CORRELATION OF HEMORHEOLOGICAL INDEXES, SERUM HCY, CAT S AND HS-CRP WITH THE DEGREE OF CAROTID ARTERY STENOSIS IN PATIENTS WITH ISCHEMIC CEREBROVASCULAR DISEASE

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ABSTRACT

Objective*: To explore the correlation between hemorheology indexes, serum Hcy, CatS and hs-CRP and the degree of carotid artery stenosis in patients with ischemic cerebrovascular disease.*

Methods: *A total of 89 patients with ischemic cerebrovascular disease treated in our hospital from May 2017 to April 2019 were recruited as the observation group, and 50 adults who received a physical examination in our hospital during the same period were selected as the control group. Patients in the observation group were divided into different subgroups according to the degree of carotid artery stenosis (52 cases in the mild stenosis group, 24 cases in the moderate stenosis group, 13 cases in the severe stenosis group), plaque nature (35 cases in the hard plaque group, 30 cases in the other types group, 24 cases in the soft plaque group), and carotid artery intima-media thickness (29 cases in the intimal thickening group, 60 cases in the plaque formation group). The whole blood viscosity, plasma viscosity, Hcy, CatS, and hs-CRP levels were compared between each subgroup, and the correlation between these indicators and the degree of carotid artery stenosis, plaque properties, and intima-media thickness was further analyzed.*

Results: *The levels of hs-CRP, Hcy, CatS, whole blood viscosity and plasma viscosity were significantly higher in different stenosis groups than levels in the control group (P<0.05). The levels of hs-CRP, Hcy, CatS, whole blood viscosity and plasma viscosity in the severe stenosis group and the moderate stenosis group were significantly higher than those in mild stenosis group (P<0.05), while the levels in the severe stenosis group were significantly higher than those in the moderate stenosis group (P<0.05). The levels of hs-CRP, Hcy, CatS, whole blood viscosity, and plasma viscosity were significantly higher in the various plaque groups compared to the control group (P<0.05), while the levels of hs-CRP, Hcy, CatS, whole blood viscosity, and plasma viscosity in the other type groups and soft plaque groups were significantly higher compared to the hard plaque groups (P<0.05). The levels of hs-CRP, Hcy, CatS, whole blood viscosity, and plasma viscosity in the soft plaque group were significantly higher than those in other types of groups (P<0.05). Additionally, the levels of hs-CRP, Hcy, CatS, whole blood viscosity and plasma viscosity were significantly higher in the intimal thickening group and plaque formation group than in the control group (P<0.05); the levels in the plaque formation group were significantly higher than those in the intimal thickening group (P<0.05). Lastly, the whole blood viscosity, plasma viscosity, Hcy, CatS, and hs-CRP of patients with ischemic cerebrovascular disease were positively correlated with carotid artery stenosis, plaque properties, and intima-media thickness (P<0.05).*

Conclusion: *Serum whole blood viscosity, plasma viscosity, Hcy, CatS, and hs-CRP are all involved in the onset and progression of ischemic cerebrovascular disease and are positively correlated with the degree of carotid artery stenosis, plaque properties, and intima-media thickness. This study demonstrates that these indicators are important for evaluating the severity of patients with ischemic cerebrovascular disease.*

Keywords: *Ischemic cerebrovascular disease, whole blood viscosity, plasma viscosity, Hcy, CatS, hs-CRP.*

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Introduction

The incidence rate of ischemic cerebrovascular disease is extremely high, which seriously threatens the lives and quality of life of many people. Research on the pathogenesis of ischemic cerebrovascular disease has been an area of major focus in the clinical professional field. Presently, factors such as age, gender, family history are associated with ischemic cerebrovascular disease – factors that cannot be altered. Therefore, prevention and treatment of intervenable risk factors has been the focus for treating ischemic cerebrovascular disease[1]. Previous reports have shown that the onset and progression of ischemic cerebrovascular disease are closely related to atherosclerotic stenosis and

unstable plaque shedding[2]. Related studies have identified many markers that can reflect the degree of vascular stenosis and plaque biology in ischemic cerebrovascular disease, such as serum cathepsin S (CatS), serum homocysteine (homocysteine, Hcy), high sensitive reactive protein (hs-CRP).

