

Aspirin Treatment Increases the Risk of Cerebral Microbleeds

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ABSTRACT: Background: The objective of the study was to determine the frequency of cerebral microbleeds (CMBs) by using phase-sensitive imaging in patients with previous transient ischemic attack (TIA) or stroke who were receiving aspirin treatment. **Methods:** We retrospectively analyzed 300 outpatients with ischemic cerebrovascular disease: 150 had been receiving aspirin treatment for >1 year (patients), and 150 controls had not previously received aspirin. Cerebral microbleeds were defined by a trained observer (blinded to clinical details) according to results of T2-weighted, T1-weighted, diffusion-weighted, and phase-sensitive magnetic resonance imaging (MRI). Numerous vascular risk factors including white matter hyperintensity (WMH), duration of aspirin treatment, age, hypertension or diabetes mellitus were investigated for a possible association with the presence of CMBs in the two groups. **Results:** The frequency of CMBs (60/150 (40%) vs 18/150 (12%); odds ratio 4.899, $p < 0.0001$) and intracerebral hemorrhage (ICH)(42/150 (28%) vs 2/150 (1%); odds ratio 28.778, $p < 0.0001$) were significantly higher in the patients than in the controls. Among patients, those using aspirin for >5 years(42/68 (62%)) showed a higher frequency of CMBs than those receiving aspirin for ≤ 5 years(18/82 (22%); odds ratio 5.744, $p < 0.0001$). WMH ($p=0.020/0.030$, $0.007/0.000$) age ($p=0.007/0.000$) and hypertension ($p=0.000/0.033$), in patients and controls respectively, were each associated with CMBs. **Conclusions:** There was a clear impact of aspirin treatment on CMBs associated with intracerebral hemorrhage in Chinese patients. The frequency of CMBs and hemorrhagic complications was higher in patients treated with long-term aspirin.

RÉSUMÉ: Le traitement par l'aspirine augmente le risque de micro saignements cérébraux. Contexte : L'objectif de l'étude était de déterminer la fréquence de micro saignements cérébraux (MSC) au moyen de l'imagerie par contraste de phase chez les patients qui recevaient de l'aspirine suite à des accès ischémiques transitoires cérébraux (ITC) ou à un accident vasculaire cérébral. **Méthode :** Nous avons analysé rétrospectivement les dossiers de 300 patients externes atteints d'une maladie cérébrovasculaire ischémique : 150 recevaient de l'aspirine depuis plus d'un an (les patients) et 150 témoins ne recevaient pas d'aspirine. Les MSC étaient identifiés par un observateur entraîné (à l'aveugle quant aux données cliniques) selon les résultats de l'IRM pondérée en T2, T1, diffusion et contraste de phase. Nous avons examiné s'il existait une association entre la présence de MSC dans les deux groupes et plusieurs facteurs de risque vasculaire dont l'hyperintensité de la substance blanche (HSB), la durée du traitement par l'aspirine, l'âge, l'hypertension et le diabète. **Résultats :** La fréquence des MSC, soit 60/150 (40%) contre 18/150 (12%) [rapport de cotes (RC) 4,899 ; $p < 0,0001$] et la fréquence des HIC, soit 42/150 patients (28%) contre 2/150 (1%) (RC 28,778 ; $p < 0,0001$) étaient significativement plus élevées chez les patients que chez les témoins. Parmi les patients, ceux qui prenaient de l'aspirine depuis plus de 5 ans, soit 42/68 (62%) avaient une fréquence plus élevée de MSC que ceux qui recevaient de l'aspirine depuis 5 ans ou moins, soit 18/82 (22%) (RC 5,744 ; $p < 0,0001$). La présence d'HSB ($p = 0,020/0,030$; $0,007/0,000$) l'âge ($p = 0,007/0,000$) et l'hypertension ($p = 0,000/0,033$) chez les patients et les témoins respectivement étaient associés aux MSC. **Conclusions :** Le traitement par l'aspirine avait un impact significatif sur les MSC associées à l'hémorragie intracérébrale chez les patients chinois. La fréquence des MSC et des complications hémorragiques étaient plus élevées chez les patients qui prenaient de l'aspirine à long terme.

