

Correlation between levels of serum homocystein, high sensitivity C-reactive protein and subtypes of large-artery atherosclerosis ischemic stroke

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【Abstract】 : Objective To investigate the levels of serum homocystein (Hcy) and high sensitivity C-reactive protein (hs-CRP) and their differences in each subtype of artery atherosclerosis ischemic stroke. **Methods:** All ACI patients were classified into large-artery atherosclerosis (n = 130) and small-vessel occlusion (n = 87) based on TOAST. The groups of large-artery atherosclerosis included progressive stroke (PS) (n=58) and complete stroke (n=72). Another group was also divided into PS (n=12) and complete stroke (n=75). Levels of serum Hcy and hs-CRP concentration were measured and compared between groups. **Results:** (1) The levels of HCY and hs-CRP in large-artery atherosclerosis group were higher than in small-vessel occlusion group; (2) The levels of HCY and hs-CRP were higher in PS than in complete stroke in two groups; (3) There was no significant difference of the levels of HCY between PS and complete stroke in large-artery atherosclerosis, while the levels of hs-CRP were higher in PS. **Conclusions:** Levels of serum Hcy and hs-CRP were related to the occurrence of large-artery closely, which may be regarded as an index to predict and evaluate the large-artery atherosclerosis. Hyperhomocysteinemia didn't indicate the PS.

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Key words: Ischemic stroke; large-artery atherosclerosis; High-sensitivity C-reactive protein; Homocysteine

Introduction

HCY is a sulfur-containing amino acid methionine metabolism intermediates. Numerous researches around the world in recent years found that high homocysteine and high lipid level are independent risk factors for ischemic stroke.^[1] The importance of primary prevention of ischemic stroke is higher even than heart disease. ^[2,3] Ischemic stroke, a commonly caused by atherosclerosis is a chronic inflammatory disease, and chronic inflammatory reaction after a vascular injury, including lipids, cells (macrophages, T lymphocytes, and smooth muscle cells), and extracellular matrix deposition. High-sensitivity C-reactive protein (high-sensitivity C-reactive protein, hs-CRP) acts as biological markers of the inflammatory response. reflects inflammatory sensitive serum biochemical markers and inflammatory factors involved in the formation of atherosclerotic, with the incidence of stroke, the relationship between the development of more and more attention. Aorta atherosclerosis total ischemic stroke 14-40%, and after the onset of signs and symptoms of a more serious neurological deficits. In this study, serum Hcy and hs-CRP levels, in order to explore its relationship with large artery atherosclerotic

ischemic stroke, the two factors further observation and analysis of in progressing stroke patients serum levels for early clinical intervention and drug therapy to provide theoretical guidance and objective basis.

1. Materials and Methods

1.1 General Information 217 AIS patients are the First Affiliated Hospital of Xinxiang Medical College, Department of Neurology, December 2010 to May 2012 hospitalized patients were male and 112 cases, 105 females, aged 29 to 60 years, an average of 50.31 ± 6.72 years old. Are the first onset, time of onset <48 h, in all cases the diagnosis meet the diagnostic criteria adopted by the Fourth National Cerebrovascular Disease Conference, and confirmed by CT or MRI. NIHSS score 2-12 patients enrolled (median 6 points), underwent carotid ultrasound, TCD examination in 2 weeks strict vascular evaluation row CTA or DSA. In accordance with the the TOAST classification method, all 217 patients were divided into 2 groups: 130 cases of large artery atherosclerosis stroke, carotid artery, anterior cerebral artery, middle cerebral artery, posterior cerebral artery lesion diameter > 1.5 cm, vascular evaluation or (and) severe vertebral - basilar artery stenosis. Small artery occlusion stroke 87 cases, the

maximum diameter of the lesions <1.5 cm, vascular evaluation after exclusion associated with unstable plaque and stenosis $\geq 50\%$ of non-responsibility macrovascular complications. In addition, in accordance with the diagnostic criteria for progressing stroke: incidence of 2-7 days of illness, ladder aggravated NIHSS increase of 2 points or more, in all cases progressive pawn Communist China 70 cases, 58 cases of which the main artery group, small arteries the group of 12 patients, and observe the statistics of the number of cases occurred in each group progressing stroke occurred time window. All cases were excluded prior to infection, tumor incidence, autoimmune disease and thyroid dysfunction, blood disorders, heart and lung disease, cancer, liver and kidney dysfunction and other diseases, a month before the onset not use folic acid, vitamin B6, and vitamin B12 and other drugs.

