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Influencing factors of hemorrhagic transformation in non-thrombolysis patients with cerebral infarction

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ABSTRACT

Objectives: Hemorrhagic transformation (HT) is a serious complication of acute cerebral infarction. The aim of study is to investigate the influencing factors of HT in non-thrombolysis patients with acute cerebral infarction, and to explore its clinical significance.

Patients and methods: From June 2016 to March 2017, a total of 346 non-thrombolysis patients with acute cerebral infarction hospitalized in the Department of Neurology of Guangdong Second Provincial General Hospital, were chosen and randomly devided into the non-HT group (control) and HT group. A record of 17 indices including the patients'age, gender, hypertension, diabetes, dyslipidemia, hyperhomocystinemia, atrial fibrillation, drinking or smoking, anticoagulation, antithrombosis, international normalized ratio (INR) and platelet count were measured. Then regression analysis was made to find the independent factors for HT.

Results: It was found that 38 of non-thrombolysis patients with acute cerebral infarction involved in this study were with HT. The indices including dyslipidemia, drinking, atrial fibrillation, antiplatelet aggregation, anticoagulation, INR > 1.7, cholesterin, triglyceride and platelet count showed statistical differences between the HT group and the non-HT group ($P < 0.05$). According to the binary logistic regression analysis, there was a negative correlation between dyslipidemia and HT (odds ratio (OR) = 0.371, 95% confidence interval (CI) 0.186-0.740, $P = 0.005$), while there was a positive correlation between atrial fibrillation (OR = 2.476, 95% CI 1.140–5.377, P = 0.022), platelet count (OR = 1.006, 95% CI 0.682–1.611, $P = 0.007$), INR > 1.7 (OR = 10.889, 95% CI 4.760–24.910, $P = 0.000$) and HT.

Conclusion: There is independent correlation between dyslipidemia, atrial fibrillation, platelet count, INR > 1.7 and HT. Dyslipidemia is the protective factor for HT, and atrial fibrillation, platelet count, INR > 1.7 are the risk factors for HT.

1. Introduction

Acute cerebral ischemia is the frequent cause of irreversible brain damage and severe disability. Ischemic stroke can be classified into five subtypes including large artery atherosclerosis (LAA), small vessel disease (SVD), undetermined etiology, and cardioembolism (CE), and other determined etiology. Small bleeding has less influence on clinical symptom and prognosis of patients, while massive hemorrhage impacts on thrombolytic and anticoagulant therapy of patients, making clinical symptom aggravated, and even causing conscious disturbance or death in serious cases [1]. Hemorrhagic transformation (HT) is a common complication of acute cerebral infarction, which is disadvantageous to the treatment and prognosis of patients [2,3]. It has been demonstrated that HT after acute cerebral infarction is markedly increased because of the thrombolytic therapy. To present, only 15% thrombolysis patients can be sent to the hospital within 3 h [4], and the proportion is even lower in China due to pre-hospital delay [5]. So, exploring the influencing factors of HT in non-thrombolysis patients with acute cerebral infarction and reducing the incidence of HT have important clinical significances on the diagnosis, treatment and prognosis of patients with cerebral infarction. In the present study, we discussed the risk factors of HT in non-thrombolysis patients with acute cerebral infarction.

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2. Materials and methods

2.1. Patients

We chose 346 non-thrombolysis patients with acute cerebral infarction hospitalized in the Department of Neurology of Guangdong Second Provincial General Hospital, China, between June 2016 and March 2017. Patients with the average age 57.48 ± 6.27 years old included 179 males (51.73%) and 167 females (48.27%), and were devided into No-HT group (the control group) and HT group. A regression analysis was taken in 17 indices including the patients'age, gender, risk factors of cerebrovascular disease (hypertension, diabetes, dyslipidemia, hyperhomocystinemia, atrial fibrillation, drinking or smoking), anticoagulation, antithrombosis, INR and platelet count.