Can. J. Neurol. Sci. 2011; 38: 863-868

Antiplatelet agents, especially aspirin, are effective for the prevention of secondary stroke and cardiovascular diseases, and have been widely used in most patients in China. Long-term antiplatelet therapy reduces the risk of recurrent stroke, myocardial infarction, and vascular death in patients with stroke or ischemic heart disease, but it may be associated with increased risk of intracerebral hemorrhage (ICH),¹⁻⁴ which is an uncommon but often fatal or disabling treatment complication. Identification of risk factors will therefore help to prevent ICH in patients receiving aspirin, especially in long-term users.

Cerebral microbleeds (CMBs) are considered to be indicative of bleeding-prone microangiopathy and ICH. They appear as round hypointense regions on T2*-weighted magnetic resonance

imaging (MRI).^{5,6} Cerebral microbleeds may indicate advanced-stage cerebral microangiopathy and are detected in around 60% of patients with primary ICH.^{7,8} Some investigations suggest that the frequency of CMBs increases if patients are treated with

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RECEIVED MARCH 2, 2011. FINAL REVISIONS SUBMITTED JULY 4, 2011.

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antithrombotic drugs,⁹⁻¹³ while other studies suggest that antithrombotic drug treatment has no effect on the frequency of CMBs.¹⁴⁻¹⁶ The significance of microbleeds in patients receiving antiplatelet therapy therefore remains controversial, and the impact of long term regular use of aspirin in patients with potential ischemic disease remains unclear.

In this study we used phase-sensitive imaging¹⁷ to determine whether the frequency of CMBs is associated with aspirin therapy in patients with ischemic cerebrovascular disease.

METHODS

The study included 300 patients with ischemic cerebrovascular disease, either stroke or transient ischemic attack (TIA). The stroke patients had previously received either aspirin or traditional Chinese medicine and the TIA patients had previously received aspirin or no therapy. Two groups of patients were selected for the study. The initial group to be selected were 150 consecutive patients who had been receiving aspirin treatment for >1 year. A control group of 150 patients who had not received aspirin were then randomly selected. Clinical factors associated with increased CMB risk, including sex, age and severe hypertension, were matched in the patients and the control groups. None of the patients in the study had previously received anticoagulant or thrombolytic therapy. For inclusion into the study patients were required to have a diastolic blood pressure between 90 and 140 mm Hg and a systolic blood pressure between 140 and 180 mm Hg.

All patients were fully informed about the nature and objectives of the study. The study was approved by the institutional health service, and informed written consent was obtained from either the patients or their caregivers.

Magnetic resonance imaging examinations of the brain were performed on a 3.0-Tesla MR scanner (Signa HDx GE Healthcare, USA). All patients underwent an MRI series comprising T1-weighted fluid-attenuated inversion recovery (FLAIR) imaging (repetition time, 1976 ms; echo time, 25.2 ms; inversion time, 860.0 ms; section thickness, 5 mm; field of view, 24 × 18 cm; matrix, 320 × 224; NEX, 1.0). In addition, T2-weighted fast spin-echo/propeller imaging (repetition time, 4700 ms; echo time, 114.0 ms; section thickness, 5 mm; field of view, 24 × 24 cm; matrix, 320 × 320; NEX, 1.0); and diffusion-weighted imaging (b = 1000; repetition time, 4450 ms; echo time, 76.6 ms; section thickness, 5 mm; field of view, 24 × 24 cm; matrix, 128 × 128; NEX, 2.0) were performed. An enhanced T2*-weighted angiography (ESWAN) scan was obtained using a repetition time/echo time, 53.3/5.1 ms; flip angle, 20°; field of view, 24 × 24; slice thickness, 1.8; slice spacing, 0 mm; matrix, 448 × 352. The phase-sensitive images obtained with ESWAN were processed using the GE ESWAN Functool software, which was a part of the Advantage Workstation 4.3.

Cerebral microbleeds were identified by a low signal in the T2*-weighted MRI and cannot be demonstrated by conventional MRI or CT scans.

