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Risk Factors, Stroke Prevention Treatments, and Prevalence of Cerebral Microbleeds in the Framingham Heart Study

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Abstract

Background and purpose—Cerebral microbleeds (CMBs) are associated with increased risk of stroke and poor cognition. Vascular risk factors and medications used for stroke prevention may increase the risk of CMB. We examined the prevalence of CMB and the association of these risk factors with CMB, postulating that risk factors for cerebral amyloid angiopathy would be associated with lobar CMB and markers of hypertensive vasculopathy with deep CMB.

Methods—We include 1,965 Framingham Original and Offspring participants (age 66.5±11.0years; 54%women) and evaluated the age- and sex-specific prevalence of CMB. We related various vascular and genetic (APOE) risk factors and medication use to presence of CMB overall and stratified by brain location (deep, lobar or mixed).

Results—CMBs were observed in 8.8% of participants, being mostly lobar (63%). CMB prevalence increased with age ($p<0.0001$) and was higher in men ($p<0.001$). Hypertension increased risk of any CMB, and in deep and mixed locations ($p<0.05$), and low total cholesterol and APOE ε4 increased risk of lobar CMB ($p<0.05$). Statin use increased risk of lobar and mixed location CMB ($p<0.05$). The latter association was not affected by adjustment for cholesterol levels, or concomitant medication use.

Conclusions—We observed the expected association of hypertension with deep CMB and low cholesterol and APOEε4 with lobar CMB. Additionally, statin use was independently associated with CMB risk. This potential adverse effect of statin use needs to be examined in other cohorts.

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Disclosures:
None.

Introduction

Cerebral microbleeds (CMB) are subclinical markers of risk of stroke, dementia and cognitive impairment.[1] The pathophysiology of CMB may vary based on their location, with lobar CMB attributed to cerebral amyloid angiopathy (CAA) and deep CMB to cerebral hypertensive vasculopathy.[1] CMB are markers of intracerebral bleeding risk in patients receiving antiplatelet,[2] anticoagulant[3] and lipid lowering[4] therapies and in clinical trials of immunotherapy for early Alzheimer's disease.[5] Traditional vascular risk factors have been related to CMB, especially in deep locations.[6, 7] The role of risk factors such as obesity, increased body mass index (BMI), metabolic syndrome and dyslipidemias is less clear, but they may increase risk of CMB directly or indirectly, and the associations may also vary according to CMB location.

We related vascular risk factors and secondary stroke prevention treatments to the presence and anatomical location of CMB.

Methods

Our study sample comprised Framingham Original and Offspring cohort participants (N=1,965) who attended a baseline examination between 1998 and 2008 and underwent a brain MRI between 2000 and 2009 with T2*GRE sequences allowing for detection of CMB. Details of sample selection, exclusion criteria, risk factor and covariate definitions, MRI protocol and data processing are presented in the online supplement (please see http://stroke.ahajournals.org). The Institutional Review Board of Boston University Medical Center approved the study protocol and informed consent was obtained from all subjects.

CMBs were defined using recently published guidelines[1] and grouped into 4 categories according to their brain location: any CMB, lobar only, deep only and deep + mixed (later called mixed). Further details on CMB reading and inter-rater reliability are presented in the online supplement.

We used logistic regression models to relate each risk factor to each outcome. All models were adjusted for age (at MRI), sex and time interval between risk factor measurement and MRI acquisition. In secondary models we further adjusted for hypertension stage I or higher (JNC-7 definition), antiplatelet use, anticoagulant use, statin use, and prevalent cardiovascular disease (CVD) (see online supplement) All analyses were performed using Statistical Analyses System (SAS) software version 9.2 (SAS Institute, Cary, NC). A two-sided p-value <0.05 was considered statistically significant.