2.2. Inclusion & exclusion criteria

Inclusion criteria of cerebral infarction: these patients conformed to the diagnostic criteria of the acute cerebral infarction developed by the Fourth National Conference on the Cerebrovascular Disease and they were all detected and confirmed by the cranial computerized tomography (CT) and cranial magnetic resonance imaging (MRI). The topography of cerebral ischemia and HT detected by T2-weighted or T1-weighted MRI and CT was provided in Fig. 1. The time period from onset to treatment was in 72 h. Exclusion criteria: except for brain trauma, hemorrhagic stroke and transient ischemia attack (TIA), our study didn't cover the patients with medical history of cerebral infarction, or suffered from complicated consciousness disorder, infection, hematological diseases, severe liver and kidney disease, as well as the patients with severe trauma or medical history of major operation in recent days. All the patients with cerebral infarction didn't receive the thrombolytic therapy. HT was diagnosed by the first detection of CT/MRI as acute cerebral infarction without intracranial hemorrhage. MRI was used to recheck the situation of patients when the disease progressed or within 14 d from the onset, and hemorrhagic lesion was confirmed except calcification detected by CT.

Diagnostic criteria of hypertension: blood pressure was tested at different times, with systolic pressure > 140 mmHg and diastolic pressure > 90 mmHg for at least 2 times, or with medical history of hypertension. Diagnostic criteria of diabetes: fasted blood-glucose > 7.1 mmol/L or random blood sugar > 11.1 mmol/L, or with medical history of diabetes. Diagnostic criteria of dyslipidemia: the cholesterol level (at the time being admitted to hospital) > 5.72 mmol/L or triglyceride > 1.72 mmol/L or hypo-high-density lipoprotein < 1.04 mmol/L. Diagnostic criteria of atrial fibrillation: electrocardiographic examination by our hospital with atrial fibrillation, or with medical history of atrial fibrillation. History of smoking: one cigarette per day before onset, no less than 4 times a week and for more than 6 months. History of drinking: drinking more than 40 g at a time before onset, no less than 4 times a week and for more than one year. All the blood samples should be submitted for inspection within 24 h after being hospitalized.

2.3. Ethical statement

Ethical approval for this study was provided by the Ethical Committee of Guangdong Second Provincial General Hospital, Guangzhou, China (Chairman Prof. Jun-Chang Tian, Ethical Committee No. 2016-SJNK-001) on Nov. 8th, 2015 and the experiment was performed in accord with the ethical principles of the Declaration of Helsinki [6].

2.4. Statistical analysis

Statistical Package for the Social Sciences (SPSS) software version 13.0 (SPSS, Inc., Chicago, IL, USA) was used in this study to analyze the data. Quantitative data was indicated by mean ± standard deviation (SD), and the comparison of two groups was analyzed by *t* Test. Count data were expressed as the percentage, and the Nonparametric Test was used for comparison. $P < 0.05$ was regarded as a statistical significance. HT group was regarded as the dependent variable, and the Enter Method of Binary logistic regression analysis was employed to exclude $P > 0.1$ categorical covariates. The binary regression analysis was to determine the risk and protective factors.

3. Results

3.1. Variable comparison of HT group and non-HT group

This study was based on 346 non-thrombolysis patients with acute cerebral infarction, among which 38 (10.98%) cases had HT, and 308 (89.17%) cases had no HT. As shown in Table 1, compared to the non-HT group, the indices such as atrial fibrillation, antiplatelet aggregation, anticoagulation, INR (> 1.7), cholesterin, triglyceride, dyslipidemia, drinking and platelet count was changed in HT group and there had the statistical differences ($P < 0.05$). The incidence of atrial fibrillation, as well as higher ratio of anti-platelet aggregation, anticoagulation and INR (> 1.7) in the HT group were much higher than those in the non-HT group ($P < 0.05$). In addition, the level of cholesterol (CHOL) and triglycerides (TG), the incidence rate of dyslipidemia, the drinking ratio, and the average level of platelet count in the HT group was significantly decreased compared to the non-HT group ($P < 0.05$). Other indices such as low-density lipoprotein (LDL), high-density lipoprotein (HDL), diabetes, hypertension, hyperhomocystinemia of the two groups showed no statistical significance ($P > 0.05$).

