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Clinical significance of acute phase reaction in stroke patients

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1. ABSTRACT

Acute cerebral ischemia triggers interleukin-6 (IL-6) release into cerebrospinal fluid and blood. IL-6 induces synthesis of the acute phase proteins (APPs) in the liver. Higher blood IL-6 level in stroke patients is associated with larger infarct size, greater neurological deficit on admission, early neurological worsening, and increased risk of death or poor functional outcome. The level of C-reactive protein (CRP), the major APP in man, rises in blood during acute stroke reaching maximal values between 5 and 7 day after stroke onset. Elevated CRP level in acute ischemic stroke predicts unfavorable outcome and is associated with increased risk of recurrent stroke or other cardiovascular events. Increased level of fibrinogen, another APP, is associated with worse outcome in patients with ischemic stroke. The acute phase reaction accompanies also intracerebral hemorrhage. Serum IL-6 and CRP level increases in the first days after intracerebral hemorrhage. Plasma IL-6 is independently associated with hematoma enlargement and fibrinogen level predicts early neurological deterioration and outcome in patients with intracerebral hemorrhage.

2. INTRODUCTION

The acute phase response (APR) is the prominent systemic reaction of the organism to disturbances in its homeostasis caused by infection, trauma, tissue injury, various immunological conditions, physical and psychological stress, and cancer (1, 2). The initiation of the APR is triggered by the release of pro-inflammatory cytokines. Interleukin-6 (IL-6) is the chief stimulator of acute phase proteins (APPs) production. In man interleukin-1 and oncostatin M are also powerful stimuli for APPs synthesis. Other cytokines (tumor necrosis factor alpha, interleukin-11, leukemia inhibitory factor, ciliary neurotrophic factor) modulate the APR. The APR is associated with rearrangement of plasma protein synthesis by the liver. An APP has been defined as one whose plasma level increases (positive APPs) or decreases (negative APPs) by at least 25% during inflammatory disorders. The major human APPs include C-reactive protein (CRP) and serum amyloid A (SAA) whose concentration could rapidly increase of up to 1000-fold. After appropriate stimulus, serum CRP concentrations begin to rise by about 6 hours and peak around 48 hours. Human CRP, member of the

pentraxin family of plasma proteins, binds with high affinity to phosphocholine and thus recognizes a variety of ligands including external components of foreign pathogens, damaged cell membranes and apoptotic cells. CRP can participate in elimination of pathogens or injured cells by activation of the classic and alternative complement pathway. It could also modulate the immune response acting as pro- or anti-inflammatory mediator. The role of SAA during APR is still poorly understood. This protein could influence the cholesterol level during inflammatory reaction by binding to high-density lipoprotein. Complement components (C3, C4), coagulation and fibrinolytic system proteins (fibrinogen, plasminogen, protein S), antiproteases (alpha1-antichymotrypsin), transporter proteins (ceruloplasmin, haptoglobin), alpha1-acid glycoprotein and several others belong to positive APPs whereas albumin, transferrin and transthyretin are examples of negative APPs.

Stroke triggers an inflammatory reaction that involves the injured brain, but could also induce systemic APR. This review discusses the clinical significance of the APR in human stroke focusing on IL-6, CRP and fibrinogen.