Results

CMB were observed in 8.8% of participants; 62% had a single CMB and 63% were lobar. Sample characteristics related to the primary analysis are presented in Table 1 and results of the primary analyses for vascular risk factors previously reported to be related to CMB risk and for medication use are presented in Table 2. Complete sample characteristics and primary analyses results are shown in the online supplementary Tables I and III respectively. Increased age was a significant predictor of CMB across all locations ($p<0.001$). Male sex

was related to presence of any CMB and lobar CMB alone ($p<0.001$). Hypertension was associated with all and deep CMB ($p<0.01$), hypertensive participants had a > 2-fold higher odds of deep CMB. Low total cholesterol levels<10thpercentile were associated with any and lobar CMB ($p<0.01$). No association was observed with the remaining risk factors evaluated (results in online supplement).

Statin use was related to all CMB ($p<0.01$), to lobar ($p<0.05$) and mixed CMB ($p<0.05$). Antiplatelet therapy use was related to deep and mixed CMB (both $p<0.05$). APOE ε4 status was significantly related to CMB in lobar location only ($p<0.05$). After multivariable adjustments, hypertension stage 1 or higher, hypertension treatment, statin use, total cholesterol <10th percentile and APOE status remained associated with CMB presence (online supplement).

Discussion

We confirmed that older age, male sex, low total cholesterol level, *APOE* status and statin use were each associated with higher odds of CMB presence, with differential patterns of associations observed depending on the location of the CMB. None of the other risk factors studied were related to risk of CMB, suggesting that vascular risk factors besides hypertension and very low lipid levels may not play a major role in hemorrhage prone cerebral small vessel disease. Although the association of serum cholesterol to risk of clinical intracerebral hemorrhage is controversial,[8, 9] our findings, suggest that very low total cholesterol levels are related to risk of CMB, which concurs with a previous report from the Rotterdam study.[6] We observed an association of antiplatelet therapy with deep and mixed CMB. Prior population based studies, have related antiplatelet therapy to CMB in any location, with slightly stronger associations for lobar CMB.[10] In contrast to our prior report,[7] we now use a larger sample and found that *APOEε4* was associated with strictly lobar CMB[11] supporting the hypothesis that CAA is the predominant vascular pathology underlying lobar CMBs.[1] We observed a novel association of statin use with CMB presence, even after adjusting for potential confounders, and without significant interactions with antithrombotic medication use, lipid levels or inflammatory markers (online supplement). Only one prior study, restricted to patients with intracerebral hemorrhage, has reported an increased risk of deep CMB with statin use, although some have related statin use with increased risk of clinical intracerebral hemorrhage.[4, 12] Statins may increase risk of CMB by mechanisms other than lipid lowering such as selective inhibition of platelet-G-coupled α-thrombin protease-associated (PAR-1) receptors, a cell bound receptor that links platelet activation and thrombin formation.[13] In our study, we cannot exclude bias by indication. Our cross-sectional design limits our ability to examine whether the observed associations are causal.

Conclusion

We report, for the first time in a community-based study, an association of statin use with risk of CMB that does not appear to be explained by the concomitant use of other medications or by very low cholesterol levels. However, our study is hypothesis generating,

needs confirmation, and certainly does not negate the benefits of statin use in prevention of ischemic cardiovascular events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Study sample characteristics (N=1965).

