Title

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Journal

Stroke, 48(3)

ISSN

0039-2499

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Publication Date

2017-03-01

DOI

10.1161/strokeaha.116.015354

Peer reviewed

HHS Public Access

Author manuscript

Stroke. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

Stroke. 2017 March ; 48(3): 781–783. doi:10.1161/STROKEAHA.116.015354.

Cerebral Microbleeds as Predictors of Mortality: The Framingham Heart Study

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Abstract

Background and purpose—Cerebral microbleeds (CMB) represent a common MRI marker of cerebral small vessel disease, increasingly recognized as a subclinical marker of stroke- and dementia- risk. CMB detection may reflect the cumulative effect of vascular risk burden and be a marker of higher mortality. We investigated the relation of CMB to risk of death in community dwelling participants free of stroke and dementia.

Methods—We evaluated 1963 Framingham Original and Offspring Cohort participants (mean age 67 years; 54% women) with available brain MRI and mortality data. Using Cox-proportional hazards models we related CMB to all-cause, cardiovascular and stroke-related mortality.

Results—Participants with CMB (8.9%) had higher prevalence of cardiovascular risk factors and use of preventive medications. During a mean follow up of 7.2±2.6 years we observed 296 deaths. In age and sex-adjusted analysis CMB were associated with increased all-cause mortality (hazards ratio [HR]=1.39, 95% CI 1.03–1.88), a relation that was no longer significant after adjustment for cardiovascular risk and preventive medication use (HR=1.15,95% CI 0.82–1.63).

Conclusions—CMBs may represent the deleterious effect of cardiovascular risk factors in the cerebral vasculature. While their presence was associated with increased all-cause mortality, the

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Disclosures:
None

effect was no longer present after accounting for vascular risk factors and preventive treatment use. Further studies are required to clarify the role of cardiovascular preventive therapies for prevention of mortality in persons with incidental detection of CMB.

Introduction

Cerebral microbleeds (CMB) are subclinical markers of cerebral small vessel disease (CSVD) associated with stroke, dementia and modifiable vascular risk factors.[1–3] CMB represent a common MRI marker of hemorrhage-prone CSVD, but are also associated with ischemic events.[4] CMB may reflect an aggregate measure of vascular disease burden and their detection may portend higher risk of mortality.[5] We investigated the association between CMB and mortality in a large sample of neurologically healthy persons dwelling in the community, accounting for vascular risk factors, preventive cardiovascular medication use, and ischemic brain MRI measures of CSVD.

Methods

We included 1,963 Framingham Original and Offspring Cohort participants with available CMB data and follow up information for mortality, after excluding participants with prevalent stroke, dementia, or other neurological conditions that could affect MRI measures (supplementary figure I). Details of sample selection, MRI protocol and vascular risk factor definitions are presented in the on-line only Data supplement. The Institutional Review Board of Boston University Medical Center approved the study protocol and informed consent was obtained from all subjects.

CMB were defined using standard criteria,[6] with good intra-rater and inter-rater reliability measures (kappa statistic 0.78 for both).[3]

Follow up for mortality was carried through ongoing surveillance. All relevant data were reviewed by a panel of 3 investigators that determined the cause of death for cases as previously described.[7] Follow up for entry to present study spans from time of MRI until death, loss to follow up or December 31, 2012.

Statistical Analysis

Baseline characteristics of study participants and incidence rates were evaluated overall and by CMB brain location (i.e. any CMB, lobar only, deep and mixed, and deep only). Using cox proportional hazards regression models, we estimated hazards ratios (HR) and 95% confidence intervals (95% CI) for all-cause, cardiovascular and stroke related-mortality. Model 1 adjusted for age and sex; model 2 additionally adjusted for systolic blood pressure, current smoking, diabetes, total cholesterol, hypertension and cholesterol treatment, aspirin, antiplatelet and anticoagulant use, APOE-ε4 status, and time between covariate assessment and MRI; model 3 additionally adjusted for MRI markers of ischemic CSVD (ln-transformed white matter hyperintensity volume and presence of covert brain infarcts). CMB burden (≥2 CMBs, 1 CMB versus no CMB [referent]) was related to each of the outcome events. Statistical analyses were done using SAS version 9.4 (Cary, NC).

Results

Among the 173 participants (8.9%) with CMB, 64% had single and 36% multiple CMB. Participants with CMB were older, more likely to be men, had higher prevalence of vascular risk factors and previous cardiovascular disease (CVD), higher use of preventive medications, white matter hyperintensity volumes and presence of covert brain infarcts (Table 1).

Over a mean (SD) period of 7.2 (2.6) years, 296 participants died of any cause, 60 died of CVD related death and 17 of stroke related death. Crude incident rates of all event types were higher among participants with CMB (Supplementary Table I).

Participants with any CMB had a modest increase in risk of all-cause mortality (HR 1.39, 95% CI 1.03–1.88), but the associations were attenuated and no longer significant after adjustment for vascular risk factors (Table 2). Similar hazard ratios were observed among participants with lobar CMB and deep/mixed CMB, though with imprecise and non-significant estimates. Results pertaining to cardiovascular mortality were limited by lower number of events in CMB subgroups. Participants with ≥2 CMBs had a higher risk of all-cause mortality after adjustment for age and sex (HR=1.56, 95%CI: 1.06–2.31), but the association was attenuated after adjusting for vascular risk factors (supplementary Table II).

Discussion

In this prospective community-based study of participants free of neurological disease, detection of CMB was associated with a modest increase in all-cause mortality, but the association was not independent of vascular risk factors and use of preventive treatments.