The MRI images were independently evaluated by two of the authors (Q Wu and H Wu) who were blinded to the patients' clinical profiles. The number of microbleeds and the grading scores for white matter hyperintensity (WMH) were determined by consensus. Lesions within the sulcal areas likely to represent adjacent pial blood vessels and areas of symmetrical hypodensity

in the globus pallidus, which were likely to indicate calcification, were excluded. The severity of CMBs was classified by using a four point scoring system according to Lee et al,¹⁸ where: absent, mild =1–5, moderate= 5–10, and severe >10. The severity of a WMH on T2-weighted images was classified as 'punctuate', 'early confluent', or 'confluent' by previously described methods.¹⁹

The presence of vascular risk factors, including controlled hypertension, diabetes mellitus or hyperlipidemia was evaluated according to the method described by Orken et al¹⁴. Hypertension was considered to be present when a patient had received antihypertensive treatment before admission or when hypertension was diagnosed during a hospital stay evidenced by systolic and diastolic blood pressures of at least 140 and 90 mm Hg on multiple occasions. Diabetes mellitus (DM) was defined as a history of DM with or without current hypoglycemic treatment, or by the demonstration of two fasting plasma glucose levels of 126 mg/dL or higher. A diagnosis of hyperlipidemia was based on a fasting serum total cholesterol level >220 mg/dL, or was considered to be present in patients currently undergoing cholesterol-lowering therapy. A history of smoking was noted when a subject was either a current smoker or an ex-smoker who had quit smoking less than five years before admission. Addiction to alcohol was considered as a risk factor if current consumption reached 300 g/week.

Statistical analysis was undertaken using the Statistical Package for the Social Sciences for Windows version 16.0 (SPSS, Chicago, Illinois). Age, expressed as mean±standard deviation (SD), was analyzed using the unpaired Student t-test between the patients and controls. Chi-square or the Fisher exact tests were used to compare clinical variables between patients who had CMBs and those who did not, and between patients who received aspirin treatment and those who did not. Multivariate logistic regression analysis was performed to identify potential risk factors and associations between cerebral microbleeds and clinical characteristics. Statistical significance was established by using a conventional $p < 0.05$ level.

RESULTS

Demographic and disease characteristics for the 300 cases are summarized in Table 1. No significant differences were found in age, sex ratio, hypertension, cardiac diseases, diabetes mellitus, hyperlipidemia, smoking, alcohol addiction, or previous stroke between the aspirin treated patients and the controls, suggesting that the two groups were well matched for all clinical characteristics and potential confounding factors. Mean±SD blood pressure was 109.6±10.2/70.1±6.9 mmHg in the patients and 110±9.0/68.8±5.3 mm Hg in the controls. Blood pressure in the hypertensive patients was 142.65 ±14.7/89.55±9.08 mm Hg. Table 2 shows that the frequency of CMBs was significantly higher in the patients (60/150; 40% than in the controls (18/150; 12%; odds ratio 4.899, $p < 0.0001$). The frequency of intracerebral bleeding (resolved hematoma, acute or subacute hematoma) was 42/150 (28%) in patients and 2/150 (1%) in controls (odds ratio 28.778, $p < 0.0001$; Table 2).

In total, there were 27 cases of ICH in patients with CMBs, but only one case in the controls with CMBs (Tables 3 and 4). As shown in Table 3, the frequency of hemorrhagic complications was higher in patients with CMBs (27/60; 45%)

Table 1: Characteristics of patients and controls

	Patients (n = 150)	Controls (n = 150)	P value*
Age (years)	65.88 ± 8.99	64.38 ± 7.47	0.147
Male	87 (58%)	83 (55%)	0.641
Hypertension	88 (59%)	81 (54%)	0.415
Cardiac diseases	59 (39%)	63 (42%)	0.638
Diabetes	34 (23%)	29 (19%)	0.478
Hypercholesterolemia	67 (45%)	61 (41%)	0.484
Smoking	68 (45%)	60 (40%)	0.350
Alcohol	72 (48%)	62 (41%)	0.246
Previous stroke	48 (32%)	52 (35%)	0.624
WMH	83 (55%)	76 (51%)	0.418
CMBs	60 (40%)	18 (12%)	<0.0001
ICH	42 (28%)	2 (1%)	<0.0001

* t test for age; chi square, Fisher exact test for other variables

than in patients without CMBs (15/90; 17 %). The frequency of each of the moderate and severe grades of CMBs was also lower in controls than in patients but the differences were not statistically significant (Table 2).

