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Low level of low-density lipoprotein cholesterol is related with increased hemorrhagic transformation after acute ischemic cerebral infarction

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Abstract. – OBJECTIVE: The prevalence of hemorrhagic transformation (HT) after acute ischemic infarction varies greatly. Risk factors of HT include ageing, severity of stroke, baseline hypertension, high NIH Stroke Scale (NIHSS) scores, hyperglycemia and cardioembolic infarction and low levels of low-density lipoprotein (LDL). We investigated the relationship between LDL, lipid profile and HT after acute ischemic infarction and suggested precautions for HT management.

PATIENTS AND METHODS: Three hundred and forty-eight patients with acute infarction were included in the study. Fasting lipid profile was examined on the next morning following hospitalization. Either MRI GRE-T2*WI or CT was performed, one week after hospitalization to detect any cerebral microbleed (CMB) and hemorrhagic transformation. The lipid profiles examined included total cholesterol (TCH), triglyceride (TG), LDL and high-density lipoprotein (HDL).

RESULTS: Among all the patients, HT was noted in 35 patients and non-HT in 313. As compared with non-HT group, HT group had lower levels of TCH, HDL and LDL, lower rates of leukoaraiosis and CMB, but higher scores of NIHSS, higher rates of diabetes mellitus, atrial fibrillation and urokinase thrombolysis. The multivariate binary logistic regression showed that cardioembolic infarction, infarction with undetermined etiology, high scores of NIHSS and diabetes were the risk factors of HT, while the protective factor was LDL (OR=0.654, 95% CI: 0.430-0.996, p=0.048).

CONCLUSIONS: Low level of LDL is likely associated with increased HT after acute ischemic infarct, so for those patients with low level of LDL, high scores of NIHSS and cardioembolic infarction at admission, aggressive lipid- lowering treatment should be prescribed cautiously to prevent the incidence of HT.

Key Words:
Acute ischemic infarction; Hemorrhagic transformation; Risk factor; Low-density lipoprotein cholesterol.

Introduction

The occurrence of hemorrhagic transformation (HT) after acute ischemic brain infarction varies from 8.5% to 30% of the patients being affected[1,2]. HT includes hemorrhagic infarction (HI) and parenchymal hematoma (PH), and symptomatic HT is the most severe type, which usually occurs after thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) and is the predictive factor for poor prognosis[3]. Active exploration of the risk factors of HT has important clinical significance in reducing the occurrence of symptomatic HT and improving the life quality of patients. Recent studies suggest that the risk factors of HT include advanced age, severity of stroke, baseline hypertension, high scores of NIH Stroke Scale (NIHSS), hyperglycemia and cardioembolic infarction[4,5]. Kim et al[6] indicated that low levels of low-density lipoprotein (LDL) might be related to HT among the patients of atherosclerotic cerebral infarction. However, it is unclear whether lipid profile is related to HT for patients with all types of ischemic stroke. The current study investigated the relationship between baseline lipid levels and HT in consecutively included patients with acute ischemic infarction, and the results suggested that low level of LDL is likely associated with increased HT after acute ischemic infarction.

Patients and Methods

Patients

The study was approved by the Human Ethics Committees at our center and all the patients had signed the informed consent.

In this study, 348 patients (141 females and 207 males) with acute infarction, admitted to the

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Neurology Department of Zhongshan Hospital Affiliated to Guangzhou Medical University of TCM from June 2009 to December 2010, were studied. Their mean age is 65.24 years (SD = 13.13, range = 31.6-84.4) and the patients without MRI or CT follow-up imaging and lipid profile workup were excluded.

Patients had to meet the diagnostic criteria of acute ischemic cerebrovascular disease according to Guidelines for management of ischemic stroke and transient ischemic attack 2008[7]. The presence of new lesions was confirmed by MRI scan and acute infarction that occurred within 2 weeks was included for analysis. Exclusion criteria included cerebral hemorrhage confirmed by CT or MRI and concomitant complications of severe anemia or severe failures of heart, liver and kidney.

Procedure

The fasting lipid profile was measured the next morning after the admission of patients. All the patients were subjected to MRI gradient-echo T2-weighted imaging (GRE-T2*WI) or CT for follow-up imaging one week after hospitalization. Related risk factors recorded were gender, age, hypertension, diabetes mellitus, current drinking or smoking, leukoaraiosis, cerebral microbleeds (CMB), old lacunar infarction, carotid atherosclerotic plaques, prior aspirin treatment, urokinase thrombolysis, lipid levels, scores of National Institute of Health Stroke Scale (NIHSS), atrial fibrillation and types of infarction according to Trial of Org10172 in Acute Stroke Treatment (TOAST) definitions.

