Original Article

Interaction of incidental microbleeds and prior use of antithrombotics with early hemorrhagic transformation: Causative or protective?

Konark Malhotra, Monica Khunger[1], Bichun Ouyang[2], David S. Liebeskind, Yousef M. Mohammad[3]

Department of Neurology, University of California Los Angeles, Los Angeles, CA, [1]Cleveland Clinic Foundation, Cleveland, OH, [2]Department of Neurology, RUSH University Medical Center, Chicago, IL, USA, [3]Department of Internal Medicine, King Saud University, Riyadh, Saudi Arabia

Abstract

Background: Gradient echo (GRE) sequence of magnetic resonance imaging (MRI) is a sensitive tool to detect hemorrhagic transformation (HT) and old cerebral microbleeds (CMBs). Presence of CMBs and prior use of antithrombotics pose a risk of HT in ischemic stroke. We evaluated the association of CMBs and antithrombotic use with resultant HT in acute ischemic stroke (AIS). **Methods:** This retrospective study included AIS patients admitted to our center between January 2009 and August 2010 who underwent GRE-weighted MRI within 48 h of admission. Demographic and clinical data including diabetes mellitus, hypertension, hyperlipidemia, prior intake of antiplatelets/anticoagulants/statins, and presence of CMBs at admission were collected and compared between patients who developed HT and those who did not. We did a multivariate analysis using logistic regression to assess the effect of CMBs and prior use of antithrombotic agents on the risk of development for early HT in ischemic stroke. **Results:** Of 529 AIS patients, 81 (15%) were found to have HT during the initial hospital course. CMBs were found in only 9 of 81 patients (11%) with HT and in 40 out of remaining 448 patients (9%) who did not develop HT. The presence of CMBs was not associated with increased risk of HT ($P = 0.53$). However, prior use of antiplatelets (33% vs. 47% in the patients without HT, $P = 0.02$) was associated with decreased risk of HT in ischemic stroke. **Conclusion:** Presence of incidental CMBs was not associated with increased risk for early HT of an ischemic stroke. Interestingly, the prior intake of antiplatelets was found to be protective against HT of ischemic stroke.

Key Words

Acute ischemic stroke, cerebral microbleeds, gradient echo magnetic resonance imaging, hemorrhagic transformation

For correspondence:
Dr. Konark Malhotra, 757 Westwood Plaza, Los Angeles, CA 90095, USA.
E-mail: konark.malhotra@yahoo.com

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Introduction

Acute ischemic stroke (AIS) is the leading cause for morbidity and is associated with a high recurrence rate that warrants aggressive evaluation.[1,2] Hemorrhagic transformation (HT) can occur in 20%–40% of AIS patients within initial week of symptom onset.[3] Hemorrhage within an ischemic stroke can dictate the timing of antithrombotic treatment for the prevention of recurrent thromboembolic events.[4,5] Intraparenchymal blood can be accurately detected using gradient echo (GRE) sequence of magnetic resonance imaging (MRI), that is sensitive to static magnetic field inhomogeneity (T2-sensitive).[6]

Hemorrhagic conversion or HT of an ischemic stroke is associated with increased morbidity and mortality.[7] Infarction of cerebral parenchyma results in friable vasculature with

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increased rate of HT within days of initial ischemic insult.[8] Early hemorrhagic conversion within 36 h of cerebral infarction has been investigated to assess for clinical outcomes.[9] Similarly, advanced age, renal impairment, large infarct volume, hyperglycemia, and leukocytosis on admission have been previously shown to be significant predictors of HT.[10,11] Further knowledge of risk factors associated with HT in ischemic stroke may improve patient selection and decision-making by physicians during acute settings.

Cerebral microbleeds (CMBs) are punctate, hypointense, parenchymal lesions <5 mm in size that are detected on T2-weighted GRE sequence of MRI.[12] CMBs are clinically considered to be silent entities but have been shown to increase the risk for spontaneous and recurrence of intracerebral hemorrhage (ICH).[13,14] CMBs have been shown to have an association with hypertension, prior ischemic event, leukoaraiosis, cholesterol levels, and cognitive impairment in ischemic stroke patients.[15-18] There is no clear association of presence of CMBs with HT in prior small sample sized studies.[19] Similarly, prior use of antithrombotic agents has not been shown to have a clear association with HT though their usage was found to be associated with larger and more severe hematomas.[10]

Data on the association of microbleeds and prior use of antithrombotic agents with HT of ischemic stroke require further investigation. In this retrospective study, our primary objective was to evaluate any association of the presence of CMBs with the development of early HT within 48 h of an ischemic stroke. We also looked for any association of prior use of antithrombotics, especially antiplatelet agents, with early HT in ischemic stroke patients as our secondary objective.