CatS participates in the pathophysiology of atherosclerosis and can also play an important role in determining the degree of neurological deficit in patients with ischemic stroke[3-4]. Hcy and hs-CRP have been confirmed to be independent risk factors affecting ischemic cerebrovascular disease[5]. Clinical studies have shown that there are many factors that cause atherosclerosis, including increased blood viscosity[6]. Therefore, this study is aimed to explore the correlation between these indicators and the degree of carotid artery stenosis by detecting levels of the hemorheological indicators serum Hcy, CatS and hs-CRP in ischemic cerebrovascular disease.

Materials and methods

General information

Eighty-nine patients with ischemic cerebrovascular disease treated in our hospital from May 2017 to April 2019 were recruited as the observation group. Of these patients, 42 were males and 47 were females, with an average age of 48.16±10.13 years. Patients in the observation group were divided into groups according to the degree of carotid artery stenosis, with 52 cases in the mild stenosis group, 24 cases in the moderate stenosis group, and 13 cases in the severe stenosis group. Patients in the observation group were additionally grouped based on the nature of the plaque, with 35 cases in the hard plaque group, 30 cases in the other types group, and 24 cases in the soft plaque group. Lastly, patients in the observation group were divided into groups on the basis of the carotid artery intima thickness, with an intimal thickening group of 29 cases and a plaque formation group of 60 cases.

Inclusion criteria

• All patients met the diagnostic criteria for ischemic stroke as indicated in the 2016 "Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke in China";

• Patients were 45 to 75 years old;

• All patients were diagnosed with ischemic stroke with head imaging and color Doppler ultrasound examination;

• All patients were admitted to the hospital within one day following the onset of illness;

• All patients and their families were informed about the study, and informed consent was obtained before the study;

• All patients met the relevant requirements of the ethics committee in our hospital and were approved.

Exclusion criteria:

• Patients who had taken antibiotics, anticoagulant drugs, or dopamine in the previous month;

• Patients who had recent trauma and trauma surgery;

• Patients with poor compliance that withdrew from the research study halfway through.

In addition, 50 adults who underwent a physical examination in our hospital during the same period were collected as the control group, consisting of 25 males and 25 females with an average age of 46.78±9.48 years. The general data of experimental subjects in the two groups were not statistically different after statistical software analysis (P<0.05).

Methods

• On the first day following admission, 5 mL of fasting venous blood was drawn from the observation and the control groups on the physical examination day and placed in a centrifuge tube. Using a Hettich ROTOFIX32A centrifuge (produced by Tegent Scientific Ltd.), the samples were centrifuged at 1500 r·min-1 for 20 minutes, after which the supernatant was removed and placed in an ultra-low temperature refrigerator for testing.

• The levels of hs-CRP and CatS of the serum in each group were detected using an ELISA kit (produced by Shanghai Xitang Biotechnology Co., Ltd.).

• The Hcy level, whole blood viscosity, and plasma viscosity of the serum in each group were detected using an automatic immune analyzer (produced by Shenzhen Boride Biotechnology Co., Ltd.).

• A correlation of the whole blood viscosity, plasma viscosity, and levels of Hcy, CatS, and hs-CRP with carotid artery stenosis, plaque properties, and intima-media thickness in patients with ischemic cerebrovascular disease was analyzed using Pearson's correlation.

Statistical methods

Measurement data such as whole blood viscosity, plasma viscosity, and level of Hcy in each group were expressed as (x±s). A comparison of two groups was carried out by performing a t-test, while a comparison of multiple groups was performed

with an F-test. A correlation analysis was carried out with a Pearson analysis. All data in this study were analyzed and processed with SPSS19.0, and P<0.05 was regarded to be statistically significant.

Results

Comparison of whole blood viscosity, plasma viscosity, and levels of Hcy, CatS, and hs-CRP in patients with different degrees of stenosis

The whole blood viscosity, plasma viscosity, and levels of hs-CRP, Hcy, and CatS of patients in different stenosis groups were significantly higher compared to the control group (P<0.05). The levels of hs-CRP, Hcy, and CatS in addition to the whole blood viscosity and plasma viscosity were significantly higher in the severe stenosis group and the moderate stenosis group compared with the mild stenosis group (P<0.05). Additionally, the levels of hs-CRP, Hcy, and CatS, whole blood viscosity, and plasma viscosity were significantly higher in the severe stenosis group compared with the moderate stenosis group (P<0.05). See Table 1.

