Tohoku J. Exp. Med., 2005, **206**, 91-98

# Assessment of Acute Phase Proteins in Acute Ischemic Stroke

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TAMAM, Y., ILTUMUR, K. and APAK, I. *Assessment of Acute Phase Proteins in Acute Ischemic Stroke*. Tohoku J. Exp. Med., 2005, **206** (2), 91-98 —— Acute phase proteins (APPs) have been implicated to play important roles during both acute and chronic inflammatory processes in different diseases including ischemic stroke. Though there are several studies showing the importance of APPs as inflammation markers in acute ischemic stroke (AIS), the time course of these proteins during acute phase of AIS is not well known. Thus, the aim of this study was to show the changes in plasma levels of six APPs (i.e., haptoglobin [Hp], ceruloplasmin [Cp], high-sensitive C-reactive protein [h-CRP], fibrinogen, complement 3 [C3] and complement 4 [C4]) during the first 10 days after acute stroke. The study group consisted of 34 female and 19 male patients ($n$ = 53; mean age 65 ± 12 years), who had first acute ischemic stroke (AIS). An age-matched control group ($n$ = 53; 32 female and 21 male subjects, mean age 62 ± 6 years) was also included. To evaluate the plasma levels of six APPs, the blood samples of patients with AIS were withdrawn on admission (day 1), and after 3, 5 and 10 days, whereas only one measurement was performed in the control group. In addition, several cerebrovascular risk factors were determined. The peak levels of APPs were higher in the AIS group than the control group ($p < 0.0001$). In serial measurements, the levels of h-CRP, Hp, C3 and C4 showed alterations during 10 days after AIS ($p < 0.0001$, $p < 0.05$, $p < 0.0001$, $p < 0.0001$, respectively). The alterations in levels of fibrinogen and Cp were not statistically significant ($p > 0.05$). After stroke, h-CRP, C3 and fibrinogen reached their highest values on the third day, Cp and C4 on the fifth day, and Hp on the tenth day. The plasma levels of h-CRP correlated positively with other five APPs studied ($p < 0.05$). These findings support the importance of inflammation processes after stroke. We suggest that the differences in levels of APPs could be used in predicting the outcome of stroke patients. ———— acute phase proteins; ischemic stroke; inflammation; CRP; complements


The initiation of inflammatory processes in the body results in production of several proteins induced by the innate immune response, which are called acute phase proteins (APPs) (Kushner 1982). These proteins play prominent roles during both the acute and chronic inflammatory processes and their plasma concentrations are used as markers of inflammation (Heinrich et al. 1990; Epstein 1999). A large number of proteins (i.e., fibrinogen, high sensitive C-reactive protein

Received February 2, 2005; revision accepted for publication March 1, 2005.
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[hCRP], complement 3 [C3], complement 4 [C4], tumor necrosis factor [TNF], and haptoglobin [Hp]) have been considered as APPs (Heinrich et al. 1990). Some of them (i.e., C reactive protein [CRP], fibrinogen) have gained wide popularity for monitoring inflammation in many different disease states parallel to the development of reliable and fast assays measuring their plasma levels (Muir et al. 1999; Szalai et al. 1999; Büyüköztürk et al. 2004).

It has largely become evident in recent years that an inflammatory process also plays an important role in the pathophysiology of ischemic stroke (Becker 1998; Bartosik-Pjusek et al. 2003; L'Allier 2004). In one of the recent studies, the detection of plasma level of CRP as an inflammation marker, was found to be beneficial in the determination of possible risk factors for subsequent vascular events or death, and severe neurological deficit and disability, and grouping of poststroke patients into relatively high-risk groups. (Di Napoli et al. 2001a).

There are other studies reporting the importance of several different APPs (i.e., CRP fibrinogen, tissue factor, sialic acid, alpha-1 antitrypsin, complements) as parameters of inflammation during acute phase after stroke (Intriso et al. 2004; Haapaniemi et al. 2004; Pedersen et al. 2004). However, there are limited data about the course of plasma levels of APPs in acute ischemic stroke (AIS) (Engström et al. 2004). Besides, to our knowledge, the relevance of two other APPs (Hp and ceruloplasmin [Cp]) with the course of stroke have not been studied in depth. Thus the aims of this study were to determine the course of plasma levels of six different APPs (i.e., Hp, Cp, hCRP, fibrinogen, C3 and C4) during the first 10 days after AIS and to evaluate the correlations between the concentrations of these APPs.