1.2 Detection: serum Hcy and hs-CRP detection Hitachi 7060 automatic biochemical analyzer. Application of serum Hcy assay kit (Mike Biotechnology Co., Ltd.) cycle enzymatic assay (normal 0-20 μ mol / L). The immune serum hs-CRP application transmission turbidimetric method (normal, 0 to 3 mg / L), including hs-CRP buffer reagents, calibrators, human serum

matrix, hs-CRP antigen (Finland, Orion Diagnostica.Oy).

1.3 patient is admitted to the the the NIH neurological deficit score (national institute of health scale of stroke NIHSS) state of consciousness, visual, feeling ignored, motor function and cerebellar function evaluation.

1.4 Statistical analysis using SPSS 16.0 software for statistical significant difference test using the t-test, data with mean \pm standard deviation \pm s said. The chi-square test packet count data analysis. Pearson correlation analysis test serum Hcy serum hs-CRP correlation between.

2. Results

2.1 Baseline information on the general situation of the two groups of patients. 217 cases of AIS patients were divided into large atherosclerosis group of 130 cases and 87 cases of small artery occlusion group, the two groups of gender, age, smoking, drinking, high blood pressure, diabetes, cholesterol, triglycerides, were not statistically different $P > 0.05$, only the low-density lipoprotein in significant difference $P < 0.05$, Table 1

Baseline data in Table 1

Group	large arteriosclerosis n=130	Small artery occlusion group n=87	P
Sex (%)	22 (55%)	20 (55.6%)	>0.05
Age (y)	49 \pm 9.34	51 \pm 10.21	>0.05
Smoking (%)	16 (40%)	14 (39%)	>0.05
Drinking (%)	8 (20%)	6 (16.7%)	>0.05
Hypertension (%)	14 (35%)	6 (44.4%)	>0.05
Diabetes (%)	12 (30%)	11 (30.6%)	>0.05
Cholesterol (mmol/L)	6.13 \pm 0.25	5.67 \pm 1.38	>0.05
Triglyceride(mmol/L)	2.27 \pm 1.35	2.66 \pm 0.33	>0.05
Low-density lipoprotein (mmol/L)	3.66 \pm 0.64	* 1.98 \pm 0.22	>0.05
NIHSS score at admission	8.87 \pm 0.69*	* 6.54 \pm 3.14	<0.05

2.2 217 patients with acute ischemic stroke patients, PS patients with a total of 70 cases of progressive stroke incidence was 32.26%; 130 cases of arteriosclerosis patients, the PS 58 patients with progressing stroke incidence was 44.6%. 2-3 days neurological deficit increase accounted for 32 cases (55.1%), 18 cases (31%) 8 (13.8%) 6-7 days aggravated aggravated in 4-5 days. 87 cases of patients with small-artery occlusion, PS 12 patients with progressing stroke incidence was 13.8%. 2-3 days neurological deficit increase accounted for eight cases (9%), and exacerbation of 4-5 days for the four cases (4.6%).

2.3 Patient's serum Hcy serum hs-CRP levels

All patients were divided into arteriosclerotic patients and patients with occlusion of the small arteries Hcy and hs-CRP values, statistical differences were significant ($P < 0.01$, $P < 0.05$) are shown in Table 2; while all the patients were divided into complete and Hcy and hs-CRP values were observed in patients with progressive also statistically significant ($P < 0.05$, $P < 0.01$), as shown in Table 3. Hcy value fully arteriosclerotic patients and patients with progressive, statistically significant difference $P < 0.05$, Hs-CRP values no statistically significant $P > 0.05$, are shown in Table 3.