Imaging analysis showed that the frequency of WMH was associated with the presence of CMBs (45/60 (75%) vs 43/90 (48%); odds ratio 3.279, p=0.001) in the patients (Table 3), and there was a trend towards an association in the controls (p=0.81) (Table 4).

Multivariate logistic regression analyses indicated that the frequencies of CMBs were associated with the frequency of WMH in the patients (odds ratio 3.329, p=0.020) and controls (odds ratio 3.988, p=0.030,) (Table 5). Multivariate logistic regression analysis also suggested that the frequencies of CMBs were significantly associated with the frequency of age (>70 years), and hypertension in the two groups (Table 5). Notably, the risk of CMBs in long term aspirin treatment (>5 years)

Table 2: Analysis for the presence of CMBs and bleeding between the patients and the controls

	Patients (n = 150)	Controls (n = 150)	Odds Ratio (95% CI)	P value*
CMBs	60 (40%)	18 (12%)	4.889 (2.707-8.802)	<0.0001
Mild (1-5)	14 (23%)	10 (56%)	0.243 (0.181-0.736)	0.009
Moderate (5-10)	34 (57%)	6 (33%)	2.615 (0.866-7.897)	0.082
Severe (>10)	12 (20%)	2 (11%)	2.000 (0.404-9.909)	0.609
ICH	42 (28%)	2 (1%)	28.778 (6.818-121.467)	<0.0001

* Chi square, Fisher exact test

Table 3: Association of CMB with WMH and ICH in patients

	CMBs(+) (n = 60)	CMBs(-) (n = 90)	Odds Ratio (95% CI)	P value*
WMH	45 (75%)	43 (48%)	3.279 (1.603-6.709)	0.001
Punctuate	15 (33%)	24 (56%)	0.971 (0.434-1.937)	0.820
Early confluent	21 (47%)	18 (42%)	2.154 (1.027-4.516)	0.040
Large confluent	9 (20%)	1 (2%)	15.706 (1.934-127.549)	0.001
ICH	27 (45%)	15 (17%)	4.091 (1.928-8.681)	<0.0001

* Chi square, Fisher exact test

Table 4: Association of CMB with WMH and bleeding in the controls

	CMBs(+) (n = 18)	CMBs(-) (n = 132)	OddsRatio (95% CI)	P value*
WMH	13 (72%)	65(49%)	2.680 (0.904-7.942)	0.081
Punctuate	6 (46%)	30(46%)	1.000 (0.303-3.302)	1.000
Early confluent	6(46%)	31(48%)	0.940 (0.285-3.103)	0.919
Large confluent	1 (20%)	4(6%)	1.271 (0.130-12.388)	1.000
ICH	1 (20%)	1 (1%)	7.706 (0.460-128.955)	0.226

* Chi square, Fisher exact test

(42/68; 62%) was higher than that in short term aspirin treatment (≤ 5 years) (18/82; 22%, odds ratio 5.744, $p < 0.0001$; Table 6). The risk of ICH was numerically higher in patients receiving long term (25%) than in those receiving shorter-term aspirin treatment (12%; $p = 0.87$) (Table 6).

DISCUSSION

The present study demonstrated that the presence of CMBs was associated with the use of the antiplatelet drug aspirin. Various studies have suggested that CMBs might be indicative of bleeding tendency and bleeding transformation after acute

ischemic stroke. The present study supports this association showing a higher frequency of hemorrhagic complications in patients with CMBs than in patients without CMBs (Table 3, $p < 0.0001$).