3.2. Results obtained by binary logistic regression analysis

According to the binary logistic regression analysis, there was a negative correlation between dyslipidemia and HT (OR = 0.371, 95% CI 0.186-0.740, P = 0.005), indicating that dyslipidemia was the protective factor for HT. There was a positive correlation between atrial fibrillation (OR = 2.476, 95% CI 1.140–5.377, P = 0.022), platelet count (OR = 1.006, 95% CI 0.682–1.611, P = 0.007), INR > 1.7 (OR = 10.889, 95% CI 4.760–24.910, P = 0.000) and HT, suggesting that three of them were the risk factors for HT (Table 2).

4. Discussion

HT is a kind of hemorrhagic infarction lesion after acute cerebral infarction, and is a specific form and a stage of natural prognosis of cerebral infarction. HT is mainly caused by the increased permeability or disorganization of blood-brain barrier after cerebral infarction, with the endothelial cell damage and erythrocyte exudation from the cerebral infarction region. And ischemia reperfusion injury is another pathogenesis of HT [7–9]. HT is classified as hemorrhagic infarction and parenchymal hematoma (PH) according to European Cooperative Acute Stroke Study II (ECASS II) criteria. Previous studies showed that the incidence of natural HT in early stage is about 9%–12% [1,10], and about 3% patients have severe HT [10]. Our study suggests that the incidence of HT is 10.98%. HT is a common complication in influencing the prognosis of patients with acute cerebral infarction [7], and more likely aggravates their conditions. Therefore, to assess the influencing factors of HT is helpful to monitor the occurrence of HT after acute cerebral infarction, to find a safe revascularization project and to take effective treatment or preventive measurements in HT patients with acute cerebral infarction [7].

Platelets are reported to be involved in the formation of thrombosis, and low platelet count can easily develop bleeding. Christoforidis et al. (2009) pointed out that low platelet count puts the patients at an increased risk of HT, and severe HT would very likely occur as the platelet count is lower than 200×10^9/L [11]. Further, according to the studies

