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Research Article

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Risk Factors for Hemorrhagic Transformation in Patients with Acute Middle Cerebral Artery Infarction

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ABSTRACT

Introduction: Hemorrhagic transformation (HT) after acute ischemic stroke (AIS) can be seen at any time following ischemic stroke. Although HT usually occurs as a complication of antithrombotic, anticoagulant, or thrombolytic treatments, it can also occur spontaneously. We aimed to investigate the occurrence of early HT and its relevant risk factors in patients diagnosed with acute middle cerebral artery (MCA) infarction who were not treated with thrombolytic agents.

Methods: We recruited 171 patients with acute MCA infarction between January 2011 and July 2012 who were not treated with thrombolytic agents and were suitable to our inclusion criteria. Controlled neuroimaging was performed immediately in patients with deterioration, otherwise on day 7 following stroke. All patients were investigated for AIS risk factors and biochemical analyses were performed. Patients with HT in controlled neuroimaging were grouped both clinically (i.e., symptomatic or asymptomatic) and radiologically, according to "European Cooperative Acute Stroke Radiological Study" (ECASS), and risk factors were examined.

Results: We enrolled 171 patients [94 men (55%) and 77 women (45%)] in the study. HT developed in 37 patients (21.63%). In terms of risk factor analysis, the most frequent etiological factor was atherosclerosis in AIS patients (50.3%). National Institutes of Health Stroke Scale scores were significantly higher both in sHT patients according to asHT patients and in HT patients on day 7 compared with their initial scores. Serum low-density lipoprotein (LDL-C), triglycerides (TG), and total cholesterol (TC) levels were significantly lower in patients with HT ($p<.001$).

Conclusion: HT is a major complication in AIS that considerably increases the morbidity and mortality. To reduce the occurrence of HT, risk factors for each patient population should be determined. Acute thrombolytic therapy should be used cautiously in high-risk patients, and appropriate alternative therapies should be revised in them.

Keywords: Acute ischemic stroke, hemorrhagic transformation, middle cerebral artery infarction

INTRODUCTION

Hemorrhagic transformation (HT) occurs predominantly in acute ischemic stroke (AIS) with cardioembolic origin and could be seen at any time following ischemic attack (1). HT is a complicated phenomenon resulting from the breakdown of blood–brain barrier (2). Several potential precipitating factors have been proposed for HT, such as, reperfusion injury, oxidative stress, leucocyte infiltration, vascular activation, and dysregulated extracellular proteolysis (3). HT could be asymptomatic and diagnosed incidentally with controlled neuroimaging, or it could be symptomatic together with clinical deterioration. Hypertension, hyperglycemia, lowered platelet count, old age, large infarcts, reperfusion time, thrombolytic therapy, ischemic white matter lesion load, and treatment with thrombotic or anticoagulant therapies increase the risk of HT (4,5,6,7).

Although HT usually occurs as a complication of antithrombotic, anticoagulant, or thrombolytic treatments, it can also occur spontaneously. Majority of the studies on HT complicating AIS include patients treated with thrombolytic agents. Studies concerning HT in the natural course of AIS are relatively less. Clarification of risk factors for HT in the natural course of the disease would guide clinicians in patient selection for acute thrombolysis, thereby leading to fewer treatment complications. In this study, we aimed to investigate both the frequency and risk factors of HT in patients with acute ischemic MCA infarction who were not treated with thrombolytic therapies.

METHODS

A total of 674 patients diagnosed with AIS at our tertiary care Neurology Clinic during January 2011 and July 2012 were monitored in this study. To maximize the homogeneity of the study population, only patients with clinically and radiologically confirmed acute MCA infarction were included. Patients treated with thrombolytic therapy, those who were on thrombotic or anticoagulant treatment prior to the stroke, or those with intracranial/intracerebral hemorrhage during the first neuroimaging in an emergency room were not included in the study. Finally, a total of 171 patients who gave informed consent and fulfilled the inclusion criteria were enrolled into the study.