Definition of Risk Factors Related to Stroke

Acute cerebral infarction was classified according to the modified TOAST[8]. Prior aspirin treatment was defined as positive, if aspirin was continuously taken for more than 2 weeks before admission and negative if aspirin was taken for less than 2 weeks. The carotid atherosclerotic plaque was defined as carotid intima-media thickness ≥ 1.2 mm. Old lacunar infarction was ascertained as high signal lesions with clear boundary in basal ganglia or brainstem on T2-weighted MR images, with the lesion diameter ≤ 15 mm and no acute infarcts on diffusion-weighted imaging (DWI). CMB was defined as homogeneous rounded areas of signal loss by MRI GRE-T2*WI with a diameter of 2-5 mm and absence of edemas around[9]. Thrombolysis criteria referred to the European Cooperative Acute Stroke Study (ECASS II) criteria. Intracranial hemorrhage was excluded by cerebral computed tomography before or on admission. For patients within 3 h after symptom onset, intravenous thrombolysis with 1-1.50 million units of urokinase was performed within 1 h. Within 3-6 h, thrombolysis therapy was performed as an individual decision based on perfusion-weighted imaging/diffusion-weighted imaging (PWI/DWI) mismatch of MRI findings and an NIHSS score of 4-24 after informed consent.

HT referred to the secondary cerebral hemorrhage after acute ischemic stroke[10], and lesions presented with punctate or multifocal hemorrhage, which could range from small punctate to a large hematoma. HT can be divided into hemorrhagic infarction (HI) and parenchymal hematoma (PH) according to European Cooperative Acute Stroke Study II (ECASS II)[11]. CT or MRI follow-up was applied to detect HT one week after hospitalization or because of clinical deterioration. HT was evaluated independently by 2 senior neurologists and a neuroradiologist, blind to the clinical data.

Statistical Analysis

All data were analyzed with SPSS 12.0 statistical software (SPSS Inc, Chicago, IL, USA). The continuous variables were expressed as mean±SD and categorical variables as percent values. Differences between groups were compared by Pearson $\chi 2$ test, Student test, or Fisher exact test. A binary logistic regression model was conducted to identify the related risk factors of HT after infarction, with HT as response variable and risk factors as explanatory variables. The forward stepwise method (i.e., the likelihood ratio forward stepwise regression) was applied for the best regression equation. Results were considered statistically significant at the p-value of ≤ 0.05.

Results

Comparison of Related Risk Factors Between HT and Non- HT Group

Among the 348 patients, HT occurred in 35 patients and non-HT in 313. Compared with non-HT group, HT group had a higher proportion of diabetes, atrial fibrillation and urokinase thrombolysis, higher scores of NIHSS, lower rates of leukoaraiosis and CMB, lower levels of total cholesterol (TCH), low-density lipoprotein (LDL) and high-density lipoprotein (HDL), all

with significant differences ($p<0.05$). The distribution of infarction types (TOAST) in two groups was significantly different ($p<0.05$). All the data are shown in Table I.

Multivariate Logistic Regression Analysis of Risk Factors for HT

The multivariate logistic regression was performed with HT as response variable and risk factors (e.g. lipid profile) as explanatory variables. It is suggested that risk factors of HT in patients with cerebral infarction were cardioembolic infarction, infarction with undetermined etiology, diabetes and high scores of NIHSS, while the protective factor was LDL (Table II).

Discussion

The exact pathogenesis of HT after acute ischemic stroke is not yet established. HT may result from the damage of blood brain barrier due to acute ischemic infarction or secondary cerebral edema, injury after ischemia-reperfusion, or adverse effects of thrombolysis with recombinant tissue type plasminogen activator (rt-PA) or urokinase, etc. Although Carlos et al[12] suggested that thrombolysis-related hemorrhagic infarction may represent early successful recanalization and lead to a reduced infarct size and improved clinical outcome, symptomatic parenchymal hematomas was an independent predictor of increased early mortality and poor functional outcomes at 3 months[13]. Exploring the pathogenesis of HT and identifying the risk factors has important practical significance for taking efficacious measures to prevent HT.

