Prediction of Hemorrhagic Transformation in Acute Ischemic Stroke among A Sample of Adult Egyptian Patients

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Abstract: Hemorrhagic transformation id a common complication after ischemic stroke especially after thrombolytic therapy. Multiple risk factors have been incriminated in the development of such complication. This study was conducted to determine the predictive factors for development of hemorrhagic transformation in patients with acute ischemic stroke among a sample of adult Egyptian patients. **Patients and methods:** Ninety-one cases with acute ischemic stroke were included and they were divided into two groups; group (A) that included 69 cases who did not develop hemorrhagic transformation, and group (B) that included 22 cases who developed the previous complication. Patients were evaluated clinically and base line CT as well as routine laboratory investigations were performed for all cases. Additionally, echocardiography and follow up CT were ordered only in selected cases. **Results:** Demographics did not differ between both groups. Hypertension was more prevalent in group B ($p < 0.001$). Neither diabetes nor ischemic heart disease were different statistically between groups. Moreover, group B had a higher NIH scores ($p < 0.001$). Regarding laboratory findings, group B had higher INR, higher LDL, and lower TGs when compared to group A ($p < 0.05$). In addition, early CT signs and higher ejection fraction were noticed in the hemorrhagic group ($p < 0.05$). On multivariate analysis, hypertension, INR, early CT findings, and LDL were significant predictors of hemorrhagic transformation with p value of 0.002, 0.008, 0.038, and 0.022 respectively, and odds ratio of 131.9, 270.3, 8.6, and 1.1 in order of speech. **Conclusion:** Based on our results, the group with hemorrhagic transformation showed higher prevalence of hypertension, higher NIH scores, higher INR, lower TGs levels, higher LDL levels, more early CT signs, and higher ejection fraction when compared to the other group. On multivariate analysis, hypertension, INR, Early CT signs, and high LDL levels were significant predictors of HT.

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Key words: acute ischemic stroke, hemorrhagic transformation.

1. Introduction

Hemorrhagic transformation (HT) is a bleeding into an area of ischemic brain after stroke. The severity of HT can vary from micro bleeding to large hemorrhages. Clinical studies frequently divide HT into four groups: small petechial hemorrhagic infarction (HI1), confluent petechial hemorrhagic infarction (HI2), small parenchymal hemorrhage (PH1, <30% of infarct, mild mass effect) and large parenchymal hemorrhage (PH2, >30% of infarct, marked mass effect)[1].

It is also often divided into symptomatic and asymptomatic groups based on the deterioration in neurological status. It is a common complication of ischemic stroke that is exacerbated by thrombolytic therapy. It occurs in as many as 10% to 40% of patients with ischemic stroke, and is associated with increased stroke morbidity and mortality[2].

It is a dynamic and complex phenomenon. Within seconds to minutes after the onset of cerebral ischemia, the level of ATP decreases substantially, compromising the activity of the Na+-K+ ATPase. This creates a series of cellular and metabolic imbalances that cumulatively lead to a disruption of the Blood brain barrier (BBB)[3].

Furthermore, ischemia results in a strong inflammatory response further distorting normal cerebrovascular anatomy and physiology. The resulting disruption of the BBB and the impairment of the autoregulatory capacity of the cerebral vasculature predispose to blood extravasation when the ischemic tissue is eventually reperfused[3].

Importantly, the degree of anatomical and physiological disruption appears highly dependent on the duration of ischemia[4].

A number of clinical factors have been associated with HT in patients with stroke. Stroke

severity and infarct size is the single factor that best correlates with HT. Other factors include older age, greater stroke severity, higher glucose level and the presence of atrial fibrillation, congestive heart failure, renal impairment, hepatic impairment, previous antiplatelet agents or a visible acute cerebral ischemic lesion on pretreatment brain imaging [5].

This study was conducted to determine the predictive factors for development of hemorrhagic transformation in patients with acute ischemic stroke among a sample of adult Egyptian patients.

2. Patients and methods

Study design

This a prospective study including Egyptian patients who presented with acute ischemic stroke at Al-Mokattam insurance hospital and Al-Azhar university hospitals (El-Hussien and Bab El-shearia hospitals) during the period between from 2015 to 2018. The study was approved by the local ethical committee.

Patient sample

Ninety-one (n = 91) cases with acute ischemic stroke were included in the study. These cases were divided into two groups; group (A) included 69 cases who did not experience hemorrhagic transformation, and group (B) included 22 cases who developed hemorrhagic transformation.