Methods

Study participants

This retrospective study was performed involving patients admitted to a single academic university medical center between January 2009 and August 2010. Adults (18 years and older) with following criteria on admission were included: acute territorial infarct in either anterior or posterior circulations, absence of hemorrhagic conversion of ischemic stroke, and presence of incidental microbleeds on T2-weighted GRE sequence of MRI. The study cohort included patients with ischemic stroke who underwent noncontrast computed tomography (CT) scan of head and MRI brain, while excluded patients who were eligible for either intravenous thrombolysis or endovascular recanalization procedures. All patients were immediately examined by attending physicians specializing in vascular neurology. Their electronic medical records and neuroimaging (CT head and MRI brain) were reviewed.

Demographic and clinical data

Baseline demographic and clinical aspects including age gender, diabetes mellitus, hypertension, hyperlipidemia, prior use of antithrombotics including antiplatelets and anticoagulants, and prior use of statins were recorded on admission. We included patients who were taking antiplatelet medications (aspirin 81–325 mg daily, clopidogrel 75 mg daily, or combination therapy) at the time of admission. Neurovascular workup included assessment regarding the risk of microbleeds for the development of HT in an ischemic stroke.

Imaging criteria

All the patients underwent CT head without contrast and MRI brain within 12 h of admission to evaluate any presence of ICH and assess the size and location of ischemic stroke. Patients were not included in our study, if there was the presence of ICH on either CT or MRI on admission, edema or mass effect, tumors, cardiorespiratory instability, and other contraindications precluding MRI. MRI brain for acute ischemia including diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), T2-weighted GRE, fluid-attenuated inversion recovery, and perfusion-weighted imaging sequences were performed in a single session. DWI restricted diffusion with corresponding ADC hypointensity was identified as acute ischemic lesions. Repeat MRI brain was performed within 48 h of admission, either due to sudden neurological deterioration (NIH ≥4) or to follow ischemic evolution routinely. GRE sequences were reviewed in detail to note for the presence of CMBs and observe for the development of HT.

Definition of microbleeds and hemorrhagic transformation

A stroke neurologist and a neuroradiologist together reviewed the MRI to identify CMBs and HT. The presence of CMBs and occurrence of early HT during the first 48 h of hospital course was investigated. Microbleeds were defined as round, punctate, homogeneous, parenchymal hypointensities <5 mm in size without surrounding edema, visualized on GRE MRI scans.[20] Hypointensities such as vessel flow voids and symmetric globus pallidus hypointensities were not taken into consideration. ICH has been associated with the burden of CMBs with the risk of ICH approaching 7.6% ($P < 0.001$) for five or more CMBs.[21] We decided to include patients with ≥4 CMBs present in either cortical or subcortical location in our analysis. HT was defined as a region of hyperdensity (CT) or hypointensity (GRE-MRI) occurring within an ischemic lesion. We included both symptomatic and asymptomatic hemorrhages for our total cases of HT. We divided HT into hemorrhagic infarcts (HI) and parenchymal hematomas (PH) based on the European Cooperative Acute Stroke Study II study criteria that have highest interrater agreement.[22] HI was subcategorized into HI1 with small petechial hemorrhage around the infarct periphery and HI2 with confluent petechiae in infarct zone. PH has been described as a homogeneous hyperdense lesion with a sharp border with or without edema or mass effect. PH was subdivided into PH1 as hematoma involving <30% of infarct area with mild mass effect and PH2 as hematoma involving more than 30% of infarct area with significant mass effect.[23] Any evidence of HT on neuroimaging within 48 h of hospitalization was referred as early hemorrhagic conversion.

Statistical analysis

Univariate analysis using Chi-square or *t*-test was performed to compare demographic, clinical, and radiologic features between patients who developed HT and those who did not. Multivariate analysis with logistic regression was carried out to assess the association of CMBs and prior use of antithrombotic agents, with the risk of development of HT in

ischemic stroke. All the analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC). $P \leq 0.05$ was considered statistically significant.

Results

Total patient cohort

Out of 529 total patients included in our study, 244 patients were male (46.1%) and the mean age of patients was 64.15. There were 408 patients with hypertension (77.1%), 178 with diabetes mellitus (33.6%), and 218 with hyperlipidemia (41.2%). Before admission, 239 patients (45.2%) were on antiplatelet agents, 64 patients (12.1%) were on anticoagulants, and 216 patients (40.8%) were on statin medication.

