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Factors influencing hemorrhagic transformation in ischemic stroke patients with atrial fibrillation: a hospital based-study

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Abstract

Background Patients with ischemic stroke and atrial fibrillation (AF) are at high risk of developing hemorrhagic transformation (HT). The aim of the current study is to evaluate the incidence of hemorrhagic transformation and associated risk factors in a hospital-based sample with ischemic stroke and AF patients. A prospective study with a total of 234 stroke patients with AF was consecutively recruited. HT incidence was determined by computed tomography (CT) or magnetic resonance imaging (MRI). Risk factors associated with HT was identified by comparing patients with and without HT.

Results The incidence of HT in ischemic stroke with AF was 22.6%. Univariate analysis established that old age, hypertension, diabetes mellitus, anticoagulant medications, NIHSS, cerebral microbleeds (CMB), superficial siderosis (SS) and size of infarction were significantly more frequent with HT. Multivariable logistic regression analysis demonstrated that old age [odds ratio (OR): 1.05, confidence interval (CI) 1.01–1.09], size of infarction (OR: 2.57, CI 1.06–6.27) and CMB ≥ 10 (OR: 4.68, CI 1.71–12.84) were significantly associated with the risk of HT.

Conclusions Older age, larger infarction size, and CMB ≥ 10 were risk factors significantly associated with HT.

Keywords Ischemic stroke, Atrial fibrillation, Hemorrhagic transformation, Infarction size, Cerebral microbleed

Background

Patients with ischemic stroke and atrial fibrillation (AF) were associated with an increased risk of developing hemorrhagic transformation (HT) [1, 2]. Therefore, early recognition of HT is essential for the appropriate management and better prognosis.

Following acute stroke, breakdown of the blood brain barrier (BBB) results in friable intracranial vasculature. This breakdown increases the risk of HT and intracerebral bleeding, specifically into the area of ischemia. AF was reported to be an independent predictor of HT [3].

In fact, HT risk was nearly fivefold higher in patients with AF than in those without AF [4].

Several studies have identified risk factors for HT in patients with cerebral infarction including vascular risk factors, laboratory and radiological findings [5–7], but most of these studies were retrospective [5, 7]. The increasing use of heme-sensitive T2* Gradient-Recall Echo (GRE-T2) and susceptibility-weighted (SWI) sequences in magnetic resonance imaging (MRI) of the brain had led to detection of many predicting radiological markers [8, 9]. The loss of integrity of the endothelial basal lamina seems to be the primary cause of hemorrhage after focal cerebral ischemia [10]. Cerebral microbleeds (CMB) are a promising radiological marker of the cerebral small vessel diseases that are prone to bleeding and cause spontaneous ICH [11]. Most currently available bleeding risk scores, which include clinical risk

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factors but not neuroimaging markers, show only modest predictive value [12].

The aim of this study is to evaluate the incidence of hemorrhagic transformation and associated risk factors in ischemic stroke with AF patients.

Methods

The present study is a prospective hospital-based study and included 250 ischemic stroke patients with AF that were recruited from stroke and intensive care units of Neurology Department from June 2019 to March 2021. Inclusion criteria included any ischemic stroke patients with AF and aged ≥ 18 years. Exclusion criteria included patients with hepatic, renal or hematological diseases. Informed consent was obtained from participating patients or their relatives. Ethical approval was obtained from the ethics committee of the neurology department.

All patients were subjected to detailed history taking with paying special attention to medical history of stroke risk factors. Medical data were obtained from the patients and/or their relatives. Complete general and neurological examinations including Glasgow Coma Scale (GCS) were performed. National Institutes of Health Stroke Scale (NIHSS) was conducted to evaluate the severity of the stroke. Electrocardiogram (ECG) was performed for all patients.

Full laboratory tests were done including complete blood count (CBC), lipid profile (total cholesterol, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C) and triglycerides), blood glucose level, liver and renal function tests, platelet count, international normalized ratios, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

At admission, all patients had performed conventional MRI, GRE T2WI (T2*WI) and diffusion-weighted image using 1.5 T MR Scanner (Achieva, Philips Medical System) and section thickness was set at 5 mm and gap was set at 1 mm. Follow-up computed tomography (CT) or MRI scans after one week of admission or immediately in case of clinical worsening was done for detection of HT. Patients were divided into two groups according to presence of the HT.

CMBs were identified as hypointense or black (signal loss) rounded regions with < 10 mm in diameter on T2*WI and validated Brain Observer Microbleed Scale was used for rating the CMBs [13].

Superficial siderosis was identified as hypointensity gyriform without matching hyperintense signal on T1-weighted sequences or FLAIR [14]. Fazekas scale was used to assess deep white matter lesions in FLAIR sequences [15]. The reference template of the brain at older age was used to evaluate cerebral atrophy [16]. Data

were analyzed by two radiologists who were blind to the study design.