Table 2. The arteriosclerotic group and small artery occlusion group serum Hcy and hs-CRP levels $\bar{x} \pm s$

Groups	n	Hcy (umol/L)	hs-CRP(mg/L)
Large arteriosclerotic	130	21.6±7.06**	6.6 ±3.99*
Small artery occlusion	87	16.7± 6.25	4.59±2.94
<i>t</i>		6.872	5.467
<i>P</i>		0.003	0.013

*Big atherosclerosis group and small artery occlusion group Hcy value of $P < 0.01$

** Atherosclerosis group with the small artery occlusion group Hs-CRP $P < 0.05$

All patients with arteriosclerosis group progressing stroke complete stroke blood Hcy and hs-CRP levels.

Groups	All patients *			Arteriosclerotic patients. * *		
	n	Hcy (umol/L)	Hs-CRP (mg/L)	n	Hcy (umol/L)	Hs-CRP (mg/L)
Progressive type	70	20.4±4.50*	6.8±2.25	58	23.5±6.56	6.6 ±3.99*
Complete type	147	18.6±4.36	4.02±1.85	72	22.3±4.51	4.59±2.94
<i>t</i>		4.573	6.527		1.322	5.016
<i>p</i>		0.025	0.008		0.22	0.013

* All patients progress complete Hcy value of $P < 0.05$

** In all patients with advanced and complete Hs-CRP values, $P < 0.01$

arteriosclerotic patients progress complete Hcy value of $P < 0.05$

arteriosclerotic patients progress and complete Hs-CRP values compare $P > 0.05$

2.4 Hcy levels of the patient group with Hs-CRP level of correlation

Pearson correlation analysis detected Hcy levels Hs-CRP levels, the results show that serum Hcy levels of serum hs-CRP level respectively in the three types of groups no correlation.

3. Discussion

High Hcy stimulation of vascular smooth muscle cell proliferation by causing vascular endothelial cell injury and dysfunction, and undermine the balance of blood coagulation and fibrinolysis system, affecting lipid metabolism of the body in a prothrombotic state, eventually leading to the risk of cardiovascular and cerebrovascular disease is increased[4,5]. Hcy not only damage such as carotid vascular endothelial cells, also involving the brain of deep perforating branches small blood vessels, leading to different types of cerebral infarction. Eikelboom et al [6] study confirmed the high Hcy hyperlipidemia ICS subtype, and the strongest correlation with the main artery lesions, small artery lesions followed. Tan et al [7] found that plasma Hcy level was higher in patients with <50 years of age ICS, the main artery lesions smaller artery lesions. Domestic research, the high Hcy higher incidence in young and

middle-aged people, and the prevention and treatment of high Hcy is especially important in young and middle-aged people [8]. This study selected cases are mainly young and middle-aged patients with stroke and mild to moderate neurological function defect needed to further validate the comprehensive observations of a larger sample. The latest clinical experimental results show that lowering homocysteine levels and can not delay the degree of carotid atherosclerosis and reduce cardiovascular events, plasma homocysteine is merely a marker of vascular endothelial injury [9]. However, regardless of the high Hcy can react as the cause or the result of cerebral infarction, serum Hcy concentration differences in size of vascular lesions, and a higher risk of stroke in young and middle-aged Hcy as disease monitoring and prognosis indicators. C-reactive protein (CRP) is synthesized by the liver as a sensitive acute phase protein, CRP is a sensitive predictors of inflammation, and at the same time is also a marker of atherosclerosis, hs-CRP levels of pro-inflammatory cytokines in the blood prompt the content and the activity was significantly increased. In the process of atherosclerosis, IL-6, of TNF and other cytokines induced liver cell synthesis of CRP release into the blood, CRP activate the complement system via the