Eighty-one patients were found to have HT during initial 48 h of hospital course. In the univariate comparisons, there was no significant difference in patient characteristics including age, gender, hypertension, diabetes mellitus, and hyperlipidemia between patients who were found to have HT and those who were not [Table 1]. Presence of CMBs did not increase the risk of HT (11.1% vs. 8.9%, $P = 0.53$). No significant association was found between prior use of anticoagulants or statins and risk of HT. However, prior use of antiplatelets (33.3% vs. 47.3% in the patients without HT, $P = 0.02$) was associated with decreased risk of HT. In the multivariate logistic regression analysis, advanced age turned out to be a significant factor associated with increased risk of HT (OR = 1.02, 95% CI = [1, 1.03], $P = 0.04$) [Table 2]. Prior use of antiplatelets maintained significant association with decreased risk of HT (OR = 0.51, 95% CI = [0.3, 0.86], $P = 0.01$). Neither of the remaining factors including CMBs was found to be associated with the risk of HT in the multivariate analysis.

Table 1: Demographic, clinical, and radiological findings in patients with acute ischemic stroke

Variables	HT (*n*=81)	No HT (*n*=448)	*P*
Age, mean (SD)	65.7±15.7	62.6±15.5	0.10
Male, *n* (%)	41 (50.6)	203 (45.3)	0.38
HTN, *n* (%)	62 (76.5)	346 (77.2)	0.89
DM, *n* (%)	21 (25.9)	157 (35)	0.11
HLD, *n* (%)	32 (39.5)	186 (41.5)	0.74
Prior use of antiplatelets, *n* (%)	27 (33.3)	212 (47.3)	0.02
Prior use of anticoagulants, *n* (%)	9 (11.1)	55 (12.3)	0.77
Statins, *n* (%)	32 (39.5)	184 (41.1)	0.79
CMBs, *n* (%)	9 (11.1)	40 (8.9)	0.53

HT = Hemorrhagic transformation, HTN = Hypertension, DM = Diabetes mellitus, HLD = Hyperlipidemia, CMBs = Cerebral microbleeds, SD = Standard deviation

Table 2: Multivariate logistic regression analysis to evaluate association of microbleeds, age, and prior use of antiplatelet agents with early hemorrhagic transformation

Variables	HT (*n*=81)	No HT (*n*=448)	*P*
CMBs, *n* (%)	9 (11.1)	40 (8.9)	0.53
Age, mean (SD)	65.7±15.7	62.6±15.5	0.04
Prior use of antiplatelets, *n* (%)	27 (33.3)	212 (47.3)	0.01

SD = Standard deviation, HT = Hemorrhagic transformation, CMBs = Cerebral microbleeds

Discussion

Contrary to prior investigations, we found that the presence of CMBs on GRE sequence of MRI was not associated with HT during the initial hospital course of AIS patients. Interestingly, a significant correlation was observed with prior use of antiplatelet agents providing a protective relationship with respect to early HT in ischemic stroke patients.

Acute ischemia is associated with the breakdown of blood–brain barrier (BBB) resulting into fragile intracerebral vessels. The pathophysiological basis for occurrence of HT is likely microvascular injury to the BBB due to ischemia with subsequent reperfusion.[24] This phenomenon is the main culprit resulting into HT, either as hemorrhagic infarction or parenchymal hematoma. The data pertaining to risk factors for HT after ischemic stroke are scarce. HT is known to occur in approximately 30% of recent ischemic brain infarcts.[25] Various authors have shown positive correlation of HT and thus poor clinical outcomes with large infarct volume, advanced age, impairment of renal function, hyperglycemia and leukocytosis on admission.[10,26,27] Various predictor scores have been formulated recently to determine HT in AIS patients with an indication for anticoagulation.[11]

In our retrospective study, presence of CMBs was not associated with the occurrence of early HT after AIS ($P = 0.53$). This result is congruent with previous studies that compared the association of CMBs with HT.[19] Age ($P = 0.04$) and prior use of antiplatelets ($P = 0.01$) were found to have significant associations with early HT in AIS patients, while remaining variables including gender, hypertension, hyperlipidemia, use of anticoagulants, and statins did not tend to correlate with the early HT in our cohort. Interestingly, use of antiplatelets prior to ischemic stroke onset showed a protective effect for early HT in our patient cohort. We found the use of antiplatelets alone (33% vs. 47% in the patients without HT, $P = 0.02$) before ischemic stroke is associated with decreased risk of early HT. BBB comprises endothelial cells of brain and capillaries, basement membrane, and tight junctions that provide resilience to its structure. It has been well studied that HT is the end result of breakdown of the resilient BBB that leads to infiltration of proteinaceous material and blood products, usually within the ischemic region. Antiplatelet agents provide antithrombotic action through inhibition of platelet aggregation and also possess imperative anti-inflammatory properties. We hypothesize that the anti-inflammatory effects of various antiplatelet agents provide support at the site of BBB or endothelium, thus providing resilience and preventing its breakdown.