Group	hs-CRP (μmol/L)	Hcy (mg/L)	CatS (pg/L)	Whole blood viscosity (mPa's)	Plasma viscosity (mPa's)
Control group	12.60±3.82	1.24±0.53	50.71±8.76	3.23±1.19	2.09±0.65
Mild stenosis group	16.00±3.93[a]	3.18±1.13[a]	55.34±10.57[a]	3.67±1.23[a]	2.24±0.80[a]
Moderate stenosis group	19.72±4.33[ab]	4.23±1.32[ab]	68.60±11.57[ab]	4.48±1.50[ab]	2.96±0.89[ab]
Severe stenosis group	23.55±4.88[abc]	5.52±1.56[abc]	80.77±9.16[abc]	5.46±1.33[abc]	3.98±1.04[abc]

Table 1: Comparison of whole blood viscosity, plasma viscosity, Hcy, CatS, and hs-CRP levels in patients with different degrees of stenosis (x±s).
Note: Compared with the control group, a indicates P<0.05; compared with the mild stenosis group, b indicates P<0.05, compared with the moderate stenosis group, c indicates P<0.05.

Comparison of whole blood viscosity, plasma viscosity, and levels of Hcy, CatS, and hs-CRP in patients with different plaque properties

The levels of hs-CRP, Hcy, and CatS, whole blood viscosity, and plasma viscosity were significantly higher in different plaque groups than the levels in the control group (P<0.05).

Additionally, the levels of hs-CRP, Hcy, CatS, whole blood viscosity, and plasma viscosity were significantly higher in the other types of groups and the soft plaque groups than those in the hard plaque groups (P<0.05). Finally, the levels of hs-CRP, Hcy, CatS, whole blood viscosity, and plasma viscosity were significantly higher in the soft plaque group compared to the other types of groups (P<0.05).

Group	hs-CRP (μmol/L)	Hcy (mg/L)	CatS (pg/L)	Whole blood viscosity (mPa's)	Plasma viscosity (mPa's)
Control group	12.60±3.82	1.24±0.53	50.71±8.76	3.23±1.19	2.09±0.65
Hard plaque group	15.58±4.02[a]	3.23±1.36[a]	58.56±6.57[a]	3.50±1.33[a]	2.20±1.43[a]
Other types of groups	19.48±4.35[ad]	4.62±1.53[ad]	72.43±10.64[ad]	4.47±2.06[ad]	2.79±1.34[ad]
Soft plaque group	23.75±5.06[ade]	5.58±1.62[ade]	84.60±11.50[ade]	5.99±1.55[ade]	3.17±1.22[ade]

Table 2: Comparison of whole blood viscosity, plasma viscosity, Hcy, CatS, hs-CRP levels in patients with different plaque properties (x±s).
Note: Compared with the control group, a indicates P<0.05; compared with the mild stenosis group, d indicates P<0.05, compared with the moderate stenosis group, e indicates P<0.05.

Comparison of whole blood viscosity, plasma viscosity, and levels of Hcy, CatS, and hs-CRP of patients in different carotid artery intima-media thickness groups

The levels of hs-CRP, Hcy, CatS and the whole blood viscosity and plasma viscosity in the intimal thickening group and plaque formation group were significantly higher compared to the control group (P<0.05). Additionally, the levels of hs-CRP, Hcy, CatS as well as whole blood viscosity and plasma viscosity were significantly higher in the plaque formation group than the levels in the intimal thickening group (P<0.05). See Table 3.

Group	hs-CRP (μmol/L)	Hcy (mg/L)	CatS(pg/L)	Whole blood viscosity (mPa's)	Plasma viscosity (mPa's)
Control group	12.60±3.82	1.24±0.53	50.71±8.76	3.23±1.19	2.09±0.65
Intimal thickening group	18.78±4.76[a]	4.53±1.28[a]	65.00±6.49[a]	4.59±1.61[a]	3.08±1.19[a]
Plaque formation group	24.12±4.98[af]	5.43±1.55[af]	86.19±12.09[af]	5.23±1.71[af]	3.79±1.35[af]

Table 3: Comparison of whole blood viscosity, plasma viscosity, and levels of Hcy, CatS, and hs-CRP of patients in different carotid artery intima-media thickness groups (x±s).
Note: Compared with the control group, a indicates P<0.05; compared with the intimal thickening group, fP.

Correlation between patient's whole blood viscosity, plasma viscosity, Hcy, CatS and hs-CRP and the degree of carotid artery stenosis

The whole blood viscosity, plasma viscosity, and levels of Hcy, CatS, and hs-CRP of patients with

ischemic cerebrovascular disease were positively correlated with carotid artery stenosis, plaque properties, and intima-media thickness (P<0.05). See Table 4.

