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SERUM C-REACTIVE PROTEIN, FIBRINOGEN AND D-DIMER IN PATIENTS WITH PROGRESSIVE CEREBRAL INFARCTION

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Abstract

Objective: Progressive cerebral infarctions increase mortality and functional disability through mechanisms which have yet to be completely understood. The goal of this study was to explore the dynamic changes of serum C-reactive protein (CRP), fibrinogen (FIB) and D-dimer (D-D) in order to better characterize progressive cerebral infarction. Methods: The amount of serum CRP, FIB and D-D was measured in 82 patients with progressive cerebral infarction by taking samples from the internal carotid artery (progressive group), and in 186 patients with non-progressive cerebral infarction (non-progressive group) by using an automatic biochemical analyzer during the next day (day 1), day 3, day 7, and day 14 after being admitted to hospital. Carotid vascular ultrasound and neurological deficit score (National Institutes of Health Stroke Scale, NIHSS) were also recorded. Results: Carotid stenosis ratio was significantly higher in the progressive group than in the non-progressive group ($P < 0.01$) on admission. In the progressive group, CRP increased significantly on day 3, followed by a decline on day 7 and day 14, but was significantly higher than those in the non-progressive group ($P < 0.01$). The levels of FIB and D-D increased in the progressive group more than those in the non-progressive group on day 3, day 7, and day 14 ($P < 0.01$). The progressive group patients' NIHSS score gradually increased after admission, which was opposite to the non-progressive group patients whom followed a downward trend. The difference between these two groups was significant ($P < 0.01$). Conclusion: Observing changes of CRP, FIB and D-D may contribute to early identification and timely treatment of progressing ischemic strokes.

Keywords

C-reactive protein • D-dimer • Fibrinogen • Neurological deficit score • Progressive cerebral infarction

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1. Introduction

It is well known that over two-thirds of stroke deaths worldwide are in developing countries. Each year, more than one million residents of China die from stroke, three times the amount of deaths from ischemic heart disease (IHD) [1]. In the past 30 years, China has experienced a rapid economic development with an increasing elderly population and a corresponding increase in life expectancy. The number of people having strokes and stroke mortality rates have increased accordingly [2-5]. The official statistics data from 31 regions in China showed that stroke became the number one cause of death among both urban and rural residents, and the mortality rates of stroke were much higher in cities than in rural areas [6, 7].

Progressive cerebral infarction refers to a worsening neural function deficiency within 48 to 72 h of an acute ischemic stroke. It accounts for 25-40% of all incidences of stroke and is associated with an increased rate of disability and lethality [8-10]. Progressive cerebral infarction may develop to cerebral ischemia, hypoxia, necrosis and finally neurological deficit. Due to the difficulty in treating such progressive situations, much attention has been devoted to this group of diseases by clinicians. Although several clinical, radiological, and biochemical factors have been associated with early neurological deterioration, most of them have a low predictive value [8-11]. Release of excitatory amino acids and oxygen free radicals, iron accumulation, nitric oxide production or apoptosis have been suggested as mechanisms for worsening clinical conditions [12, 13], but the pathophysiological mechanism for progressive stroke symptoms is not known.

C-reactive protein (CRP), a marker of the reactant plasma protein component of the inflammatory response, has been associated as a risk factor for future IHD and cerebral vascular disease in several prospective studies [14, 15]. There is evidence of increased thrombin generation and fibrinogen (FIB) turnover, altered fibrinolytic activity, and disturbed endothelial function in acute stroke [16]. D-dimer (D-D), a marker of cross-linked fibrin turnover, has also been associated with the risk of future IHD, independently predicting a progressing ischemic stroke [17-21]. The goal of this study was to assess the dynamic changes of serum CRP, FIB and D-D levels in patients with progressive cerebral infarction from central China.