Aspirin is the most commonly used antiplatelet agent and has been studied in salt-loaded, stroke-prone hypertensive rat models. It was shown to suppress BBB damage by reducing various inflammatory markers.[28] Few prior studies also have failed to show a robust significance of both aspirin and rtPA-by-aspirin interactions ($P = 0.06$) for PH in ischemic stroke patients.[29] Other antiplatelet agents such as cilostazol tend to inhibit platelet aggregation and provide vasodilator effects, especially to treat peripheral vascular diseases.[30,31] Cilostazol, a selective type III phosphodiesterase inhibitor, was found to be more effective as compared to aspirin in

secondary prevention of all types of infarcts, especially hemorrhagic conversion of ischemic stroke.[4,32] It confers neuroprotective benefit based on its anti-inflammatory and anti-apoptotic properties and mediates as a scavenger of free radicals.[33] It also provides endothelial protection via inhibition of lipopolysaccharide-induced apoptosis, induced nitric oxide production, and inhibition of neutrophil adhesion to endothelial cells.[34] Since endothelium is one of the main constituents of BBB, anti-inflammatory properties of various antiplatelet agents likely confers endothelial protection at BBB level and confers protective effects for HT as found in our study.

Old cerebral microhemorrhages or CMBs are chronic hemosiderin deposits, detected as areas of signal loss or hypointensity without adjacent edema on GRE sequence of MRI. Morphology of CMBs can vary on imaging scans and can mimic with HT at times; however, CMBs are usually homogenous, measuring <5 mm, and are expected to be located outside the area of infarction. CMBs have a trait of vasculopathy on histological analysis,[35] while HT is a result of cerebral parenchymal injury with a relatively normal cerebral vasculature. The likelihood of early HT after ischemic stroke might be increased in patients with most vulnerable microvascular system. Although the pathogenesis of cerebral bleeding after ischemic stroke is multifactorial, the increased observation of hemorrhage in patients with microbleeds likely correlate with the emergence of various new MRI sequences including GRE and susceptibility weighted imaging, providing detailed information of old incidental microbleeds secondary to microangiopathy or amyloid angiopathy. CMBs are indicators of bleeding-prone microangiopathy and may predict incidental HT, though the data remains scarce. Given the potential vulnerability in the microvasculature of these patients, we tried to determine the relationship, if any, between the presence of microbleeds and the occurrence of HT in an ischemic stroke.

Asymptomatic CMBs have been shown to be associated with aspirin-induced ICH.[36] CMBs are more frequently noticed in hemorrhagic stroke patients as compared to ischemic stroke patients.[37] Various case reports and prospective studies have portrayed HT after embolic infarcts and the hemorrhagic tendency associated with CMBs.[38-40] Presence of CMBs has been shown to be a predictor of HT in a case series involving 100 AIS patients.[13] On the contrary, few retrospective studies have failed to show any association of underlying CMBs and incidental HT in AIS patients.[19,41] Similarly, many authors have found no relationship between CMBs and postthrombolytic HT incidence rates.[3] The dilemma of association between CMBs and HT remains, with a plausible explanation that CMBs are a type of microangiopathy with lobar ICH tendency, but without any clear association with specific variety such as HT in AIS.

Our study has several limitations beyond its retrospective design. This was a single-center study comprising AIS patients with a potential for selection bias due to referral sources. We did not classify ischemic stroke based on the mechanism or severity that might have influenced the study results. While volume of infarct is a known predictor of HT, we might have included larger patient population with small sized infarcts that might have resulted in lower number of HT in these patients ($n = 81$). Multiple predictors of HT including tobacco dependence, alcohol abuse, renal impairment, leukoaraiosis, blood glucose levels, and leukocytosis on admission were not accounted in our analysis. There might be other potential confounding factors associated with HT that was not evaluated in our study. Given these limitations and potential biases, future large multicenter studies are required to confirm or disprove some of the correlations observed in our study. Contrary to the fear of early HT with the prior use of antiplatelet agents, the protective effect as noted in our study is encouraging. However, further large-scale prospective, multicenter, and multiethnic trials are warranted for further delineation.

Conclusions

Presence of old CMBs was not associated with increased risk for early HT of ischemic stroke in our study. CMBs likely reflect bleeding due to microangiopathy in brain, while does not predict all forms of cerebral hemorrhages such as hemorrhagic conversion of AIS. Interestingly, the prior intake of antiplatelet agents was found to be protective against early HT of ischemic stroke possibly related to anti-inflammatory effects at endothelial level of blood–brain barrier.

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Conflicts of interest
There are no conflicts of interest.

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