Indexes	Stenosis		Plaque properties		Intima-media thickness	
	r	*P*	*r*	*P*	*r*	*P*
Whole blood viscosity	0.606	0.019	0.574	<0.001	0.734	<0.001
Plasma viscosity	0.735	0.029	0.489	0.042	0.589	0.039
Hcy	0.544	0.039	0.876	<0.001	0.699	0.022
CatS	0.593	0.019	0.634	0.005	0.7711	<0.001
hs-CRP	0.779	<0.001	0.396	<0.001	0.784	0.007

Table 4: Correlations between patient's whole blood viscosity, plasma viscosity, Hcy, CatS, and hs-CRP levels and the degree of carotid artery stenosis.

Discussion

Atherosclerosis is the main pathological disease process that promotes ischemic cerebrovascular disease, and the carotid artery is the region that is the earliest to be affected[7]. Clinical reports have shown that the progression and rupture of atherosclerosis are inseparable from the body's inflammatory response and play an important role in the progression of ischemic cerebrovascular disease[8].

Hepatocytes release a large amount of hs-CRP, which is sensitive to mobilization of the inflammatory response and activation of interleukin-6[9]. Clinical studies have confirmed that hs-CRP can activate the complement system through classic pathways, produce various inflammatory mediators and harmful oxygen-free radicals, and severely damage vascular endothelial cells, ultimately inducing vascular tissue spasm. Another report showed that serum hs-CRP can also indicate the severity of atherosclerosis and the prognosis of patients[10]. Clinical studies have confirmed that excessive Hcy levels can be an independent risk factor for atherosclerosis; an increase in the Hcy level can stimulate the production and release of plasmin activator inhibitors, causing platelet aggregation, adhesion, and increased blood coagulation, which can easily lead to thrombosis and ultimately to atherosclerosis[11, 12].

Many proteases and endogenous inhibitors participate in the formation of atherosclerosis. For example, CatS and its inhibitors can play an important role in the process[13]. Previous clinical research has shown that CatS expression is present in the fibrous cap and media smooth muscle layer at the damaged area, which can cause formation of intimal thickening and an unstable atherosclerotic plaque and is associated with a significantly increased incidence rate of ischemia cerebrovascular disease[14]. The hemorheology index is an important reference index that can indicate cardiovascular and cerebrovascular diseases. Changes in the hemorheology index is associated with dysfunction of vascular endothelial cells, causing many cell molecules and plasma components to concentrate at the diseased location, inducing atherosclerosis. The whole blood viscosity of patients with atherosclerosis is usually higher compared to healthy people and is closely related to disease severity and poor prognosis. While clinical studies have shown that plasma viscosity can affect the viscosity of the whole blood, both plasma and whole blood can be used as indicators to evaluate the formation of atherosclerotic plaques in patients with coronary heart disease and play an important role in early treatment and disease intervention[15].

The results of this study showed that the levels of hs-CRP, Hcy, and CatS, whole blood viscosity, and plasma viscosity were significantly higher in the various stenosis groups compared with the control group (P<0.05), and higher levels were associated with worsening degrees of carotid artery stenosis. These findings show that these indicators can predict the degree of carotid artery stenosis in patients with ischemic cerebrovascular disease. Hard plaques are stable plaques, soft plaque are unstable plaques, and flat plaques and mixed plaques have intermediate stability. Among these plaque types, hard plaques have fewer inflammatory cells and are not prone to rupture. In soft plaques, there are many inflammatory cells and serious infiltration, which can easily cause the plaque to rupture and hemorrhage, leading to thrombosis and inducing ischemic cerebrovascular disease. The results of this study showed that the levels of hs-CRP, Hcy, CatS, whole blood viscosity, and plasma viscosity were significantly higher in groups with different plaque properties than levels in the control group (P<0.05), and soft plaque group>other type group>hard plaque group.

These findings suggest that levels of these factors may be used as important indicators to assess the progression of atherosclerotic plaque in patients with ischemic cerebrovascular disease. The levels of hs-CRP, Hcy, CatS, whole blood viscosity and plasma viscosity in the intimal thickening group and plaque formation group were significantly higher than levels in the control group (P<0.05); and the plaque

formation group>the intimal thickening group. The results of this study show that the above indicators may help predict plaque shedding in ischemic cerebrovascular disease. In addition, we also found that whole blood viscosity, plasma viscosity, Hcy, CatS, and hs-CRP levels of patients with ischemic cerebrovascular disease were positively correlated with carotid artery stenosis, plaque properties, and intima-media thickness ($P<0.05$).