2. Materials and methods

2.1 Subjects

In this retrospective study, 82 patients with first-ever progressive cerebral infarction from the internal carotid artery system (progressive

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group) and 186 patients with first-ever non-progressive cerebral infarction (non-progressive group) were selected from Zhongnan Hospital of Wuhan University between June 2011 and May 2015. The selection criteria for cerebral infarction were based on the diagnostic code drafted at the Fourth Cerebral Vascular Disease Academic Conference in 1995, coupled with confirmation by cranial CT scan or MRI [3-5]. Exclusion criteria included transient ischemia attack, cerebral hemorrhage on admission or hemorrhage secondary to ischemic stroke, reversible ischemic neurologic deficit, ischemic stroke with an absence of symptoms, criteria consistent with ischemic stroke, but without sufficient clinical data. Stroke severity was assessed [3, 4] by using the National Institutes of Health Stroke Scale (NIHSS) score at the next day (day 1), day 3, day 7, and day 14 after being admitted to hospital. The patients whose NIHSS score increased more than two points after hospitalization within 3 days were categorized into the progressive group, while the patients whose NIHSS score increased less than two points were categorized into the non-progressive group [22]. The duration of time before symptom onset in the two groups was from 1 to 2 days. Carotid vascular ultrasound was recorded within 3 days. Hypertension was defined as a previous record of hypertension or the requirement for the regular use of antihypertensive drugs. Diabetes mellitus was defined as a previous record of diabetes or the requirement for regular hypoglycemic drugs. IHD was diagnosed when there was a history of angina pectoris or myocardial infarction. Alcohol consumption ≥ 5 years or current alcohol intake ≥ 1000 g per week was defined as a drinking history. Smoking ≥ 5 years or current smokers' ≥ 10 cigarettes per day or smoking cessation ≤ 2 years was considered as a smoking history [3, 4, 23].

Effective management including modern western medicine with one or more types of Chinese herb medicine was used, and physical rehabilitation was carried out after admission [1, 3-5]. Routine medications for all ischemic stroke patients in both groups included anti-platelet agents, anti-hypertensive, hypoglycemic and anti-hyperlipidemic drugs, as well as water-salt electrolyte formulations. These medicines should be taken following the advice of a physician and according to symptoms of each patient [1, 3-5]. There was no significant difference between the two groups of patients in medications. Although the levels of serum triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and carotid stenosis ratio in progressive group were higher than those in non-progressive group on admission, they have been prescribed for the same dose of anti-hyperlipidemic drugs. This study was carried out in accordance with the Declaration of Helsinki, and approved by the institutional review boards of the local Bioethics Committee in Zhongnan Hospital of Wuhan University. The clinical characteristics of two groups are listed in Table 1.

2.2 Laboratory tests

Venous blood samples were collected from all patients, to do a regular investigation after hospital admission. Serum CRP, FIB and D-D levels were measured [3, 4] by automatic biochemical analyzer during the next day (day 1), day 3, day 7, and day 14 after being admitted to the hospital. Biochemical parameters including fasting serum glucose, TC, TG, high density lipoprotein cholesterol (HDL-C), and LDL-C were also measured within 24 h after admission.

2.3 Statistical methods

All data was expressed as the mean ± standard deviation (SD). The chi-squared (χ^2) test was used to compare proportions and the student t-test to compare continuous variables between groups. Value of $P < 0.05$ was considered statistically significant.

3. Results

3.1 Characteristics of patients between two groups

There were no significant differences in age, gender, duration of disease, hypertension, diabetes mellitus, IHD, atrial fibrillation, heavy drinking and smoking history, levels of fasting glucose and HDL-C between two groups ($P > 0.05$). The levels of serum TC, TG, LDL-C and carotid stenosis ratio in the progressive group were higher than those in the non-progressive group on admission ($P < 0.05$ or $P < 0.01$, see Table 1).

3.2 Serum CRP, FIB and D-dimer and NIHSS score between two groups

There were no significant differences in CRP, FIB and D-D level and NIHSS score on day 1 between two the groups after admission. In the non-progressive group, CRP decreased on day 7, and day 14. In the progressive group,

Table 1. Clinical characteristics of the patients between two groups (mean ± SD).