Clinical Characteristics	**TOTAL (n=1965)**	**All CMB (n=173)**	**Lobar only (n=109)**	**Deep only (n=38)**	**Any Deep [deep + mixed] (n=64)**	**No CMB (n=1792)**
Men	904(46.0)	100 (57.8)	66 (60.6)	19 (50.0)	34 (53.1)	804 (44.9)
Age(years) at Exam closest to baseline-MRI	66.5 (11.0)	74.2 (9.4)	73.1(10.0)	75.7 (8.8)	76.1 (8.0)	65.8 (10.9)
Age(years) at MRI	67.2 (10.7)	74.8 (9.1)	73.6 (9.8)	76.3 (8.1)	76.7 (7.5)	66.5 (10.6)
Time between exam and MRI(years)	0.67 (1.2)	0.60 (1.4)	0.58 (1.3)	0.67 (1.8)	0.64 (1.6)	0.68 (1.2)
Vascular risk factors						
Hypertension	1101 (56.0)	135 (78.0)	79 (72.5)	32 (84.2)	56 (87.5)	966 (53.9)
Total-Cholesterol(mg/dL)	191 (37)	179 (39)	179 (38)	183 (43)	181 (33)	192 (37)
LDL(mg/dL)	110 (32)	101 (32)	100 (31)	104 (34)	103 (33)	111 (32)
Medication Use						
Aspirin	799 (40.7)	94 (54.3)	58 (53.2)	24 (63.2)	36 (56.3)	705 (39.4)
Antiplatelet	564 (28.7)	71 (41.0)	42 (38.5)	19 (50.0)	29 (45.3)	493 (27.5)
Anticoagulant	86 (4.4)	19 (11.0)	12 (11.0)	2 (5.3)	7 (10.9)	67 (3.7)
Statin	606 (30.9)	82 (47.4)	49 (45.0)	19 (50.0)	33 (51.6)	524 (29.3)
APOE Status						
Any ε4	449 (23.3)	44 (25.7)	33 (30.8)	8 (21.1)	11 (17.2)	405 (23.1)
ε 3/ε3	1219 (63.2)	108 (63.2)	59 (55.1)	26 (68.4)	49 (76.6)	1111 (63.2)

* values are mean (SD) for continuous variables and n (%) for categorical variables

Table 2

Logistic regression models for the association between vascular risk factors, medication use and prevalent CMB.

	All CMB (n=173)		Lobar only (n=109)		Deep only (n=38)		Any Deep [deep + mixed] (n=64)	
	OR	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Age(years)	**1.08**	**(1.06–1.10)**	**1.07**	**(1.05–1.09)**	**1.10**	**(1.06–1.13)**	**1.11**	**(1.08–1.14)**
Men vs. Women	**1.82**	**(1.31–2.51)**	**1.99**	**(1.33–2.97)**	1.38	(0.72–2.65)	1.57	(0.94–2.63)
Vascular risk factors								
Hypertension Stage 1 or higher†	**1.71**	**(1.15–2.54)**	1.32	(0.84–2.10)	**2.45**	**(0.99–6.09)**	**3.13**	**(1.45–6.78)**
Total-cholesterol(mg/dL)	1.00	(0.99–1.00)	1.00	(0.99–1.01)	0.99	(0.98–1.01)	1.00	(0.99–1.01)
Total-cholesterol<10th percentile*	**1.91**	**(1.20–3.03)**	**1.99**	**(1.14–3.44)**	2.25	(0.93–5.49)	1.76	(0.84–3.70)
LDL-cholesterol<10th percentile*	1.28	(0.75–2.19)	1.69	(0.94–3.06)	0.53	(0.12–2.29)	0.63	(0.22–1.82)
Medication Use								
Statin use	**1.67**	**(1.20–2.31)**	**1.52**	**(1.02–2.27)**	1.83	(0.95–3.54)	**1.92**	**(1.15–3.21)**
Aspirin use	1.27	(0.91–1.77)	1.22	(0.81–1.82)	1.93	(0.97–3.83)	1.39	(0.82–2.34)
Antiplatelet use	1.35	(0.96–1.91)	1.20	(0.79–1.83)	**2.14**	**(1.08–4.25)**	**1.71**	**(1.00–2.92)**
Anticoagulant use	1.72	(0.97–3.03)	1.76	(0.89–3.48)	0.70	(0.16–3.06)	1.54	(0.65–3.65)
APOE								
Any APOE ε4 vs. none	1.29	(0.88–1.87)	**1.62**	**(1.05–2.50)**	1.01	(0.45–2.24)	0.79	(0.40–1.55)

Models are adjusted for age, sex, interval examination-brain MRI.

† Hypertension stage-1 based on JNC-7 definition: SBP ≥140mmHg or DBP ≥90mm Hg or hypertension treatment regardless of blood pressure.

* Referent is ≥10th percentile. Percentile cutoffs were defined in the total sample. Total-Cholesterol 10thpercentile is 162mg/dL and 86mg/dL for LDL-cholesterol. Note: All cholesterol levels represent the average over three exams, corresponding to a ~12-year period prior to the participant's index exam.