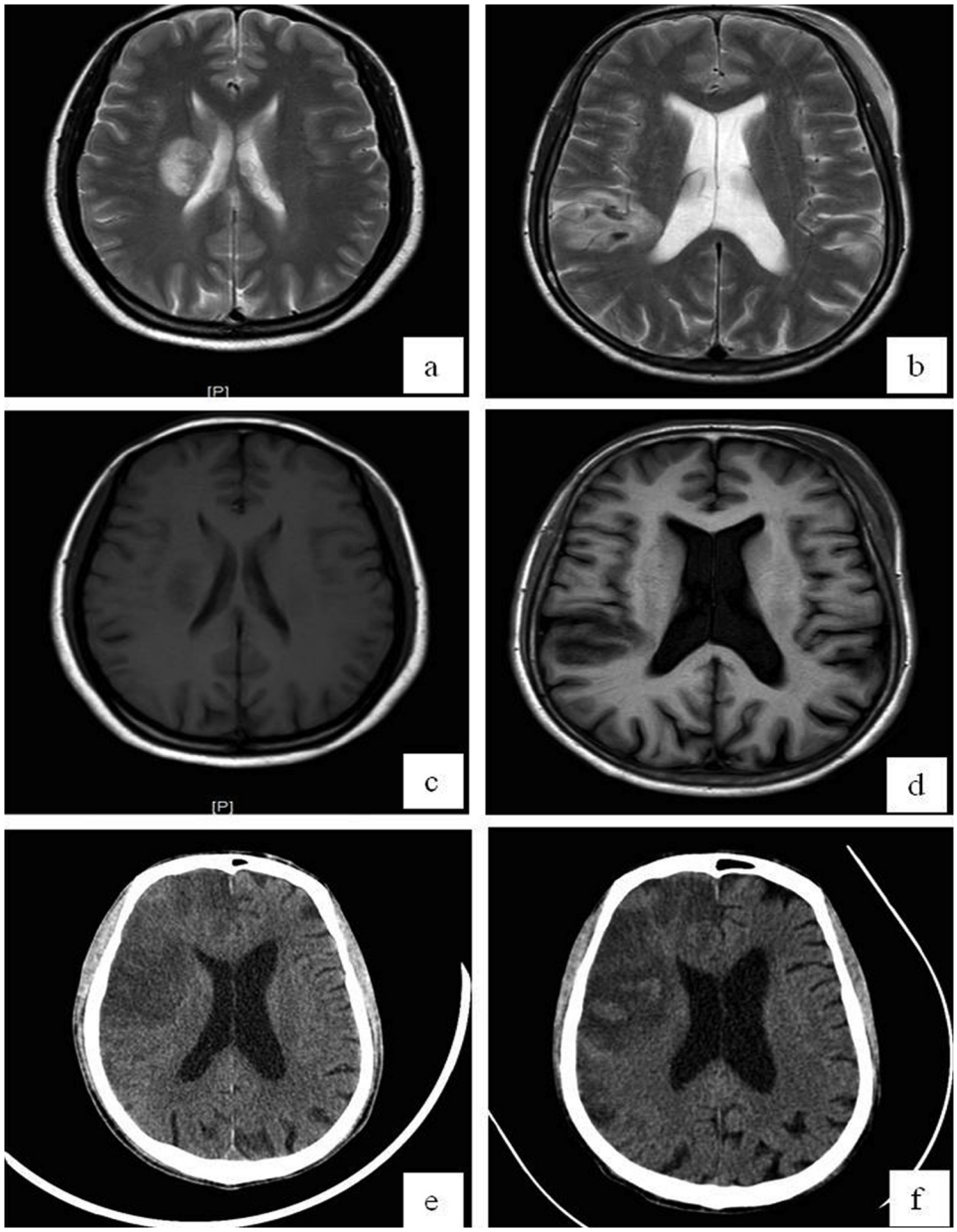

Fig. 1. Topography of cerebral ischemia and hemorrhagic transformation. Images of cerebral ischemia (a) and hemorrhagic transformation (b) were detected by T2-weighted magnetic resonance imaging. Images of cerebral ischemia (c) and hemorrhagic transformation (d) were detected by T1-weighted magnetic resonance imaging. Images of cerebral ischemia (e) and hemorrhagic transformation (f) were detected by computerized tomography.

of Prodan et al. (2010,2015), the lower level of coated-platelets is associated with the presence of early HT in patients with non-lacunar ischemic stroke [12,13]. In our study, the average level of platelet in the HT group is lower than that of the non-HT group. The binary logistic regression analysis shows a positive correlation between platelet count and HT, indicating that the platelet level is an independent risk factor for HT. The results also mean a high incidence of HT in those non-thrombolysis patients suffering from cerebral infarction with the low level of platelet. Such conclusion is similar but not identical to the former researches. Therefore, patients suffering from acute cerebral infarction with the low platelet count ($< 176.41 \times 10^9$/L) need more attentions especially in timely CT re-check and close monitoring of HT.