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Table 1. Risk factors of HT patients

	Hemorrhagic transformation			Radiological classification			Clinical classification		
	HT (−) (n=134)	HT (+) (n=37)	p*	HI (n=25)	PH (n=12)	p*	aHT (n=20)	sHT (n=17)	p*
Risk factors (%)									
Hypertension	91.0	86.5	.534	84.0	91.7	.470	80.0	94.1	.225
Diabetes mellitus	37.3	43.2	.512	40.0	50.0	.566	30.0	58.8	.076
Atrial fibrillation	20.1	18.9	.868	12.0	33.3	.136	15.0	23.5	.404
Hyperlipidemia	31.3	24.3	.409	24.0	25.0	.624	25.0	23.5	.612
Chronic renal insufficiency	3.7	2.7	.615	4.0	0	.676	0	5.9	.459

*The χ^2 test was used for non-continuous variables. P value of <.05 was considered as significant. n: number of patients; HT: hemorrhagic transformation; PH: parenchymal infarct; aHT: asymptomatic hemorrhagic infarction; sHT: symptomatic hemorrhagic infarction

Table 2. Clinical features and laboratory testing results of HT patients

	Hemorrhagic transformation			Radiological classification			Clinical classification		
	HT (−) (n=134) Mean±SD	HT (+) (n=37) Mean±SD	p*	HI (n=25) Mean±SD	PH (n=12) Mean±SD	p*	aHT (n=20) Mean±SD	sHT (n=17) Mean±SD	p*
SBP (mmHg)	151.1±23.3	148.6±22.0	.555	156.2±27.0	138.1±12.0	.08	151.6±26.4	149.0±23.0	.755
DBP (mmHg)	91.5±12.5	88.0±9.4	.068	89.6±12.0	84.6±3.4	.134	89.8±10.9	85.8±6.9	.204
Blood glucose (mg/dL)	125.5±58.9	143.6±72.8	.119	133.3±63.3	165.0±88.7	.280	130.6±48.4	159.0±93.2	.243
Hgb (mg/dL)	12.6±1.7	12.8±1.8	.540	12.8±1.8	12.9±1.9	.932	12.7±1.7	13.0±1.9	.685
TC (mg/dL)	199.3±37.5	182.3±43.1	.019	176.5±40.6	194.2±47.5	.248	173.5±38.5	192.5±47.1	.184
LDL-C (mg/dL)	138.7±24.3	114.9±39.0	.001	111.8±38.8	121.2±40.4	.503	111.5±33.5	118.4±45.4	.571
TG (mg/dL)	158.9±48.6	118.8±63.1	<.001	111.5±46.0	134.0±89.7	.318	112.3±41.7	126.5±82.5	.502
HDL-C (mg/dL)	41.9±11.1	42.2±14.7	.887	40.7±12.2	45.3±19.3	.464	41.9±12.9	42.6±17.0	.881
PLT (k/μL)	215.0±80.2	250±104.5	.028	261.0±106	228.6±100	.386	236.8±81.2	266.5±127.4	.396

*Continuous variables were compared between the groups by the Student's t-test. P value of <.05 was considered as significant

n: number of patients; SD: standard deviation; HT: hemorrhagic transformation; HI: hemorrhagic infarct; PH: parenchymal infarct; aHT: asymptomatic hemorrhagic infarction; sHT: symptomatic hemorrhagic infarction; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hgb: hemoglobin; TC: total cholesterol; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; TG: triglycerides; PLT: platelet

All patients were subjected to detailed physical and neurological examinations followed by a thorough query for medical history either from patients or from their close relatives. National Institutes of Health Stroke Scale (NIHSS) scores were noted both during the initial examination and on day 7 following the stroke. Arterial blood pressure, complete blood count, serum glucose levels, lipid profile, including low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TG), liver function tests, renal function tests, and electrocardiogram findings were noted. Following the initial evaluation, all patients were given appropriate medical therapy; i.e., antithrombotics for those with atherosclerotic origin and anticoagulants for those with cardioembolic origin.

Controlled neuroimaging, namely cranial computed tomography (CT) and/or cranial magnetic resonance imaging (MRI), was performed immediately in patients with deterioration, otherwise on day 7 following the stroke. Patients with HT in controlled neuroimaging were divided into groups, according to the radiological criteria of "European Cooperative Acute Stroke Radiological Study" (ECASS) (8). These include hemorrhagic infarcts (HI) and parenchymal hematoma (PH). On the other hand, patients were grouped according to their clinical deterioration as asymptomatic HT (asHT; HT is present, but there were no changes in NIHSS scores) and symptomatic HT (sHT; HT is present together with an increase in NIHSS scores). The etiological classification of AIS was performed according to the TOAST classification (9).