Patient consent

A written formal consent was obtained from the patients or their relatives in the patient was unconscious before participating in this clinical study.

Inclusion criteria

1. Embolic stroke of acute onset.
2. Thrombotic stroke of acute onset.
3. Patients more than 18 years.

Exclusion criteria

1. Stroke for more than two weeks**.**
2. Hemorrhagic stroke.
3. Patients less than 18 years.
4. Hemorrhagic Blood diseases like hemophilia, DIC, congenital protein c or s deficiency, idiopathic thrombocytopenic purpura, congenital platelets function defects, factors II, V, VII, X, XII deficiency, or Von Willebrand disease).

Patient evaluation

All the included cases were subjected to complete history taking, full clinical and neurological examination in addition to NIH score. Routine laboratory investigations were ordered for all our cases including lipid profile, and bleeding profile.

Additionally, 12-lead ECG was performed for all cases. However, echocardiography was done only in indicated cases. Baseline brain CT was performed within 24 hours after onset of symptoms. Moreover, follow up CT was done after 2 weeks or when indicated.

Statistical analysis

Data was analyzed by using SPSS software, version 20 (Chicago, IL). Quantitative data were expressed as means with standard deviation and comparison between data within two groups was done using independent samples t-test (t). Categorical data were expressed as number and percentage within group. Comparison of data within two groups was conducted by using chi-square test ($\chi 2$). Validity of ejection fraction in differentiating hemorrhagic lesions was expressed in terms of sensitivity, specificity, NPV, PPV and accuracy. Multivariate logistic regression analysis was used for detection of the risk of hemorrhage among cases. P values <0.05 are considered significant.

3. Results

Table (1): Demographics and clinical data.

	No hemorrhage (n = 69)	Hemorrhage (n = 22)	Test of significance
Age (years)	58.14±8.8	59.32±5.9	t=0.58 p=0.56
Sex -Male -Female	 31(44.93%) 38(55.07%)	 12(54.55%) 10(45.45%)	$\chi 2$=0.62 p=0.43
DM	38(55.07%)	13(59.09%)	$\chi 2$=0.11 p=0.74
HTN	12(17.39%)	21(95.45%)	$\chi 2$ = 43.9 p< 0.001*
IHD	37(53.62%)	8(36.36%)	$\chi 2$=1.99 p=0.16
NIH score	9.94±3.5	13.77±3.4	T = 4.5 p< 0.001*

Starting with demographics, the mean age of the included cases was 58.14 and 59.32 years for group A and B respectively. Group A included 31 males (44.93%) and 38 females (55.07%). On the other hand, Group B included 12 males (54.55%) and 10 females (45.45%). Neither age nor sex were significantly different between the two study groups (p> 0.05).

Regarding comorbidities, hypertension had a significantly higher prevalence in group B (95.45% vs. 17.39% - p < 0.001). Nevertheless, diabetes mellitus and ischemic heart disease were not significantly different between the two groups. Moreover, group B expressed a significantly higher NIH scores (13.77 vs. 9.94 – p < 0.001). The previously mentioned demographic and clinical data are shown in table (1).

It was evident that all laboratory values did not make a statistically significant difference between both groups. However, INR and LDL were significantly higher in group B. Additionally, TGs expressed lower values in the same group. These data are illustrated in table (2).

Table (2): Laboratory data of the study cases.

	No hemorrhage (n = 69)	Hemorrhage (n = 22)	Test of significance
ALT (U/l)	27.7±9.3	24.7±9.5	t =1.33 p =0.19
AST (U/l)	23.62±8.1	21.73±9.4	t =0.91 p =0.36
INR	1.07±0.16	1.26±0.22	t = 4.55 p< 0.001*
Plt (*10^3/ml)	247.6±65.3	250.68±65.9	t =0.19 p =0.85
WBCs (*10^3/ml)	7.39±2.6	6.95±1.8	t =0.73 p =0.47
HBA1C (%)	6.09±1.7	6.27±1.6	t = 0.43 p =0.67
Creatinine (mg/dl)	1.06±0.26	1.05±0.23	t =0.22 p =0.80
TGs (mg/dl)	219.93±36.7	193.64±45.4	t = 2.75 p = 0.007*
LDL (mg/dl)	115.9±23.3	138.41±20.1	t = 4.06 p< 0.001*

Early CT signs were frequently seen in group B cases (p < 0.001). The same group also showed higher ejection fraction when compared to the other group (p = 0.002). On the other hand, presence of atrial fibrillation did not differ significantly between both groups. These data are illustrated in table (3).

Table (3): Investigation findings in the study cases.