classical pathway, resulting in a large number of terminal attack product causing intimal damage and subsequent activation of platelets, cause platelet aggregation, adhesion formation of unstable atherosclerotic plaque. In addition, CRP can induce expression of endothelial cell adhesion molecules involved in atherosclerosis formation of the migration and proliferation of smooth muscle in the process, accelerated artery atherosclerosis development. Application immune transmission than nephelometry Clinical testing methods to the detection limit of 0.005 to 0.10 mg / L, CRP measured in such a method called Hs-CRP. Hs-CRP is a more valuable predictor of cerebrovascular disease, comprehensive, sensitive to reflect the patient's inflammation exists, provide a more sensitive indicator for clinical. Studies have found that the the TOAST in each subtype ACI patients serum hs-CRP levels have different levels of increased small artery occlusion group, serum levels of hs-CRP and hs-CRP level of positive rate was significantly lower than the main artery atherosclerosis [10]. Korean scholars arterial thrombosis in 886 cases of brain stroke patients were divided into cortical infarction, lacunar infarction, deep perforating branches and the watershed infarction detection admission serum hs-CRP found that cortical infarction serum hs-CRP levels than other 3 groups increased significantly [11]. Different subtypes of ischemic stroke, serum CRP levels differ, this difference may be by the CRP gene single nucleotide polymorphisms decision [12]. The study also found that the large the arteriosclerotic group of early serum hs-CRP levels the smaller artery occlusion group increased significantly, suggesting that hs-CRP levels is closely related to arteriosclerotic stroke occurred. The reason may be more intense inflammatory reaction caused by large-artery atherosclerosis. More domestic and foreign scholars have made a correlation found between hs-CRP and infarct volume was positively correlated with hs-CRP and infarct volume. This study is still a lack of observation with the relationship between the severity of the stroke lesion. About the concept of progressive stroke (progressive stroke, PS) and the time window has yet to reach a unified understanding of the authoritative literature at home and abroad there is no large-scale clinical studies of Ps not uncommon but occurred in clinical work progressing stroke to prognosis brought a lot of uncertainty, has been the focus and difficulty of the diagnosis and treatment process, forecast and prevention of clinical research has also been reported many risk factors. This clinical study detailed observation time window for stroke progression, the authors suggest that: within 24 hours of stroke is still at the stage of a natural progression, and 7 days after the observation found no stroke progress. Therefore, the time window of 2-7 days would be more appropriate. Progressing stroke occurred the proportion

of domestic mostly reported total stroke of about 30% [13] observed in this study is also true, and observed a higher incidence of 2-3 days, large arteriosclerosis progressing stroke incidence is much higher than the small vascular group (respectively: 44.6%, 13.8%). High Hcy expression in progressing stroke, this study found that large arteriosclerosis group progressing stroke and full stroke difference was not statistically significant, to consider the high Hcy progressing stroke relationship is not close. This is possible because Hcy the arterial lesions serum levels higher progressing stroke occurs in the main artery group mostly caused with the conclusions of other scholars. hs-CRP levels in progressing stroke research conclusions of many scholars the same, serum high-sensitivity C-reactive protein (hs-CRP), white referral prime -6 (IL-6) and matrix metalloproteinase protease -9 (expression of MMP-9) is so far found that the more sensitive to inflammatory cytokines involved in the whole process of atherosclerosis, of multiple organ such as the heart, and cerebrovascular atherosclerosis have a strong start, catalytic role in ischemic stroke, especially in PS plays an important role in the occurrence and development [14].

The cause of ischemic stroke is complex, different causes may have different effects on the prognosis. TOAST subtype classification standards focus on the classification of the etiology of ischemic stroke, according to this classification method proposed large, small vessel disease doctrine occupies an important position in the pathogenesis of cerebral infarction. Has been widely used in clinical. TOAST classification standards of clinical manifestations of ischemic stroke, outcome, rehabilitation research results also show that contribute to the clinical subtypes of ischemic stroke patients in the treatment and prevention of more targeted. TOAST classification criteria of the study, designed to observe the size of vascular lesions type of stroke early serum Hcy and hs-CRP levels and identify two causes of diagnostic significance, another indicator for clinical TOAST classification ideas and progressing stroke early detection and prediction of the neurological deterioration discussed. Since this is just a cross-sectional observation, the need for these two factors in the dynamic changes before and after the onset of stroke further clinical studies.

Evaluation of nerve function defect need for an objective and repeatable evaluation tools the NIHSS scoring method is the evaluation of neurological function scoring system most commonly used in the clinical studies [13], with respect to the SSS, CNS more systematic and comprehensive evaluation of neurological deficit. NIHSS scores with the stroke standardized treatment has been widely used in the clinical evaluation of a patient time required within 5 minutes, easy operation of the clinician.

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