43 (0.62–9.53)
	N	4.8		
Hypertension	Y	5.1	1.06 (0.40–2.82)	0.53 (0.19–1.49)
	N	4.9		
Diabetes	Y	3.1	0.61 (0.08–4.71)	0.35 (0.04–2.75)
	N	5.0		
Age: per 5-y increase			1.39‡ (1.17–1.66)	1.42‡ (1.18–1.71)
SBP: per 20-mm Hg increase			1.76‡ (1.17–2.63)	1.31 (0.80–2.14)
TChol: per 40-mg/dL increase			1.04 (0.63–1.70)	1.30 (0.77–2.22)
HDL: per 20-mg/dL increase			0.79 (0.46–1.36)	1.20 (0.65–2.23)

\*Adjusted for age and sex.

† $P < 0.05$ .‡ $P < 0.01$ .

Y indicates yes; N, no.

intracerebral hematoma. We did not consider subgroup analyses for subjects with basal ganglionic or thalamic lesions because there were so few. In contrast, 73% of our subjects with CMBs had cortical/subcortical lesions compared with 55% to 57% in 2 other studies of healthy volunteers.<sup>2,9</sup> It is possible that the higher proportion of cortical/subcortical lesions in our older sample may reflect age-related progression of cerebral amyloid angiopathy.

However, we found little direct evidence to support an association between all CMBs or cortical/subcortical CMBs and amyloid angiopathy. We found no significant associations between APOE  $\epsilon$  allele status and CMBs. Subjects with CMBs had smaller brain volumes corrected for head size, but these differences were accounted for by age and sex. If CMBs are markers of amyloid angiopathy-related processes like Alzheimer disease, we might have expected an independent relationship between the lesions and lower brain volumes. Similarly, we found little direct evidence to support the hypothesis that CMBs are related to atherosclerotic microangiopathy. Although subjects with CMBs had a higher burden of WMHI, the difference was explained by age and sex. We did not find relationships between cigarette smoking, diabetes, or cholesterol levels and CMBs. We acknowledge the possibility of type II errors given the low number of subjects with CMBs in the sample. Certainly, if any relationships exist between these risk factors and CMBs they are not as strong as those of age and gender.

The strengths of this study were prospectively gathered cardiovascular risk factor information, quantitative measurement of brain volume and WMH, multiple raters for interpretation of MRI scans with consensus to define CMB status, and APOE genotypic data. Another strength was the use of consecutive MRI scans scheduled in no particular order performed on a diverse group of healthy community-based subjects.

Our study was limited by restriction to a predominantly white, middle class population with little ethnic diversity. In addition, the power of the study was limited by the low prevalence of CMBs. Furthermore, only a small proportion of the FSC and FSO had gradient-echo MRI data available, and these individuals were younger and healthier than those not included in the study. For this reason, if there is truly a relationship between CMBs and cardiovascular risk factors, then the prevalence of CMBs in the general population might be higher than that of this study sample. The use of 1.0-tesla as opposed to 1.5-tesla MRI might have led to some underestimation of prevalence. If present, however, the magnitude of underestimation is likely to be small, because ours and other studies that used 1.0-tesla magnets reported a similar prevalence of CMBs to those that used 1.5-tesla magnets.<sup>9,22,23</sup> There is a degree of subjectivity in the interpretation of CMBs. Our kappa coefficients for interrater agreement ranged from 0.33 to 0.57 between 3 raters, which is lower than the 0.4 to 0.65 range reported in another study.<sup>2</sup> Our use of multiple raters and consensus addressed this problem, but improvements in MRI technology to allow better differentiation of calcium and small vascular structures from hemosiderin are ultimately required.

In summary there is a low prevalence of CMBs in the community and a marked increase in prevalence after the age of 75 and with male sex. We did not find any independent associations with other cardiovascular risk factors, APOE alleles, brain volume, or WMH index. To further define risk factors and prognosis for these lesions, future MRI studies would benefit from either very large sample sizes or a focus on populations with a high prevalence, such as persons older than age 75.

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