Statistical Analysis

Statistical analysis was carried out with Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 15.0 software for Windows. Categorical variables were compared with χ^2 test. Non-categorical variables were compared using Student's t-test (parametric), Mann–Whitney U test (non-parametric), where appropriate. P value of <.05 was considered as significant.

RESULTS

A total of 171 patients [94 men (55%) and 77 (45%)] were recruited into the study. Mean age was 71.24±8.55 years (range, 44–85 years). HT developed in 37 patients (21.63%). According to the radiological classification, 25 were HI (67.6%) and 12 were PH (32.4%). Twenty patients were asHT (54.1%) and 17 were sHT (45.9%). There was no difference among the HT patient groups according to age [t(169)=1.044, p=.298] or gender (χ^2=.61, p=.805). Time of initial neuroimaging ranged between 6 and 32 hours (mean, 14±6.2 hours) following the stroke.

Arterial hypertension was the most frequent risk factor (86.5%) in patients with HT, whereas chronic renal insufficiency was the least frequent risk factor (2.7%). However, risk factors did not differ between the patients with and without HT. Clinical features, laboratory testing, and risk factors are summarized in Tables 1 and 2.

LDL-C levels [114.9±39 mg/dL; t(44)=3.51, p=.001], TC levels [182.2±43.1 mg/dL; t(169)=2.372, p=.019], and TG levels [118.8±63.1 mg/dL; t(169)=4.152, p<.001] were significantly lower in patients with HT. There was no association between HDL-C and HT. Serum biochemistry panels of patients with PH and HI were not significantly different (p>.05). Clinically symptomatic and asymptomatic HT patients did not differ according to blood pressure (systolic or diastolic). Although systolic blood pressure was higher in HI patients than PH patients, this finding was not statistically significant (Table 2).

Atherosclerosis was the most frequent etiological factor in the whole stroke group (47.4%) as well as in patients with HT (48.6%); on the other hand, small vessel occlusion was the least frequent with a frequency of 8.8% in the whole stoke group (Table 3). NIHSS scores were significantly higher in both sHT patients, compared with asHT patients, [13.4±4.2 vs. 8.2±5.2; t(35)=−3.306, p=.002] and HT patients on day 7 compared with their initial scores [12.2±6.4 vs. 10.6±5.4; t(35)=−4.716, p<.001] (Table 4).

DISCUSSION

Hemorrhagic transformation has been reported in 13%–71% of AIS patients (10). The amount of hemorrhage varies widely from small petechial lesions to large intracerebral hematoma. Small petechial hemorrhages are usually asymptomatic and could only be diagnosed during controlled neuroimaging. HT, particularly the small petechial hemorrhage, could be best visualized in T2-weighted gradient-echo sequences of MRI in a few days or weeks following AIS (10). This is why the time of neuroimaging is important. There is disparity in different ethnic populations regarding the occurrence of HT because of genetic, cultural, and living-style differences (11). It has been reported that the timing of controlled neuroimaging and imaging technique (CT or MRI) are important factors in diagnosing HT. Terruso et al. (12) reported the development of HT in 12% of AIS patients (n=240) who were not treated with thrombolytic therapy. Choi et al. (13) reported HT in 11.9% of stroke patients, including those treated with thrombolytic agents. In another study, Celik et al. (14) found that 8.5% of all AIS patients had HT and 40.7% of patients had acute MCA infarction. Okado et al. (15) investigated the HT occurrence in time and reported the frequency of HT as 6.2% on day 4, 27.5% on day 5, and 40.6% on day 30. We found the frequency of HT in patients with acute MCA infarction as 21.6%, in accordance with the literature.