The relationship between abnormal lipid metabolism and HT is another hot topic in recent years, and researches have provided different results. Lipid maintains not only the integrity and fluidity of cell membrane, but also the structural integrity of vessel wall. Hyperlipidemia leads to the increased blood viscosity, disrupts the homeostatic of vessel wall metabolism and cerebral blood flow regulation, diminishes collateral circulation in cerebral blood vessel and causes severe ischemia reperfusion injury [14]. All of these may possibly give rise to HT. According to the study Kim et al. in 2009, cholesterol (CHOL) at the low level elevates the incidence of HT in patients with large-artery atherosclerosis (LAA), but has no significant correlation with HT in patients with LAA. Low level of LDL can significantly increase the incidence of HT in patients with LAA, indicating that LDL is an independent risk factor for HT in patients with LAA. Furthermore, low level of LDL is associated with the greater risk of HT after acute ischemic stroke (IS) attributable to LAA [15]. D'Amelio et al. (2011) analyzed 240 patients with anterior IS, and pointed out that the risk of HT is significantly higher in the groups of patients with the lowest TC and low-density lipoprotein cholesterol. Multivariate regression analysis proved that the lower TC and LDLC levels are independent risk factors for HT [16]. In contrast, some researcheres suggested that LDL is a protective factor for HT [17,18] and lipid-lowering treatment should

Table 1
Comparison of indices between HT group and non-HT group.

Variables	HT group (38 cases)	Non-HT group (308 cases)	T or χ^2	P value
Age	55.60 ± 9.94	57.71 ± 8.21	0.49a	0.73
Gender (male)	18(47.4%)	161(52.3%)	0.326b	0.568
LDL (mmol/L)	2.83 ± 0.55	2.83 ± 0.61	0.61a	0.952
CHOL (mmol/L)	4.53 ± 1.14	4.94 ± 1.29	−2.55a	0.013
TG (mmol/L)	1.48 ± 0.34	1.59 ± 0.34	−2.31a	0.024
HDL (mmol/L)	1.23 ± 0.13	1.24 ± 0.16	−0.61a	0.524
Dyslipidemia	11(28.9%)	161(52.3%)	8.021b	0.005
Drinking	9(23.7%)	117(38.0%)	4.295b	0.038
Smoking	14(36.8%)	67(21.8%)	2.953b	0.086
Diabetes	12(31.6%)	87(28.2%)	0.184b	0.668
Hypertension	17(44.7%)	150(48.7%)	0.024 b	0.877
Platelet count (×109/L)	176.41 ± 62.39	209.13 ± 80.66	−2.885a	0.004
Hyperhomocystinemia	13(34.2%)	78(25.3%)	1.378b	0.240
Antiplatelet aggregation	19(50.0%)	251(81.5%)	19.574b	0.000
Anticoagulation	21(55.3%)	61(23.7%)	23.519b	0.000
Atrial fibrillation	21(55.3%)	65(21.1%)	21.133 b	0.000
INR(> 1.7)	20 (52.6%)	14(4.5%)	73.907 b	0.000

Note: *a* refers to *t value*, and *b* refers to χ^2.

Table 2
Results of binary logistic regression analysis.

Items	OR	95% CI	P value
Dyslipidemia	0.371	0.186-0.740	0.005
Atrial fibrillation	2.476	1.140-5.377	0.022
Platelet count	1.006	0.682-1.611	0.007
INR > 1.7	10.889	4.760-24.910	0.000

be prescribed cautiously to prevent the incidence of HT [18]. Using the binary logistic regression analysis, our study showed that there is no difference in LDLC between the HT group and non-HT group, and LDLC is not the related influencing factor for HT. The level of TC and TG, and the incidence of dyslipidemia of the HT group are significantly lower than those of the non-HT group. There is no correlation between TC, TG and HT. Moreover, there is a negative correlation between hyperlipidemia and HT, indicating that dyslipidemia is a protective factor of HT after acute cerebral infarction. CHOL is one of the constituents of cell membrane, which is related with membrane permeability. Adequate CHOL is important for maintaining the integrity of cerebral vessels. It is inferred that dyslipidemia may damage the integrity of both cerebral vessels and blood-brain barrier, resulting in blood exudation in cerebral vessels and HT. Our study is not entirely agreed with the researches of former scholars, which will impel us to study large samples in order to further understand the effects of lipids on the incidence of HT.