## Subjects and Methods

*Subjects*

This study included 53 consecutive patients (34 women, 19 men; mean age 65 ± 12 years) with AIS admitted to Neurology inpatient clinics of Dicle University Faculty of Medicine Hospital within the first 24 hours after the onset of first-ever stroke between August 2003 and August 2004. The definition of the World Health Organization was used for defining a stroke: a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs of focal loss of cerebral function with symptoms lasting more than 24 hours or leading to death before that, with no apparent cause other than that of vascular origin. The diagnosis AIS was established both clinically and radiologically (Computed Tomography [CT] or Magnetic Resonance Imaging [MRI] of brain structures). Hemorrhagic stroke was excluded by brain imaging.

Thirteen potential patients were excluded from the study during the formation of study group as they have met exclusion criteria for the study. The exclusion criteria for the study were; a history of previous stroke or recent transient ischemic attack, a history of cardiovascular event (i.e., myocardial infarction and unstable angina), presence of the clinical (history and physical examination) and laboratory evidence of a focal active or recent bacterial infection including in-hospital infections before the onset of stroke, having chronic obstructive pulmonary disease or inflammatory conditions (such as chronic inflammatory bowel disease or arthritis); having impaired hepatic and renal function, and having a history of surgery or trauma in the previous month. The diseases meeting the exclusion criteria were investigated and checked by medical history, chest x-ray, urine and biochemical complete blood tests and complete physical examinations of all patients. None of the patients composing the final study group ($n = 53$) died or excluded during the study period.

An equal number of age and sex matched healthy control group free from vascular, hematological and neurological disease, were also included in the study ($n = 53$; 32 women, 21 men; mean age: 62 ± 6 years).

All patients, in case of unconsciousness their closest relative, and the subjects in the control group signed a written informed consent to be included in the present study. The study was approved by the Dicle University Ethics Committee and carried out according to the institutional guidelines and the principles of the Declaration of Helsinki.

All patients and control group underwent baseline clinical examinations, which included medical history, physical examination focused on neurological signs, 12-lead electrocardiogram (ECG), and ankle-brachial blood pressure index. Routine hematologic and biochemical profiles were achieved for both study and control groups. Several laboratory and clinical parameters,

and cardiovascular risk factors (i.e., age, gender, smoking, body mass index [BMI], lipid profiles, serum levels of total cholesterol, and LDL, HDL), presence of arterial hypertension (as documented by systolic blood pressure [BP] ≧ 140 mmHg and/or diastolic BP ≧ 90 mmHg), heart rate (bmp), diabetes mellitus (DM) (treatment with antidiabetics or appearance of diabetes during the stay) were specifically noted.

*Measurements of levels of APPs*

The plasma levels of Hp, Cp, h-CRP, fibrinogen, C3 and C4 were measured once for the control group, whereas the patients' blood samples were taken on admission (day 1), and on 3rd, 5th and 10th days. Blood chemistry levels including glucose, lipid profile and fibrinogen were analyzed in the hospital biochemistry laboratory by using standard techniques.

*Laboratory assays*

Venous blood samples were taken from the antecubital vein, and serum was separated by centrifugation within 1 hour of collection. Just after collecting, the tubes were placed on ice in order to avoid complement inactivation. Complement components were measured with a nephelometric assey Behring BN-101 nephelometry (Dade Behring, Marburg, Germany). The plasma levels of hCRP were measured with a immunonephelometry using BN systems (Dade Behring, Marburg, Germany). Serum concentrations of Hp and Cp were measured by nephelometry (Dade Behring, Marburg, Germany). All calibrators were supplied by the manufacturers (Dade Behring, Marburg, Germany). The reference intervals for APPs were as follows; h-CRP; 1.0 - 3.0 mg/l, C3; 90 - 180 mg/l, C4; 10 - 40 mg/l, Hp; 30 - 200 mg/l, Cp; 20 - 60 mg/l)

*Statistical analyses*

All values are presented as mean ± S.D. Student *t*-test was used for the comparisons between control and AIS groups. For the correlations between h-CRP and other parameters, Pearson correlation test was used. One way ANOVA for repeated measures and post-hoc Tukey's test for pairwise comparison were performed for comparison of the time course changes in concentrations of APPs. The statistical level of significance was set at $p < 0.05$. Analyses were performed with SPSS for Windows, version 11.