	Progressive group (n = 82)	Non-progressive group (n = 186)	*P* value
Age (years), mean (SD)	70.2 (9.9)	69.3 (9.7)	0.84
Male, n (%)	51 (62.6)	117 (62.8)	0.65
Hypertension, n (%)	52 (63.6)	115 (62.9)	0.78
Diabetes mellitus, n (%)	14 (16.6)	31 (16.9)	0.88
Ischemic heart disease, n (%)	9 (11.0)	20 (10.7)	0.83
Atrial fibrillation, n (%)	8 (10.2)	19 (10.3)	0.77
Heavy drinking, n (%)	50 (60.8)	111 (59.8)	0.68
Smoking, n (%)	27 (33.3)	63 (33.8)	0.72
Glucose (mmol/l), mean (SD)	5.80 (0.70)	5.78 (0.71)	0.67
TC (mmol/l), mean (SD)	7.75 (1.26)	5.79 (1.24)	< 0.01
TG (mmol/l), mean (SD)	5.33 (0.84)	3.12 (0.64)	< 0.01
HDL-C (mmol/l), mean (SD)	0.88 (0.16)	0.90 (0.17)	0.89
LDL-C (mmol/l), mean (SD)	4.23 (0.56)	3.82 (0.62)	< 0.05
Carotid stenosis, n (%)	37 (44.6)	58 (31.2)	< 0.01

Abbreviations: TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

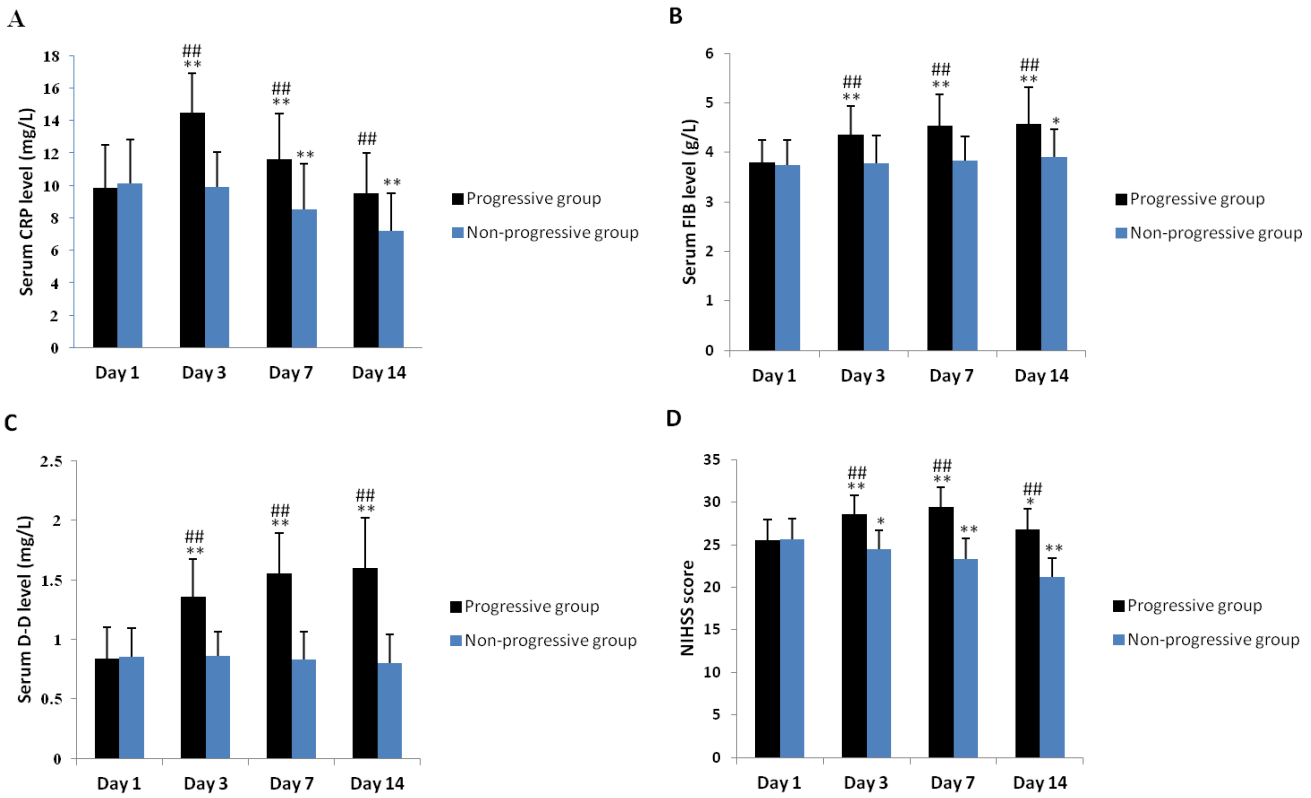

Figure 1. Changes of serum CRP, FIB, D-D and NIHSS score between progressive group and non-progressive group (mean ± SD). A. Serum CRP level. B. Serum FIB level. C. Serum D-D level. D. NIHSS score. * P < 0.05, ** P < 0.01 in comparison with Day 1 in the same group; # P < 0.05, ## P < 0.01 in comparison with non-progressive group on the same day. Abbreviations: CRP, C-reactive protein; FIB, fibrinogen; D-D, D-dimer; NIHSS, National Institutes of Health Stroke Scale.