Infarct size was measured during a second CT or MRI scan and was determined by the largest diameter of the lesion [17]. The size of infarct was ranked as follows: small size (< 1 cm), medium size (1–3 cm) and large size (> 3 cm) [17].

Statistical analysis was performed using SPSS statistics (V.20.0, 2010; IBM Corp., NY, USA) [18]. Qualitative variables were presented as numbers and percentages, whereas quantitative variables were expressed as mean (\pm SD) or median (IQR) for normally and non-normally distributed data, respectively. Comparison between groups was performed using the χ^2 , *t*-test or Mann–Whitney *U* nonparametric test as appropriate. The Alpha level of significance was set at *p*-value of 0.05 or less. Association of risk factors identified in univariate analysis with HT was assessed using multivariable logistic regression analysis. Level of association between HT and risk factors was presented as adjusted odds ratios.

Results

A total of 234 from 250 ischemic stroke patients with AF completed the study. Five patients refused to continue the study, 7 patients had missing data and 4 patients were discharged before having the second neuroimaging had been done. Demographic and clinical characteristics of the studied AF ischemic stroke patients are presented in Table 1. There were 119 (50.9%) male and 115 (49.1%) female patients with the mean age (\pm SD) of patients was 64.04 (\pm 9.58) years. The incidence of HT was 22.6% as detected in 53 patients. The prevalence of CMB was 40.6%, 41.5% had WML, superficial siderosis was 16.2% and cortical atrophy was detected in 38.5% of the patients. Stroke severity, as assessed using NIHSS scale on admission, was 13.77 (\pm 6.27).

As regard site of infarction, there were 172 patients (73.5%) that had anterior circulation infarction in which 68% had middle cerebral artery and 5.5% had anterior cerebral artery. Forty-eight patients (20.5%) had posterior circulation infarction and the remaining of patients (14 patients) had multiple infarction sites. Regarding the site of microbleed, CMBs were found more often in lobar areas than deep areas.

The patients were classified into 2 groups based on the presence of HT (group without HT and group with HT) (Table 2). Patients with HT were more likely to be older in age, hypertensive, diabetic, on anticoagulant medications and had higher NIHSS score at admission. Analysis of neuroimaging data showed statistically significant difference between both groups regarding the presence of CMB, SS and size of infarction. CMB was significantly higher in group with HT (64.4%) than in group

Table 1 Baseline characteristics of the patients group

Variables	Characteristic of ischemic stroke with AF (234)	
Age ^a	64.04 (± 9.58)	
Gender ^b (male)	119 (50.9%)	
Hypertension ^b	134 (57.3%)	
Diabetes mellitus ^b	95 (40.6%)	
Smoking ^b	47 (20.1%)	
Dyslipidemia ^b	92 (39.3%)	
Previous stroke/TIA ^b	38 (16.2%)	
Ischemic heart disease ^b	73 (31.2%)	
Antiplatelets ^b	67 (28.6%)	
Anticoagulants ^b	75 (32.1%)	
Anticoagulant duration (years) ^a	0.70 (± 1.33)	
SBP ^a	146.11 (± 23.59)	
DBP ^a	85.58 (± 10.39)	
FBS ^a	133.27 (± 48.97)	
Total leukocyte count ^a	10.84 (± 6.03)	
Platelets count ^a	240.14 (± 66.37)	
International normalized ratios ^a	1.26 (± 0.37)	
Total cholesterol ^a	192.82 (± 49.82)	
LDL-C ^a	129.82 (± 41.53)	
HDL-C ^a	42.51 (± 13.99)	
Triglycerides ^a	123.46 (± 50.40)	
ESR ^a	29.48 (± 5.83)	
CRP ^a	11.76 (± 10.18)	
Creatinine ^a	0.75 (± 0.21)	
GCS ^a	13.01 (± 2.38)	
NIHSS ^c	14 (8–18)	
Hemorrhagic transformation ^b	53 (22.6%)	
Infarction size ^b	Small	83 (35.5%)
	Medium	73 (31.2%)
	Large	78 (33.3%)
CMB ^b	0	139 (59.4%)
	< 10	60 (25.6%)
	≥ 10	35 (15%)
Superficial siderosis ^b	38 (16.2%)	
WML ^b	97 (41.5%)	
CNS atrophy ^b	90 (38.5%)	

TIA transient ischemic attack, HDL high-density lipoprotein-cholesterol, LDL low-density lipoprotein-cholesterol, ESR erythrocyte sedimentation rate, CRP C-reactive protein, GCS Glasgow Coma Scale, NIHSS National Institutes of Health Stroke Scale, CMB cerebral microbleed, WML white matter lesions

^a Mean (± SD)

^b N (%)

^c Median (IQR)

* significant at alpha level of significance ≤ 0.05

without HT (33.2%) and the presence of ≥ 10 CMB was related to higher risk of HT. Patients in the group with HT had larger infarction size (49.1%) compared to the group without HT (28.7%) (Table 2). HT was detected

in 39 patients that had anterior circulation infarction, 10 patients had posterior circulation infarction and 4 patients had multiple infarction sites. However, most of HT cases took place in the anterior circulation, there was no statistically significant difference regarding the site ($\chi^2 = 0.298, p = 0.862$).