## Results

*The characteristics features of study and control group*

The study included 53 patients with a first-ever ischemic stroke and 53 age- and sex-matched control group (Table 1). The variables of age, gender, presence of smoking habit, plasma levels of total cholesterol, triglycerides and LDL did not show any significant differences between the AIS and control groups ($p > 0.05$). The AIS group had significantly higher mean systolic and diastolic blood pressures and heart rate, higher levels of plasma glucose in comparison with control group, while mean plasma levels of HDL were significantly lower. Of 53 patients with AIS, only 10 of them had type-2 DM, while none of the control group had DM.

*The course of plasma levels of APPs in AIS and control subjects*

The peak plasma levels of all APPs (Hp, Cp, h-CRP, fibrinogen, C3 and C4) were significantly higher in AIS group compared to control group ($p < 0.0001$) (Table 1). In AIS group, serial measurements of plasma levels of h-CRP, Hp, C3 and C4 demonstrated significant alterations during the first 10 days of ischemic stroke according to baseline levels. Nevertheless the change in plasma levels of two other APPs, Cp and fibrinogen, never reached to significant levels during serial measurement in the first 10 days. The plasma levels of Cp peaked at the 5th day, whereas fibrinogen level peaked at the 3rd day (Table 2).

During the acute phase of ischemic stroke, the plasma levels of Hp increased gradually and steadily from the 1st day until the 10th day to reach its peak levels. The increase in Hp levels was statistically significant at the 10th day ($p < 0.05$) (Table 2).

The mean h-CRP levels were also elevated on the 1st day and reached to a peak level on the 3rd day ($p < 0.0001$) and then started to decrease below the baseline level on the 10th day after stroke ($p < 0.05$). The basal levels of complement elements (C3 and C4) in AIS group were at the same level as the control group, however C3

TABLE 1. *Several demographic and clinical features of AIS and control groups*

| | AIS | Control | *p* |
|---|---|---|---|
| *n* | 53 | 53 | - |
| Age (years) | 64.7 ± 11.7 | 61.6 ± 5.7 | NS |
| Gender (M / F) | 19/34 | 21/32 | NS |
| Smoker | 13 (25%) | 12 (23%) | NS |
| BMI (kg/m$^2$) | 24.8 ± 3.5 | 25.6 ± 4.7 | NS |
| Diabetes mellitus | 10 | 0 | - |
| Systolic BP (mmHg) | 141 ± 21 | 122 ± 13 | $p < 0.0001$ |
| Diastolic BP (mmHg) | 86 ± 13 | 78 ± 5 | $p < 0.0001$ |
| Heart rate (bpm) | 92 ± 23 | 75 ± 8 | $p < 0.0001$ |
| Total cholesterol (mg/100 ml) | 184 ± 41 | 194 ± 35 | NS |
| Triglycerides (mg/100 ml) | 148 ± 77 | 144 ± 75 | NS |
| HDL (mg/100 ml) | 38 ± 9 | 44 ± 8 | $p < 0.001$ |
| LDL (mg/100 ml) | 127 ± 92 | 123 ± 34 | NS |
| Glucose (mg/100 ml) | 158 ± 81 | 90 ± 8 | $p < 0.0001$ |
| hCRP (mg/100 ml) peak | 43.6 ± 56.7 | 1.4 ± 1.2 | $p < 0.0001$ |
| Haptoglobin (g/l) peak | 2.41 ± 0.93 | 1.26 ± 0.37 | $p < 0.0001$ |
| Ceruloplasmin (mg/100 ml) | 34 ± 7.4 | 28.6 ± 5.9 | $p < 0.0001$ |
| Fibrinogen (mg/100 ml) | 4.3 ± 0.8 | 3.1 ± 0.3 | $p < 0.0001$ |
| C3 peak | 135 ± 20 | 113 ± 12 | $p < 0.0001$ |
| C4 peak | 26.6 ± 5 | 21 ± 3.9 | $p < 0.0001$ |

NS, non significant; AIS, acute ischemic stroke; BMI, body mass index; BP, blood pressure; M, male; F, female; BP, blood pressure; hCRP, high sensitive C-reactive protein.