It is widely accepted that HT occurrence in patients who were not treated with thrombolytic agents is related with strokes that were cardioembolic in origin. Choi et al. (13) reported cardiac embolism (46.9%) as the most frequent etiological factor in HT patients and atherosclerosis (36.2%) as the most frequent etiological factor in HI patients. In their study including 203 stroke patients, Bayramoglu al. (16) reported the cardiac embolism (62%) as the most frequent etiological factor. On the other hand, Celik et al. (14) found no statistically significant difference among patients who developed HT in the first week following AIS, according to atherosclerotic or cardioembolic origin. In a multicenter study with 1125 patients, Paciaroni et al. (17) found HT in 9% of the patients, and cardiac embolism was the major cause in patients with HT. In our study, the major cause for AIS was atherosclerosis (50.29%), while the patients with HT mostly had cardioembolic origin (29.7%).

Cholesterol plays an important role in the integrity of cerebral vessel walls. Thus, it has been suggested that low serum cholesterol levels increase the tendency of micro vessel rupture leading to an increased risk for HT. There is a discrepancy in studies regarding the relationship between serum cholesterol levels and HT. In spite of some studies reporting the causal relationship between low TC and LDL-C levels with HT, other studies report no relationship (13,18,19,20,21). Statins were previously shown to be effective in the primary and secondary prevention of AIS (22). Bang et al. (19) investigated the prophylactic effects of statins on the development of HT in 104 stroke patients and found that low LDL-C, TC, and TG levels had increased the occurrence of sHT independent of statin use. Later, Nardi et al. (23) abridged the results of their meta-analyses under two captions: 1. Serum levels of HDL-C, TC, and TG levels are not different, despite the low LDL-C levels in patients with HT following AIS and 2. Serum levels of TC are lower in sHT patients; however, LDL-C, HDL-C, and TG levels are not different. In our study, we found lower serum TK, LDL-C, and TG levels in patients with HT.

In the literature, there is also a conflict of data on the effect of initial arterial blood pressure and HT. Majority of the studies report no significant relationship between HT and high systolic blood pressure on admission. Arterial hypertension has been associated with the occurrence of HT in the form of intracerebral hematoma (17,23,24). In our group, patients with HT had higher initial systolic blood pressure levels, although this finding did not reach statistical significance. In previous studies, high levels of serum glucose and thrombocyte counts have been associated with higher incidence in HT patients, but we found no difference in this study. HT risk

Table 3. Etiological classification for AIS patients

	HT (−) (n=134)	HT (+) (n=37)	%	p*
Large vessel atherosclerosis	68 (50.7%)	18 (48.6%)	50.3	.821
Cardioembolism	26 (19.4%)	11 (29.7%)	21.6	.177
Small vessel occlusion	11 (8.2%)	4 (10.8%)	8.8	.414
Uncertain cause	29 (21.6%)	4 (10.8%)	19.3	.139

*The χ^2 test was used for non-continuous variables. P value of <.05 was considered as significant.

n: no of patients; AIS: acute ischemic stroke; HT: hemorrhagic transformation

Table 4. NIHSS scores of HT patients

NIHSS scores	HI (n=25) Mean±SD	PH (n=12) Mean±SD	p*	asHD (n=20) Mean±SD	sHD (n=17) Mean±SD	p*
On admission	10.2±5.74	11.5±4.71	.474	8.2±5.23	13.4±4.19	.002
On day 7	11.2±6.74	14.0±5.45	.218	8.5±5.60	16.5±4.40	<.001

*Continuous variables were compared between the groups by the Student's t-test. P value of <.05 was considered as significant.

n: no of patients; SD: standard deviation; NIHSS: National Institute of Health Stroke Scale; HT: hemorrhagic transformation; PH: parenchymal hematoma; asHT: asymptomatic hemorrhagic transformation; sHT: symptomatic hemorrhagic transformation

was significantly increased in patients with high initial NIHSS scores. We may suggest that the severe neurological deficits on admission increase the risk of HT. The size of the infarct area and ischemic-gliotic white matter lesion load has been a well-known risk factor for HT (7,17,23). Lack of measurements of the infarct size and previous ischemic lesion load are the major limitations of this study.

In conclusion, HT is a major complication of AIS, increasing the morbidity and mortality. To reduce the occurrence of HT, risk factors for each ethnic population should be determined. We suggest that acute thrombolytic therapy should be cautiously used in patients with high risk, and appropriate alternative therapies (modified dosage for thrombolytic agents or combining the secondary therapeutic agents) should be revised in those.

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