Animal experiments and epidemiologic studies have demonstrated that increased incidence of spontaneous cerebral hemorrhage is associated with low levels of TCH[14-16], and recent evidence suggests that LDL cholesterol concentration is inversely related to incident intracerebral hemorrhage[17]. However, up to now there is no prospective study to explore the correlation between lipid profile and HT after acute ischemic stroke, so the relationship is still not definitive. A meta-analysis by Cordenier et al[18] showed that pretreatment with statins before stroke was associated with lower mortality in hospital, but did not improve 3

Table I. Comparison of related risk factors between HT and non-HT group.

Variables	non-HT group (n=313)	HT group (n=35)	$\chi 2$/t value	p-value
Male	187 (59.74%)	20 (57.14%)	0.088	0.766
Age (year)	65.65 ± 12.75	61.57 ± 15.89	1.749	0.081
Drinking	75 (23.96%)	6 (17.14%)	0.820	0.365
Smoking	129 (41.21%)	16 (45.71%)	0.262	0.609
Hypertension	187 (59.74%)	20 (57.14%)	0.088	0.766
Diabetes mellitus	97 (30.99%)	17 (48.57%)	4.417	0.036
Atrial fibrillation	21 (6.71%)	7 (20.0%)	7.516	0.006
Leukoaraiosis	181 (57.83%)	13 (37.14%)	5.460	0.019
CMB	150 (47.92%)	10 (28.57%)	4.746	0.029
Old lacunar infarction	212 (67.31%)	19 (54.29%)	2.550	0.110
Use of aspirin	63 (20.13%)	6 (17.14%)	0.176	0.674
Carotid atherosclerotic plaques	153 (48.88%)	11 (31.43%)	3.848	0.050
Urokinase thrombolysis	24 (7.67%)	11 (31.43%)	19.647	< 0.001
TCH (mmol/L)	5.33 ± 1.40	4.57 ± 1.29	3.079	0.002
TG (mmol/L)	1.99 ± 1.87	1.52 ± 0.91	1.466	0.144
NIHSS score	10.38 ± 2.48	16.63 ± 3.04	13.067	0.001
HDL (mmol/L)	1.3323 ± 0.38	1.18 ± 0.31	2.313	0.021
LDL (mmol/L)	3.42 ± 1.12	2.74 ± 1.04	3.486	0.001
TOAST				
Arteriosclerotic infarction	194 (61.98%)	19 (54.29%)		
Cardioembolic infarction	17 (5.43%)	11 (31.43%)	31.022	< 0.001
Undetermined etiology infarction	15 (4.79%)	4 (12.12%)		
Small vessel infarction	87 (27.80%)	1 (2.86%)		

CMB, cerebral microbleeds; TCH, total cholesterol; TG, triglyceride; NIHSS, National Institute of Health Stroke Scale; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TOAST, trial of org10172 in acute stroke treatment.

Table II. Multivariate logistic regression analysis of risk factors for hemorrhagic transformation (variables in the equation).

Variables	Odds ratio	95% CI	*p*-value
Cardioembolic infarction	24.956	2.734-227.801	0.004
Undetermined etiology infarction	19.381	1.834-205.104	0.014
Diabetes	4.973	2.004-12.338	0.001
LDL	0.654	0.430-0.996	0.048
NIHSS score	1.187	1.109-1.292	< 0.001

CI, confidence interval; LDL, low-density lipoprotein; NIHSS, National Institute of Health Stroke Scale.

months functional outcome of mRS score ≤ 2, furthermore, increased the prevalence of symptomatic HT after thrombolysis. A registry and review study in France[19] indicated that statin treatment before intra-arterial, intravenous or combined thrombolysis had no effects on outcomes at 3 months but may increase the occurrence of symptom HT. Engelter et al[20] summarized a total of 11 multicenter intravenous thrombolysis clinical trials that included 4012 patients, and found that compared with prior statin nonusers, prior statin users had a trend of high appearances of HT (20.1% *vs*. 17.4%) and symptomatic HT (6.9% *vs*. 5.1%). But the adjusted OR for each category of HT and symptomatic HT showed no difference between statin users and nonusers after adjustment for other risk factors.

Cappellari et al[21] conducted a retrospective analysis of 250 patients treated with intravenous thrombolysis to assess the effect of statin treatment on short- and long-term outcome. They revealed that statins treatment started within 24h after intravenous thrombolysis improved neurological function (24-72 h) and outcomes at 3 months, whereas statins treatment started before the stroke and continued in the acute phase was associated with symptomatic intracerebral hemorrhage (OR: 6.65; 95% CI: 1.58-29.12; p=0.010).