Atrial fibrillation (AF), a common cause of cardioembolism (CE), is associated with severe hypoperfusion, leading to more frequent severe HT and worse stroke outcomes [19]. Currently, most of the findings have demonstrated that AF is a risk factor for spontaneous HT after infarction and influences the patient's prognosis [20]. In a study of Paciaroni (2008), AF is found to be associated with an increased risk of parenchymal hematoma, and a negative correlation can also be observed between AF and HT using the logistic regression analysis [21]. Ong et al. (2016) also proved that AF is an independent risk factor for in-hospital mortality and HT after acute cerebral infarction [22]. However, in the study of Lou et al. (2014), AF increases the rate of PH and it is associated with PH but not with HI. AF is not the independently influencing factor of the poor prognosis of thrombolysis patients with acute cerebral infarction [23]. This study shows the AF rate of the HT group is 55.3%, which is much higher than that of the non-HT group. Logistic regression analysis suggests that AF is the independent risk factor for HT, which is consistent with the previous studies [21,22]. Therefore, we should pay attention to the patients suffering from acute cerebral infarction with AF, and to use anti-AF treatment to reduce the incidence of HT.

Anticoagulation and antithrombosis treatments might cause HT [24–26]. In this study, there is no statistical difference between antiplatelet aggregation and anticoagulation of the HT group and the non-HT group. Moreover, antiplatelet aggregation and anticoagulation treatments are not associated with HT after acute cerebral infarction. These results are considered to be a result of different antiplatelet aggregation and anticoagulation medicines taken by the patients involved in our study, because different medicines have different impacts on HT [27–29]. Notably, patients with AF usually use the treatment of anticoagulation, which probably leads to INR elevation. Initial INR elevation or recent use of anticoagulation may increase the rate of HT after thrombolysis in acute cerebral infarction [30]. Our study finds that the INR (> 1.7) rate of HT group is much higher than that of non-HT group, the high level of INR (> 1.7) increases the incidence of HT, and INR (> 1.7) is the independent risk factor for HT. Previous studies suggested that patients with AF need anticoagulation treatment, but routine anticoagulation elevates INR and increases the rate of HT. However, Some new anticoagulants do not increase the risk of HT [28,29]. So we can treat the patients suffering from AF with new anticoagulants to avoid an INR elevation and a high incidence of HT.

In a recent study, 6% of children with arterial ischemic stroke present with a diagnosis of hypertension. And hypertension indicates the association with an increased risk of in-hospital death for the children with arterial ischemic stroke [31]. Compared to men, the stroke risk in women with mild hypertension is higher [32]. Antihypertensive therapy has been associated with a significant reduction in stroke incidence. Arboix et al. (2004) compared risk factors, clinical features, neuroimaging data, and outcome between ischemic stroke patients with hypertension and without hypertension. It is proved that age > 85 years and valvular heart disease are negatively associated with hypertensive ischemic stroke. Hypertension is the main cardiovascular risk factor only for lacunes and atherothrombotic infarction, suggesting ischemic stroke is associated with small- and large-artery disease [33]. In this study, we found no evidence to prove that hypertension is harmful to HT patients.

In conclusion, there are multi-factors attributing to the incidence of HT in non-thrombolysis patients. The low platelet count, INR (> 1.7) and AF are independent risk factors for HT, while dyslipidemia is the protective factor for HT after acute cerebral infarction. Through exploring the influencing indices of HT, we can control the risk factors timely, and avoid the incidence of HT effectively.

Declaration of interest statement

All authors declared no conflicts of interest.

Ethics approval

Ethical approval for this study was provided by the Ethical Committee of Guangdong Second Provincial General Hospital, Guangzhou, China (Ethical Committee No. 2016-SJNK-001).

Informed consent

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

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