Multivariable logistic regression analysis was used to evaluate the association of significant factors in univariate analysis with risk of HT. Age [odds ratio (OR): 1.05, confidence interval (CI) 1.01–1.09], size of infarction (OR: 2.57, CI 1.06–6.27) and CMB ≥ 10 (OR: 4.68, CI 1.71–12.84) were found to be a significant risk factors of HT (Table 3).

Discussion

The frequency of HT was 22.6% in the present prospective study. This frequency was slightly higher than the frequency of HT (19.2%) we previously reported in ischemic stroke patients without AF [19] and that could be due to the inclusion of higher risk group of ischemic stroke patients. Our frequency of HT was similar with the result of D'Anna and colleagues who reported a frequency of 20.6% HT in patients with AF [20]. Similar to stroke patients without AF, large infarction size and CMB were significantly associated with incidence of HT [19]. However, NIHSS was not statistically significant using logistic regression analysis. This could be explained by the nature of stroke in AF patients that is characterized by high NIHSS [21].

The present study has shown that old age, size of infarction, and CMB ≥ 10 were independently associated with increased risk for HT in ischemic stroke patients with AF. Our results suggest that large infarction size independently predicts HT in ischemic stroke patients with AF. This was consistent with the results of several studies in patients of other ethnicities [6, 7, 19–24]. According to the current European guidelines on AF, it was recommended to consider the size of brain infarction and HT before starting anticoagulation. In addition delaying oral anticoagulation was suggested with moderate or large infarction size [25]. It has been reported that HT risk increases by fourfold by increasing the of infarct size from one level to the next [4].

In the current study, we investigated the effect of different grades of CMBs that could predict the risk of future HT. Our data provide some evidence to suggest that CMBs ≥ 10 could be a predictor for HT. This was supported by a recent study demonstrated that the presence of CMB ≥ 5 on MRI might identify subgroups of AF ischemic stroke patients with high ICH risk [26]. Consistent with our result, several studies demonstrated increased HT in patients with CMB [19, 27–30]. CMB could be an indicator for the severity of cerebral

Table 2 Comparison between patients with and without HT regarding demographic, vascular risk factors, clinical data and neuroimaging markers

Variables	Hemorrhagic transformation in ischemic stroke with AF (234)		p-value	
	Without HT(181)	With HT (53)		
Age ^a	62.80 (± 9.20)	68.28 (± 9.72)	< 0.001*	
Gender ^b (male)	92 (50.8%)	27 (50.9%)	0.98	
Hypertension ^b	96 (53.0%)	38 (71.7%)	0.02*	
Diabetes mellitus ^b	66(36.5%)	29 (54.7%)	0.01*	
Smoking ^b	38 (21.0%)	9 (17.0%)	0.52	
Dyslipidemia ^b	75 (41.1%)	17 (32.1%)	0.22	
Previous stroke/TIA ^b	25 (13.8%)	13 (24.5%)	0.06	
Ischemic heart disease ^b	54 (29.8%)	19 (35.8%)	0.41	
Statin ^b	47 (26.0%)	16 (30.2%)	0.54	
Antiplatelets ^b	49 (27.1%)	18 (34.0%)	0.32	
Anticoagulants ^b	52 (27.6%)	23 (47.2%)	0.04*	
Anticoagulant duration (years) ^a	0.63 (± 1.31)	0.94 (± 1.39)	0.15	
Total leukocyte count ^a	11.12 (± 6.60)	9.89 (± 3.33)	0.19	
Platelets count ^a	244.22 (± 66.64)	226.23 (± 64.11)	0.08	
ESR ^a	29.58 (± 6.12)	29.17 (± 4.73)	0.61	
CRP ^a	11.51 (± 9.45)	12.62 (± 12.41)	0.48	
Creatinine ^a	0.76 (± 0.21)	0.72 (± 0.20)	0.29	
GCS ^a	12.87 (± 2.47)	13.49 (± 2.01)	0.09	
NIHSS ^c	12 (8–18)	18 (12–20)	< 0.001*	
Infarction size ^b	Small	72 (39.8%)	11 (20.8%)	0.01*
	Medium	57 (31.5%)	16 (30.2%)	
	Large	52 (28.7%)	26 (49.1%)	
CMB ^b	0	121 (66.9%)	16 (35.6%)	< 0.001*
	< 10	45 (24.9%)	11 (24.4%)	
	≥ 10	15 (8.3%)	18 (40.0%)	
Superficial siderosis ^b	24 (13.3%)	14 (26.4%)	0.02*	
WMH ^b	73 (40.3%)	24 (45.3%)	0.52	
CNS atrophy ^b	66 (36.5%)	24 (45.3%)	0.51	