The current study included consecutive inclusion patients with acute infarction, which consists of several types of ischemic stroke according to TOAST (e.g. arteriosclerotic infarction, small vessel infarction, cardioembolic infarction, undetermined etiology infarction). Risk factors were recorded and MRI GRE-T2* was performed to diagnose HT in all patients, as MRI GRE-T2* is sensitive to detect HT and CMB. We found that compared with non-HT group, HT group had lower levels of TCH, HDL and LDL, with significant differences (p<0.05). The multivariate logistic regression showed that low level of LDL increased the incidence of HT (OR = 0.654, 95% CI: 0.430-0.996, p=0.048) and there was no significant relationship between HT and TCH or HDL. In conclusion, low level of LDL was inversely related to HT. In addition, cardioembolic infarction, undetermined etiology infarction, high scores of NIHSS and diabetes were the risk factors of HT. Kim et al[6] also reported that a low level of LDL cholesterol was independently associated with HT in large artery atherothrombosis, but not in cardioembolic infarction. However, D'Amelio et al[22] retrospectively analyzed the correlation HT and lipid levels at admission in a consecutive series of 240 patients with anterior ischemic stroke, and suggested that a lower TC and lower LDLC levels are associated with an increased risk of HT. Uyttenboogaart et al[23] assessed a prospective hospital-based stroke registry and discovered that high admission triglyceride levels were independently associated with a higher risk of symptom HT, but total cholesterol levels, LDL levels and statins use had no influence on both the occurrence of symptom HT or functional outcome. Rocco et al[24] found that in an open, prospective study of 1,066 stroke patients undergoing thrombolysis therapy, neither the lipid profile nor prior statins use were associated with increased odds of symptom HT, functional outcome or mortality at 3 months.

The pathogenic mechanisms by which the low level of LDL increased the risk of HT are not yet established. The increased symptomatic hemorrhagic transformation after recanalization therapy for ischemic stroke was correlated with lower admission low-density lipoprotein cholesterol level, but may not correlate with statins use[25]. But after acute ischemic stroke or transient ischemic attack, an aggressive lipid-lowering treatment with 80 mg of atorvastatin per day was associated with a 66% increase in the relative risk of hemorrhagic stroke as compared with placebo [26]. The

aggressive lipid-lowering related hemorrhagic stroke may result from a lower level of LDL (1.9 mmol/L compared to 3.3 mmol/ L among placebo patients), but not from atorvastatin. An adequate level of the lipid may maintain the integrity of the small cerebral vessels, while the too lower level of lipid will destroy the integrity of the small vessels and result in blood extravasation over the unstable integrity of endothelial cells in the small cerebral vessels[27].

After severe ischemic infarction, especially complicated with sepsis and other critically illness, the integrity of the small cerebral vessels were vulnerable to damage. Therefore, for those patients with high-risk HT, aggressive lowering-lipid treatment should be prescribed with caution. In addition, for those patients without prior lowering-lipid treatment, lower lipid levels may reflect poor general medical condition and increase the risk for HT[28]. Moreover, the development of myopathy or hepatic dysfunction from statins may also be increased in the critically ill patients. As a result, the application of aggressive lipid-lowering treatment for severe stroke patients should be individualized considering each patient's likelihood to benefit or be harmed and be based on future high-quality clinical evidence.

Conclusions

It has been recently found in a large number of patients that history of hypertension, diabetes mellitus and stroke show correlation with the HT and its prognosis[29]. The correlation between the lipid profile and HT from the recent literature is contradictory, and because of this, an incontrovertible relationship between statins and ICH is yet to be demonstrated. There can be several reasons responsible for the observed differences among different studies. These include: (1) the inclusion criteria and treatments (e.g. intra-arterial thrombolysis, intravenous thrombolysis, combined thrombolysis) differ considerably among different studies. (2) The methodologies employed in these studies are different and most of the studies are retrospective studies. There is no perspective study with high quality and rigorous design. (3) The definition of HT varies in different studies and thus may affect the results directly. And, (4) there are many confusing and unclear factors in lipid measurements. The present conclusions need to be confirmed by expanding the sample size and conducting prospective multiple centers studies. Even though the present study suggests that low level of LDL is likely associated with increased HT after acute ischemic infarct, and that aggressive lipid-lowering treatment should be prescribed cautiously to prevent the incidence of HT for patients with high scores of NIHSS and cardioembolic infarction, these results need to be confirmed in a larger study with more number of patients.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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