TABLE 2. *The course of acute phase proteins (APPs) during acute phase of stroke in AIS group*

| APP | Day 1 | Day 3 | Day 5 | Day 10 |
|---|---|---|---|---|
| h-CRP (mg/l) | 21 ± 28 [a] | 43.6 ± 56.7 [b,c] | 24.2 ± 36.2 | 9.3 ± 9.4 |
| Haptoglobin (mg/100 ml) | 193.6 ± 87.3 [d] | 208.9 ± 94.5 | 231.5 ± 92.9 | 241.6 ± 93.1 |
| Ceruloplasmin (mg/100 ml) | 32.1 ± 5.6 | 32.9 ± 5.6 | 34 ± 7.5 | 33.4 ± 5 |
| Fibrinogen (mg/100 ml) | 412.1 ± 67.9 | 429.2 ± 77.6 | 423.1 ± 77.8 | 396.8 ± 85 |
| C3 (mg/100 ml) | 112.4 ± 15.9 [e] | 134.8 ± 19.8 [g] | 132.9 ± 20.6 [f] | 122 ± 13.3 |
| C4 (mg/100 ml) | 22.1 ± 5.1 [d,e] | 26.3 ± 5.8 | 26.6 ± 5 | 25.1 ± 4.4 |

AIS, acute ischemic stroke; h-CRP, high sensitive C-reactive protein; C3, complement 3; C4, complement 4.

[a] $p < 0.005$ day 1 vs 3, [b] $p < 0.0001$ day 3 vs 10, [c] $p < 0.05$ day 3 vs 5, [d] $p < 0.05$ day 1 vs 10, [e] $p < 0.0001$ day 1 vs 3 and 5, [f] $p < 0.05$ day 5 vs 1 and 10, [g] $p < 0.002$ day 3 vs 10.

and C4 values reached to peak levels on the 3rd and 5th days, respectively with a statistically significant difference from the baseline level. ($p < 0.0001$) (Table 2).

All of the other APPs demonstrated a positive correlation with h-CRP. (Fig. 1)

## DISCUSSION

The results of this study corroborated the fact that strong inflammatory response occurs in