TIA transient ischemic attack, HDL high-density lipoprotein-cholesterol, LDL low-density lipoprotein-cholesterol, ESR erythrocyte sedimentation rate, CRP C-reactive protein, GCS Glasgow Coma Scale, NIHSS National Institutes of Health Stroke Scale, CMB cerebral microbleed, WML white matter lesions

^a Mean (± SD)

^b N (%)

^c Median (IQR)

* Significant at alpha level of significance ≤ 0.05

microangiopathy that could explain the abnormal permeability of the arteriolar BBB leading to extravasations of blood components [28, 31]. Therefore, it was suggested that these lesions might be indicative of a bleeding prone state in HT after acute ischemic stroke.

Regarding age in the present study, age was a statistically significant independent predictor for HT. This was in agreement with the result of other studies that identified age as one of the most risk factor for HT [32–34]. Moreover, a recent met-analysis included 15 studies with 3480 ischemic stroke patients documented the significant association of HT and age [5].

Our results led to the identification of predictive factors in AF stroke patients who are clinically relevant high-risk for developing HT. Our findings suggest that caution should be considered when prescribing antithrombotic therapies to patients with old age, large cerebral infarction and CMB. Incorporation of MRI screening into clinical practice for patients with AF will lead to considerable improvements in stroke prevention and predictive ability for identification of risk factors for HT. Our study was limited by the study design as the study involves a sample of patients at a single hospital and not a multicenter study, although it is a large

Table 3 Multivariable logistic regression analysis of variables associated with HT in ischemic stroke patients with AF

Risk factors	OR	95% CI	p-value
Age	1.05	1.01–1.09	0.01*
Hypertension	1.05	0.47–2.31	0.90
Diabetes mellitus	1.62	0.79–3.32	0.18
Anticoagulant	1.73	0.82–3.65	0.15
NIHSS	1.04	0.983–1.12	0.15
CMB	4.68	1.71–12.84	0.01*
Superficial siderosis	1.79	0.69–4.59	0.23
Size of infarction	2.57	1.06–6.27	0.03*

OR odds ratio, CI confidence interval, NIHSS National Institutes of Health Stroke Scale, CMB cerebral microbleed

*Significant at alpha level of significance ≤ 0.05

hospital in Egypt that serves a wide neighboring area. In addition, we did not study association of HT incidence with the type of AF because a large number of our patients were accidentally diagnosed after admission. Therefore, we could not detect its exact type since persistent and permanent diagnosis would require a much longer time scale than our study. Even with these limitations, our data strongly suggest that age, size of infarction, and CMB are important predictors of HT in ischemic stroke patients with AF. Future risk scores should include CMB as a neuroimaging marker in addition to clinical parameters to identify patients with stroke at risk of HT and further studies are urgently needed to determine how neuroimaging markers may contribute to improvement of risk prediction of HT.

Abbreviations

AF	Atrial fibrillation
HT	Hemorrhagic transformation
CT	Computed tomography
MRI	Magnetic resonance imaging
CMB	Cerebral microbleed
SS	Superficial siderosis
OR	Odds ratio
CI	Confidence interval
BBB	Blood brain barrier
GCS	Glasgow Coma Scale
NIHSS	National Institutes of Health Stroke Scale
ECG	Electrocardiogram
CBC	Complete blood count
HDL-C	High-density lipoprotein-cholesterol
LDL-C	Low-density lipoprotein-cholesterol
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein

Acknowledgements

Not applicable.

Author contributions

RF, TE, HH, and BR were involved in crafting the study topic and design. All authors participated in manuscript drafting. All authors read and approved the final manuscript.

Funding

This study received no funding.

Availability of data and materials

The data results generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of the neurology department (January, 2018), Faculty of Medicine, Zagazig University. An informed written consent was obtained from all participants. The participants were informed about the purpose of the study.

Consent for publication

Is not applicable in this section.

Competing interests

The authors declare that they have no competing interests.

Received: 16 June 2023 Accepted: 13 October 2023

Published online: 24 October 2023

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