In conclusion, serum whole blood viscosity, plasma viscosity, and levels of Hcy, CatS, and hs-CRP are all involved in the onset and progression of ischemic cerebrovascular disease. Furthermore, these are positively correlated with the degree of carotid artery stenosis, plaque properties, and intima-media thickness. These indicators may therefore be important indicators for evaluating the severity of patients with ischemic cerebrovascular disease.

References

1) Chen FY, Fang XY, Zhang H. Effect of polydatin on expression of p53 and Notch1 in brain tissue of ischemic cerebrovascular disease. J Biol Regul Homeostatic Agents 2018; 32: 133-138.
2) Del Brutto VJ, Chaturvedi S, Diener HC, Romano JG, Sacco RL. Antithrombotic Therapy to Prevent Recurrent Strokes in Ischemic Cerebrovascular Disease. J Am Coll Cardiol 2019; 74: 786-803.
3) Gremião IDF, Oliveira MME, Monteiro de Miranda LH, Saraiva Freitas DF, Pereira SA. Geographic Expansion of Sporotrichosis, Brazil. Emerg Infect Dis 2020; 26: 621-624.
4) Cavalleri D, Murphy M, Seewald W, Nanchen S. Laboratory evaluation of the efficacy and speed of kill of lotilaner (Credelio?) against Ctenocephalides felis on cats. Parasit Vectors 2018; 11: 408-415.
5) Yang XL, Jia YT. Correlation between Neonatal Birth Weight and Serum MPO, hs-CRP Level in Pregnant Women with Preeclampsia and Its Clinical Significance. Chin Foreign Med Res 2019; 89: 15-23.
6) Levine MJ. Empagliflozin for Type 2 Diabetes Mellitus: An Overview of Phase 3 Clinical Trials. Curr Diabetes Rev 2017; 13: 405-423.
7) Sun L, Bai Y, Zhao R, Sun T, Cao R, et al. Oncological miR-182-3p, a Novel Smooth Muscle Cell Phenotype Modulator, Evidences from Model Rats and Patients. Arterioscler Thromb Vasc Biol 2016; 36: 1386-1397.
8) Zhang SS, Zou J, Li PY, Zheng XM, Feng D. Curcumin Protects against Atherosclerosis in Apolipoprotein E-Knockout Mice by Inhibiting Toll-like Receptor 4 Expression. J Agric Food Chem 2018; 66: 449-458.
9) Cheng BL, Wang FX, Yang DR. Clinical Application of Combined Detection of hs-CRP, β-HCG, and Progesterone in Predicting Threatened Abortion. J Mod Lab Med 2019; 45: 789-795.
10) Li K, Wei P, Qin Y, Wei Y. Is C-reactive protein a marker of obstructive sleep apnea? A meta-analysis. Medicine (Baltimore) 2017; 96: 6850.
11) Gao Y, Wang T. The application of combination detection of CysC,hs-CRP,Hcy,D-D in the diagnosis of acute cerebral infarction. Chin J Pract Nerv Dis 2018; 6: 125-128.
12) Wei N, Mao YP, Shang QN. Influences of salvia miltiorrhiza injection combined with labetalol hydrochloride on serum hcy/β2-mg levels and outcome of maternal and infant in patients with gestational period hypertension. Chin J Gen Pract 2018; 79: 15-19.
13) Pennisi MG, Tasker S, Hartmann K, Belák S, Addie D, et al. Dirofilarioses in cats: European guidelines from the ABCD on prevention and management. J Feline Med Surg 2020; 22: 442-451.
14) Luan XB, Zhang FC, Weng ZY, Zhang Y, Ma L. Effect of lipid lowering mixture on blood lipid metabolism, LDL oxidation susceptibility and blood viscosity and coagulation in experimental hyperlipidemia rats. J Hainan Med Univ 2019; 4: 156-162.
15) Zhao JH, Liu L, Zhou Y, Li HW, Ning Z, et al. Relationship between Blood Lipids, Blood Viscosity, HCY and Cardiovascular Disease in Tibetan Patients at Different Altitudes. Progress Mod Biomed 2019; 56: 17-28.

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