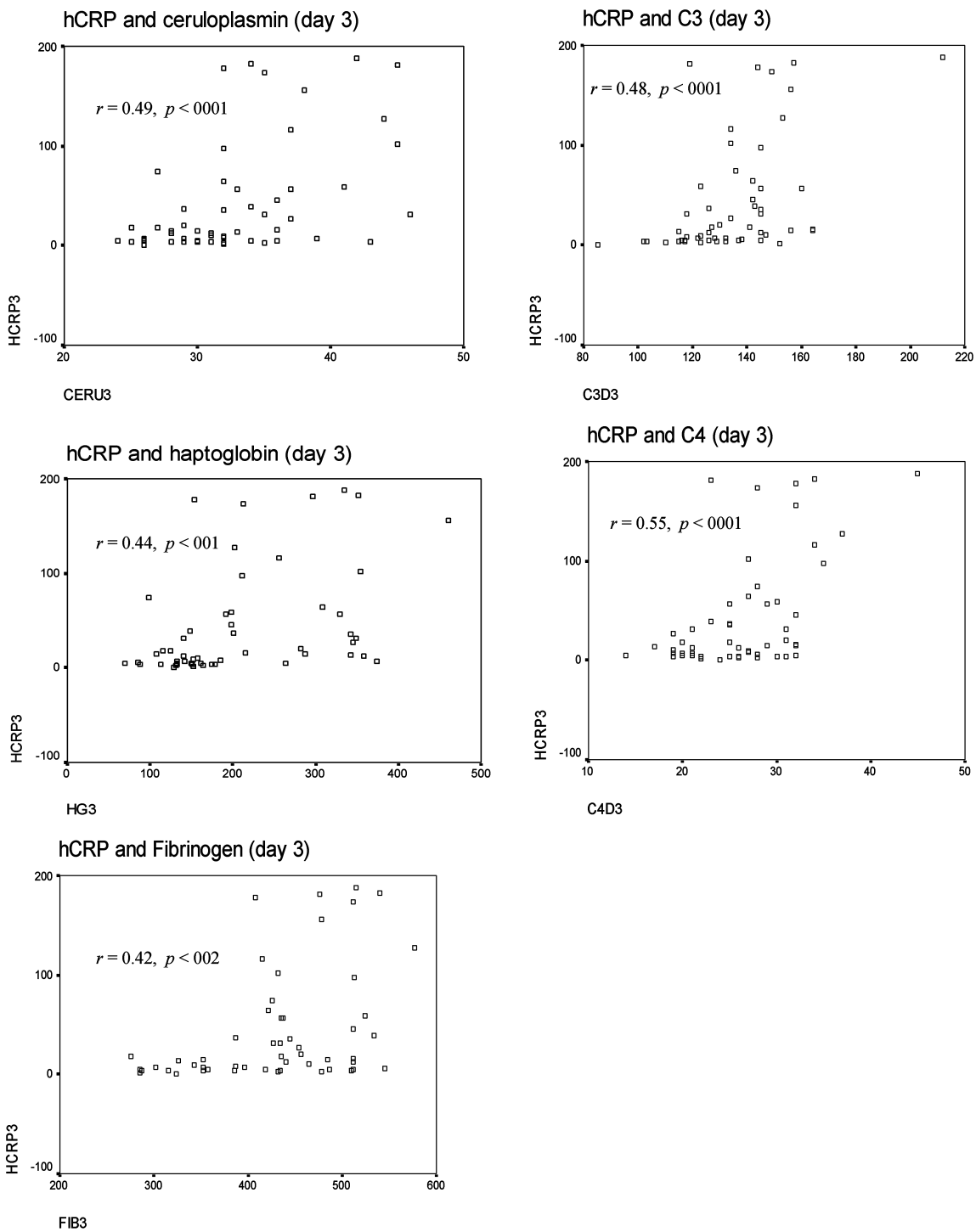


Fig. 1. The correlations between plasma levels of high sensitive C-reactive protein (hCRP) and plasma levels of haptoglobin, ceruloplasmin, fibrinogen, C3 and C4 on third day after ischemic stroke in AIS group.

HCRP3, plasma level of hCRP on third day after stroke; FIB3, plasma level of fibrinogen on third day after stroke; HG3, plasma level of haptoglobin on third day after stroke; C4D3, plasma level of complement 4 on third day after stroke; C3D3, plasma level of complement 3 at third day after stroke; CERU3, plasma level of ceruloplasmin on third day after stroke; AIS, acute ischemic stroke.

the acute phase of ischemic stroke as the peak plasma levels of six APPs studied (i.e., h-CRP, fibrinogen, C3, C4, Cp and Hp) were significantly higher than levels in the control group. Similar to our findings, in several previous studies (Muir et al. 1999; Di Napoli et al. 2001b; Pedersen et al. 2004) baseline or peak levels of several different APPs were found to be significantly higher than control groups. CRP, fibrinogen, complement levels are consistently found to be elevated in acute ischemic stroke cases as well as several other APPs (i.e., TNF, alpha-1 antitrypsin, alpha-1 glycoprotein) (Kargman et al. 1998; Intiso et al. 2004).

The close association between inflammation and mortality in acute vascular diseases (i.e., acute myocardial infarction and stroke) are clearly known (Di Napoli et al. 2000; Winbeck et al. 2002). Thus, the serial determination of inflammatory predictors in patients developing acute vascular disorders would be beneficial for follow-up and redirecting the treatment. The fact that the dynamics of the increases in level of APPs change from one protein to another based on the properties of the relevant APP should be kept in mind in evaluating the changes in these APPs (Bartosik-Pjusek et al. 2003). Nevertheless it is also clear that this finding could guide us planning a suitable timetable to check the appropriate APP in an effort for predicting prognosis in stroke cases.