Other studies have found that CMB are associated with increased risk of death among persons with dementia,[8] stroke,[9] and in a single community based study.[10] CMB may reflect the deleterious effect of long-term exposure to vascular risk factors in the cerebral vasculature. Our observation that participants with CMB had higher burden of ischemic CSVD (i.e. more covert brain infarcts and higher white matter hyperintensity volumes) supports this hypothesis. Further, prior studies suggest that CMB may be detectable before other organ involvement such as kidney or heart. Thus, CMB detection may offer a window of opportunity for clinicians to act upon modifiable risk factors to prevent mortality.

Among the strengths of our study are the large population based cohort design, careful ascertainment of cardiovascular risk and preventive medication use, and inclusion of brain MRI markers of ischemic brain injury, all factors that may impact our outcomes of interest. Clinical outcomes were ascertained using detailed review of all medical records. We included participants free of neurological disease, with a younger mean age than in prior studies. Brain MRI measurements were reliable and obtained blinded to clinical and demographic characteristics.

We submit that our results are unlikely to be biased by selection of participants into the study as their selection was unrelated to the exposure or outcome. Misclassification of exposure is possible, related to under detection of CMB compared to studies using higher

MR strength or more sensitive MRI protocols, but any misclassification would be non-differential, most likely to underestimate true effects. Our analyses involving pre-specified CMB subgroups are limited by the smaller sample and fewer events among these subgroups. Last, Framingham participants are primarily of European ancestry thus preventing generalization of results to other ethnic or racial groups.

Our results suggest that the association of CMB presence and mortality is not independent of vascular risk factors in asymptomatic community dwelling persons. The reduction of risk after adjustment for vascular risk factors and preventive treatment use needs further evaluation to clarify the role of preventive cardiovascular treatments for reduction of mortality in persons with incidental detection of CMB.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source of Funding:

National Heart, Lung and Blood Institute (NHLBI) contract (N01-HC-25195; HHSN268201500001I); National Institute of Neurological Disorders and Stroke grants (R01 NS017950), National Institute of Aging (R01 AG008122; K23AG038444; 1 R03 AG048180-01A1; AG054076; AG049607); National Institute of Health grants (1RO1 HL64753; R01 HL076784; 1 R01 AG028321, P30 AG010129), and NHLBI grants (HL67288, and 2K24HL04334).

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Table 1

Study sample characteristics

Characteristics	≥1 CMBs	
	No (N=1790)	Yes (N=173)
Continuous, mean (SD)		
Age at MRI (years)	66.5 (10.6)	74.8 (9.1)
Years between covariate measurement and MRI	0.7 (1.2)	0.6 (1.4)
Years of follow-up for all-cause mortality	7.3 (2.6)	6.4 (2.4)
Systolic blood pressure (mm Hg)	128 (18)	134 (21)
Diastolic blood pressure (mm Hg)	73 (10)	70 (11)
Total cholesterol (mg/dL)	192 (37)	179 (39)
Categorical, n (%)		
Women	987 (55.1)	73 (42.2)
Diabetes	220 (12.9)	32 (19.9)
Current smoker	181 (10.1)	12 (6.9)
Hypertension	965 (53.9)	135 (78.0)
Hypertension treatment	800 (44.7)	116 (67.1)
Aspirin use	704 (39.4)	94 (54.3)
Antiplatelet use	492 (27.5)	71 (41.0)
Anticoagulant use	67 (3.7)	19 (11.0)
Cholesterol treatment	670 (37.5)	94 (54.3)
Statin use	524 (29.3)	82 (47.4)
APOE Status		
Any ε4	405 (23.1)	44 (25.7)
Covert brain infarcts	237 (13.2)	47 (27.2)
White matter hyperintensities volume, median (25^{th}, 75^{th} percentile)	0.08 (0.04, 0.18)	0.23 (0.07, 0.58)
Prevalent cardiovascular disease	277 (15.5)	64 (37.0)
Death, any cause	241 (13.5)	55 (31.8)
Cardiovascular death	47 (2.6)	13 (7.5)
Stroke death	13 (0.7)	4 (2.3)

Table 2

Association of CMB presence with mortality.

		All-cause mortality (N=296)			CVD Mortality (N=60)		
Exposure	**Model**	**N**	**HR**	**95% CI**	**N**	**HR**	**95% CI**
Any CMB (vs. no CMB)	1	1963	1.39	1.03–1.88	1963	1.65	0.88–3.10
	2	1818	1.20	0.85–1.70	1818	1.58	0.75–3.35
	3	1818	1.15	0.82–1.63	1818	1.71	0.80–3.67
Lobar only (vs. no CMB)	1	1899	1.41	0.97–2.04	1899	1.95	0.94–4.03
	2	1760	1.19	0.77–1.84	1760	1.63	0.65–4.08
	3	1760	1.14	0.74–1.77	1760	1.77	0.69–4.53
Deep + mixed (vs. no CMB)	1	1854	1.33	0.85–2.08	-	-	-
	2	1721	1.21	0.73–1.99	-	-	-
	3	1721	1.17	0.71–1.94	-	-	-

Empty cells data not shown due to less than 5 events.

Model 1 is adjusted for age at MRI and sex.
Model 2 is additionally adjusted for SBP, hypertension treatment, current smoking, diabetes, total cholesterol, cholesterol treatment, aspirin use, antiplatelet use, anticoagulant use, prevalent CVD, APOE4, and time between covariate assessment and MRI.
Model 3 is adjusted for model 2 covariates plus CBI and ln-transformed white matter hyperintensities volume.