	No hemorrhage (n = 69)	Hemorrhage (n = 22)	Test of significance
CT early signs	11(15.94%)	18(81.81%)	$\chi 2$=33.3 p<0.001*
AF (in ECG)	33(47.82%)	8(36.36%)	$\chi 2$=0.89 p=0.35
EF (in Echo)	49.22±9.1	55.9±4.9	t=3.3 p=0.002*

On analysis of ejection fraction as predictor for hemorrhagic transformation, it had a sensitivity of 81.8%, accuracy of 62.6%, and specificity of 56.5% with a cut off value of 51.5%. These data are illustrated in table (4) and figure (1).

Table (4): Validity of ejection fraction in differentiating hemorrhagic lesions.

	AUC	Cut off point	Sensitivity	Specificity	PPV	NPV	Accuracy
EF	0.73	51.5	81.8	56.5	37.5	90.7	62.6

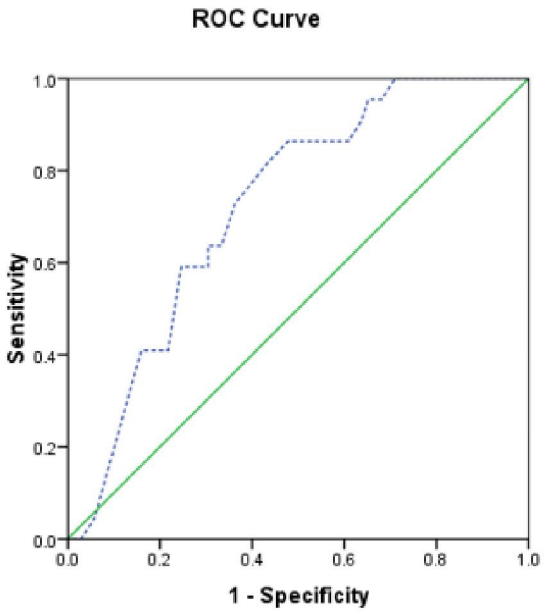

Figure (1): ROC curve for EF in differentiating hemorrhagic cases.

On performing multivariate analysis for detection of predictors, hypertension, high INR, early CT signs, and higher LDL were all significant predictors of HT. Data are shown in table (5).

Table (5): Multivariate analysis for detection of hemorrhage among cases.

Predictors	β	P value	Odds ratio	95.0% C.I. for odds ratio	
				Lower	Upper
hypertension	4.9	0.002*	131.9	6.2	2801.0
INR	5.6	0.008*	270.3	4.2	17360
CT early signs	2.1	0.038*	8.6	1.1	65.0
LDL	0.1	0.022*	1.1	1.01	1.1

4. Discussion

Hemorrhagic transformation of acute ischemic stroke occurs in both treated and non-treated stroke patients, it has a different radiological appearance, it may be detected on CT brain when the patients deteriorates clinically. There is a need to assess the risk of hemorrhagic transformation, causes, mechanisms, and clinical deterioration caused by such complication [5].

The mechanism of hemorrhagic transformation in acute ischemic stroke is not clearly understood, but several risk factors are associated with hemorrhagic transformation including thrombolytic agents, baseline neurological deficit, heart disease, elevated blood pressure, delayed administration of thrombolytic therapy, delayed reperfusion, cardioembolic stroke, diabetes mellitus[1].

Assessment of neurological outcome of stroke is important for management and prognosis, so assessment scales as NIHSS is widely used to assess the severity of an ischemic stroke. Moreover, it is also used in many trials for assessment and prediction of stroke outcome[6].

With regard to the type of hemorrhage, HT can be divided into hemorrhagic infarction (HI) and parenchymal hematoma (PH)[7]. HI is a

heterogeneous hyperdensity occupying a portion of an ischemic infarct zone on computed tomography (CT) images, whereas PH refers to a more homogeneous, dense hematoma with mass effect. Each of them has two subtypes: HI type 1 (HI1) and HI type 2 (HI2) for HI and PH type 1 (PH1) and PH type 2 (PH2) for PH. On radiographic images, HI1 is characterized by small hyperdense petechiae, whereas HI2 refers to more confluent hyperdensity throughout the infarct zone. Both of the two types are without mass effect. PH1 refers to the homogeneous hyperdensity occupying less than 30% of the infarct zone, with some mass effect, and PH2 refers to the homogeneous hyperdensity occupying over 30% of the infarct zone, with significant mass effect[8].