In our study, the plasma levels of h-CRP, fibrinogen reached their peak levels in 3rd day of observation. In parallel to our findings, Bartosik-Pjusek et al. (2003) also reported that the plasma levels of CRP and fibrinogen were highest on the third day after stroke. CRP is generally considered as the major influencing factor and the first acting APP in the acute phase of stroke (Di Napoli et al. 2000). In the current study, significant positive correlation between h-CRP and all of the 5 other APPs (Fig. 1) might be a reflection of the close relationship between the initial APP and other APPs studied. Mainly fibrinogen and CRP are suggested to have a close relationship as inflammatory markers in the acute phase of ischemic stroke (Reganon et al. 2003). Tohgi et al. (2000) reported that during the acute episode of thrombotic stroke patients, plasma fibrinogen significantly correlated with CRP levels. We also found a positive correlation between these two APPs ($p < 0.002$). Another finding of our study was the pattern of change in fibrinogen levels. In the present study, after stroke the increase in fibrinogen levels reached their peak level at third day as a part of the acute inflammatory response, then started to decline with insignificant differences between levels measured on different days. Interestingly this pattern of change is similarly presented in a recent study with an observation period of 7 day (Bartosik-Pjusik et al. 2003). Fibrinogen is considered as an APP at the interface between inflammation and coagulation and is found to be an independent stroke risk factor, which remains persistently elevated after stroke in association with an increased risk of further vascular events (Wilhelmsen et al. 1984; Beamer et al. 1998).

CRP is a possible activator of the classical complement pathway playing a crucial role in tissue damage (Di Napoli et al. 2001b). The increase in systemic complement activation contributes to the inflammatory process and tissue damage both in brain and in remote organs after ischemic stroke. Di Napoli et al. (2001c) reported that patients with activated complement system, as detected by total C3 and C4 serum levels, had significantly higher morbidity or mortality rate regarding vascular events. In our AIS group, C3 significantly increased to their highest level at third day after stroke. After that day, C3 levels decreased steadily. Despite this decrease, the plasma levels were still significantly higher than the baseline level. The similarity in the pattern of changes in plasma levels of h-CRP and C3; and the significant correlations between these APPs in our sample supported the previous data suggesting a possible role for CRP in inducing complement activation.

Hp is a plasma glycoprotein involved in the acute phase response to inflammation (Kushner 1982). In a recent study (Engström et al. 2002), the increase in Hp plasma levels in presence of hypercholesterolemia are shown to substantially increase the risk of ischemic stroke and cardio-

vascular death. Additionally, Hp is found to constitute a novel marker of adiposity in humans which might be a possible risk factor for ischemic stroke (Chiellini et al. 2004). In our study, the plasma levels of Hp presented a steady increase from the first day, reaching its peak level at the 10th day with statistical significance. Kargman et al. (1998) in a sample of 19 acute stroke patients, reported that Hp levels reached a peak about 2 weeks after the stroke. This finding is similar with ours, if the time schedule of acquiring of blood sample in that study (at day 3, week 1 and week 2) is considered. But still there is limited data about the relationship between Hp levels and outcome after ischemic stroke.

We also investigate Cp levels as another APP for stroke. In our sample, Cp levels were significantly higher than control group supporting its role as an indicator of inflammation in stroke patients. It reached to a peak level at fifth day after stroke, but the changes in concentration levels were insignificant. In literature there are consistent reports marking the relationship between serum Cp levels and atherosclerosis and other cardiovascular diseases (Fox et al. 2000). However this has not been established for the association between Cp and acute stroke yet. In an epidemiological study, Reunanen et al. (1992) reported that high serum Cp levels were significantly associated with higher future odds of myocardial infarction but not of stroke. In a recent study however, higher Cp levels as a part of inflamation sensitive proteins are shown to increase relative risk of developing stroke (Engström et al. 2002). In the current study, the increase in the plasma levels of Cp in ischemic stroke and its association with other APPs, especially CRP, indicated that Cp could be an important parameter for AIS.

There are several limitations in this study that should be borne in mind while evaluating its results. This is a relatively small cohort study. As the stroke subtype (i.e., thrombotic, cardioembolic and lacunar subtypes) is not considered in our study, it is likely that the changes of APPs studied may not represent the response to infarct itself or atherosclerosis of the major vessels. It may be a response to the facilitated clot formation/ fibrinolysis in the heart, hemorrgahic transformation or some other processes. Additionally, the stroke volume is not considered in this study which also restricts the usefulness of our data.

In conclusion, all APPs studied in this study (i.e., h-CRP, C3, C4, fibrinogen, Hp, CP) were significantly higher than the baseline levels of the control patients, supporting the importance of inflammation processes after stroke. We suggest that the differences in the levels of APPs could be used in predicting the outcome of stroke patients.

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