CRP increased significantly on day 3, followed by decline on day 7 and day 14, but significantly higher than those in the non-progressive group ($P < 0.01$). FIB and D-D increased significantly in the progressive group compared to those in the non-progressive group ($P < 0.01$). In the progressive group, the NIHSS score progressively increased, while in the non-progressive group, the NIHSS score presented with a downward trend after admission. The difference between these two groups was significant ($P < 0.01$, see Fig. 1).

4. Discussion

In China, early clinical progression of cerebral infarction is common and is associated with an increased mortality. An understanding of the factors contributing to progressive cerebral infarction will help clinicians implement optimal management. There are a number of prognostic factors of ischemic stroke which have been identified, but the studies on risk factors associated with neurologic deterioration have yielded contradictory results [24,25]. One previous study [26] showed that age, family stroke history, smoking history, hypertension on admission, high serum glucose on admission, and fever were related to progressive ischemic stroke in the Han population of northeast China. Further study confirmed that hypertension history of more than 5 years is an important risk factor for progressive cerebral infarction [26]. The elevation of systolic blood pressure 16 h to 5 days after admission and abnormal circadian blood pressure are both associated with progression of the disease [27]. Hyperglycemia itself probably results in neurotoxicity and induces a procoagulant state [28]. Another study [24] found that early focal hypodensity with cortical and cortical-subcortical distribution and brain swelling on initial cranial CT has been associated with a worsening neurological condition within the first 2 to 4 days after stroke onset. In this study, there were no significant differences in age, gender, duration of disease, hypertension, diabetes mellitus, IHD, atrial fibrillation, heavy drinking and smoking history, levels of fasting glucose and high HDL-C between the progressive group and the non-progressive group on admission.

Although the clinical importance of plaque morphology, hemodynamic situation over the stenosis and the collateral circulation in the acute phase of stroke would certainly be valuable to evaluate in relation to the clinical course and outcome. A previous study [29] showed that patients with severe carotid disease had no significant differences in the rate of progression or recurrence compared to those without. Using transcranial Doppler, Álvarez *et al*. reported [30] cerebral hemodynamic reserve impairment within the first 24 h of acute ischemic stroke is associated with a higher risk of early neurological deterioration. Impaired

cerebral hemodynamic reserve at stroke onset probably indicates that the vasodilator compensatory mechanisms are exhausted and consequently that there is a high risk of recruitment of the oligemic ischemic tissue into infarction. Analysis of cerebral artery stenosis also revealed that age; diabetes mellitus and plasma FIB were risk factors for cerebral artery stenosis [31]. In this study, the levels of serum TG, TC and LDL-C, and carotid stenosis ratio in progressive group were higher than those in non-progressive group on admission.

Following brain infarction, the reduction of cerebral blood after ischemia initially causes oxygen and glucose deprivation and acute cell death, eventually leading to increasing edema and enlargement of the infarct lesion [32-35]. Haemostatic activation may be an important cause or contributor to progressing ischemic stroke [36]. Increased D-D level may reflect ongoing thrombus formation within cerebral vessels or may be a marker of systemic hypercoagulability. One study [37] found elevated D-D level in patients with progressing stroke when samples were withdrawn within 7 days of symptom onset. In this study, CRP level increased in progressive group significantly on day 3, followed by decline on day 7 and day 14, but significantly higher than those in the non-progressive group. FIB and D-D levels also increased significantly in the progressive group. In addition, the NIHSS score increased in the progressive group after admission, while the non-progressive group presented with a downward trend; the difference between the two groups was significant.

Taken together, this study showed the dynamic changes of serum CRP, FIB and D-D in patients with progressive cerebral infarction, which may be involved in the mechanism of stroke progression. It is very helpful for the physician to monitor the changes of CRP, FIB and D-D together to predict the progression of cerebral infarction. Additional multiple center studies with large numbers of subjects are warranted to confirm it.

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