The incidence of spontaneous HT ranges from 38% to 71% in autopsy studies and from 13% to 43% in CT studies, whereas the incidence of symptomatic HT is from 6% to 20%[9].

The incidence depends on many factors, such as age, blood glucose level, thrombolytic agent used, route of administration, and time window allowed for the initiation of the therapy [10]. The rate of HI is higher than that of PH. In particular, in a large cohort of consecutive patients with acute ischemic stroke, the incidence of HI from the refereed paper was found to be about 9%, whereas that of PH was about 3%[11].

In our study, we emphasized that our patients were well defined with acute stroke symptoms of both embolic and thrombotic causes, with exclusion of patients with stroke more than 2 weeks, patients with acute hemorrhagic stroke, patients with hemorrhagic blood diseases with medical history, and patients below eighteen years old.

Full medical history was taken with special emphasis on vascular risk factors e.g: Hypertension, Diabetes Mellitus, cardiac diseases, and lipid profile.

Montaner and his colleagues stated that primary mechanism for HT in cardioembolic stroke appears to be reperfusion of infarcted or ischemic brain tissue after distal migration or dissolution of the thrombus [12].

Occasionally, delayed hemorrhage occurs without reperfusion and in these cases, the source of the hemorrhage is postulated to be collateral circulation to the damaged area.

In our study, the severity of the presented neurological deficit on admission of both hemorrhagic transformation, non-hemorrhagic transformation groups using NIHSS scoring proved to be statistically significant. In line with our study, Terruso and his associates found that NIHSS score is a powerful predictor of HT[13].

We found that the presence of early signs of infarction in the initial CT scan was associated with increased risk of HT. This result is concomitant with Wang et al. who stated that some early CT findings are strong predictors of HT and patients exhibiting these signs are at high risk of HT[14].

Hypertension is associated with an increased risk of HT in stroke patients, whether acute or chronic. Acute elevation in blood pressure is presumed to affect BBB permeability and increase HT, the effect of chronic hypertension on cerebral circulation may also increase the risk of HT. On the other hand, chronic hypertension alters the vasculature, increasing vascular resistance reducing vascular compliance and impairing collateral circulation[15].

In the study we found that there is statistically difference between group A and B as regarded presence of HTN as a medical history which agreed with Jauch[16].

Age of the patient was not associated with increased risk of HT in our study. that agreed with Larrue et al. [17] but did not agree with Skrobot et al. **[18].** This discrepancy may be due to either differences in patient characteristics or differences in statistical methods used for analysis.

Nogueira stated that the atrial fibrillation is associated with increased risk of HT. Atrial fibrillation is associated with higher volumes of more severe baseline hypoperfusion, leading to greater infarct growth, more severe HT[19].

In our study, we found that atrial fibrillation is not statistically significant for HT and that result came in line with the research published by Tu and his colleagues[20].

In this study, higher ejection fraction measures via echocardiography was detected in cases with HT when compared to the other group. Nevertheless, little data exists about this association in literature. Using a cut point of 51.5%, ejection fraction had a sensitivity of 81.8% and accuracy of 62.6% for predicting HT. However, it has a low specificity (56.5%).

In our study we found that hyperglycemia (DM) was statistically not significant for HT, which is not agree with Xing et al., who stated that hyperglycemia during acute ischemic stroke predisposes to parenchymal hematoma PH[21]. However, this finding agreed with Kunte et al. who stated that diabetic patients with acute ischemic stroke, prior and continued use of sulfonylureas drugs is associated with reduced symptomatic HT[22].

Kim BG found that low levels of LDL and possibly triglycerides are associated with higher risk of HT after acute ischemic stroke attributable to large artery atherothrombosis but not cardioembolism. These results are particularly important because LDL can be influenced by statins therefore the question of whether anticoagulation is safe in patients with low LDL or on statins treatment deserves more attention. Tillnow, a consensus has not been reached[23]

In our study patients with HT had lower serum levels of cholesterol but a higher level of triglycerides than patients without HT which was statistically significant.

Prodanstated that lower platelet count is associated with the presence of early HT in patients with ischemic stroke. It is likely that the decreased overall number of platelets available for activation and aggregation directly increased the risk of HT[24]. In our study we found that the difference of platelet count in HT patients was not statistically significant.

Conclusion

Based on our results, the group with hemorrhagic transformation showed higher prevalence of hypertension, higher NIH scores, higher INR, lower TGs levels, higher LDL levels, more early CT signs, and higher ejection fraction when compared to the other group. On multivariate analysis, hypertension, INR, Early CT signs, and high LDL levels were significant predictors of HT.

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