The frequency of CMBs has previously been linked to age, sex, history of cerebrovascular diseases, hypertension and diabetes mellitus.^{9-16,20-22} It has also been established that bleeding complications are common adverse events of aspirin when used to prevent ischemic stroke arising from recurrent cerebral embolism. Overuse of antiplatelet therapy by itself may increase the risk of ICH, whereas ischemic events treated with

Table 5: Multivariate logistic regression analysis for the associated factors with CMBs in the patients/controls

	Odds Ratio (patients/controls)	95% CI for Odds Ratio (patients/controls)	P value* (patients/controls)
WMH	3.329/3.988	1.206-9.195/1.144-13.902	0.020/0.030
Age (> 70 years)	3.650/3.790	1.437-9.276/1.783-6.769	0.007/<0.0001
Hypertension	11.899/3.973	3.888-36.418/1.115-14.157	<0.0001/0.033
Smoking	2.248/0.940	0.737-6.859/0.186-4.749	0.155/0.940
Cardiac diseases	0.891/0.336	0.362-2.196/0.101-10.120	0.802/0.076
Diabetes	0.988/0.806	0.373-2.621/0.190-3.425	0.981/0.771
Previous Stroke	0.795/0.434	0.376-2.398/0.986-9.896	0.798/0.084

* Multivariate analysis

Table 6: Analysis for the association between CMBs and ICH with the duration of aspirin treatment in the patients

	≤5years (n = 82)	>5years (n = 68)	Odds Ratio (95% CI)	P value*
CMBs	18(30%)	42 (70%)	5.744 (2.807-11.753)	<0.0001
ICH	10 (12%)	17 (25%)	1.070 (0.466-2.460)	0.873

* Chi square, Fisher exact test

the use of aspirin may have predisposed patients to microbleeds. Both are important clinical issues in primary and secondary stroke prevention.

The mechanisms underlying CMBs remains unclear, but there is a probable link with ICH. In our study CMBs seen on gradient echo MRI were histopathologically correlated with extravasation of blood and microangiopathy.⁶ Nighoghossian et al²³ demonstrated an increased occurrence of cerebral bleeding in patients with CMBs and suggested that the associated vascular vulnerability contributes to hemorrhagic transformation. Naidech et al reported an association between reduced platelet activity induced by aspirin, intraventricular hemorrhage and death after ICH.²⁴ They also found that aspirin was associated with increased ICH volume and a worse functional outcome.²⁰ By contrast a previously reported retrospective analysis of 106 patient with ICH found no evidence to suggest that regular use of aspirin was associated with CMBs.¹⁶

In our study, we found that the frequencies of CMBs were significantly associated with the presence of WMH, age (>70 years) and hypertension in patients with or without antiplatelet treatment. Notably, the frequency of bleeding complications was higher in the patients than in the controls (Table 1, $p < 0.0001$), suggesting that antiplatelet treatment increases the risk of bleeding. More importantly, we found that the risk of CMBs in long term aspirin treatment (>5 years) was higher than that in short term aspirin treatment (Table 6), and that patients with CMBs were older and had more hypertension and more WMH than the patients without CMBs. The presence of large confluent WHM was more prevalent in patients than in controls (Table 3), providing speculative evidence that WMH may cause CMBs and that aspirin may increase their incidence (Table 2).

Our study also suggests that the presence of CMBs is not associated with previous stroke, cerebral infarction, or with diabetes (Table 5). The limitations of small sample size and short duration of follow-up in the present study prevent us from concluding definitively that there is a higher incidence of CMBs and ICH during long-term antiplatelet therapy with aspirin. However, the study shows that there are no statistically significant differences in the frequency of ICH between patients who received long-term aspirin and those requiring short term aspirin treatment (Table 6). However, the presence of macroscopic hematoma, which was often present in patients with ICH, tended to make it more likely that microbleeds would be identified by MRI and so added bias to the evaluation. An additional limitation to our study was the cross-sectional design

which meant that it was not possible to conclude that CMBs were solely related to aspirin treatment. Selection bias was also an issue with previous retrospective studies of this type.¹⁶

With these limitations in mind, the results of the present study do clearly suggest an impact of aspirin treatment on the rate of CMBs associated with ICH. Screening for CMBs before the initiation of long-term antiplatelet therapy may help reduce the incidence of drug-related cerebral hemorrhage. In addition, aspirin should be prescribed with caution, particularly, in patients with microbleeds at many sites.

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