3. TEMPORAL COURSE OF ACUTE PHASE PROTEINS DURING STROKE

Many studies demonstrated the higher serum/plasma level of IL-6 and CRP in patients with acute stroke compared to persons without stroke (3-13). IL-6 and CRP level could increase during stroke, however, temporal course of these proteins was different in different studies. In one of the earliest study investigating the APR after stroke, Fassbender *et al.* measured serum IL-6 level in 19 ischemic stroke patients without pre-existing infection admitted to the hospital within 4 hours after symptoms onset (14). They observed a significant increase in the levels of IL-6 on hours 6, 8, 10, 14 and days 1, 3 and 5 compared to IL-6 concentrations measured 4 hours after symptoms onset. On day 7 levels did not differ significantly from those obtained initially at hour 4. In the study of Tarkowski *et al.* serum IL-6 level was significantly higher in stroke patients compared with healthy controls during the whole observation period (day 0, 1, 2, 3, 7-9, 21-26, >90), however, it did not display any distinct time-related variation in contrast to changes in cerebrospinal fluid where IL-6 peak level was observed on days 2 and 3 (3). Szczudlik *et al.* measured serum IL-6 level in 22 patients with ischemic stroke and 17 controls (10). Serum samples were collected on the 2nd day of stroke at 6:00, 10:00, 18:00, 22:00 h and at the same time points in control group. Serum IL-6 levels were significantly higher in stroke patients than in controls in each time point. Three months after stroke IL-6 concentrations did not differ significantly between groups. Ferrarese *et al.* measured serum IL-6 level and IL-6 bioactivity in supernatants of blood cells stimulated with lipopolysaccharide (6). Blood samples were obtained from 40 stroke patients (including 11 patients with hemorrhagic lesions) without infections and 20 healthy controls. They found elevated IL-6 level in serum of stroke patients at all time points (days 1-2, 4, 10, 30, 90) compared to controls. Moreover the release of IL-6 from blood cells stimulated *in vitro* was significantly higher in stroke patients than in control group until 1 month after stroke onset. In study of Acalovschi *et al.* serum IL-6 significantly rose in ischemic stroke patients without infections in the first 24 hours after stroke onset whereas CRP showed a significant increase on days 3 and 7 (9). Emsley *et al.* studied the changes in IL-6 and CRP in 36 patients with ischemic stroke admitted within 12 hours after stroke symptoms onset and 36 control subjects matched not only for age and sex, but also for degree of atherosclerosis (8). In that study CRP level was significantly higher on admission and remained elevated until 3 months compared to control group. CRP level was higher in patients sampled 4-12 hours after stroke onset than in those sampled 0-4 hours. The greatest elevation of CRP occurred at days 5-7. An increase in plasma CRP after the admission sample was evident in 94% of patients by day 5 to 7 and plasma CRP increased by >25% of the admission value was observed in 90% of patients (15). There was no significant difference in CRP concentration measured in stroke patients 12 months after stroke compared to controls. An increase in plasma IL-6 concentration was seen on next day after admission and this elevation did not persist beyond 5-7 days. When patients with evidence of infections were excluded there was no difference in IL-6 level between groups. Seventy-seven percent of patients showed any increase in plasma IL-6 after the admission sample and an increase >25% of the admission value by day 5 to 7 was seen in 61% of patients. In the study of Taman *et al.* plasma CRP level was elevated in stroke patients on day 1, reached a peak on day 3 and started to decrease on the day 10 after stroke (13). Di Napoli *et al.* noted that the levels of CRP in ischemic stroke patients changed between admission and discharge from the hospital. Different patterns were observed: persistently normal value in 19.5% of all patients (N=128), increasing values in 6.3%, decreasing values in 28.1%, and persistent elevation in 46.1% (16). Winbeck *et al.* measured CRP level in 127 consecutive patients with a first ischemic stroke without recent infection (17). CRP was measured on admission <12 hours, within 24 hours and within 48 hours after symptoms onset. The mean CRP concentration increased significantly during the first 48 hours after symptom onset. In 13% of patients the CRP concentration decreased and in 49% of patients the CRP concentration increased within 24 hours after symptoms onset. Marquart *et al.* measured plasma CRP level in 50 patients with acute ischemic stroke and in 30 healthy control subjects and 20 controls matched for stroke risk factors (12). The majority of patients suffered from mild stroke. First sample was taken 16±4.3 hours after stroke onset. CRP level measured on days 1, 14 and 90 was higher in stroke patients compared to healthy controls but not to risk factors control subjects. 'Normal' CRP value was found in 38% of patients on days 1 and 90. Christensen and Boysen observed the significant CRP increase within 24 hours after admission only in patients with severe stroke but not in those with mild or moderate stroke (18). Similarly Elkind *et al.* found no evidence of time trend of CRP in 21 patients with mild ischemic stroke, however, CRP level in these patients was higher than in 1776 stroke-free subjects from the same community (19). In the study of Audebert at al. successful thrombolysis reduced CRP

concentrations on days 3 to 5 (20). Beamer *et al.* investigated the changes of APPs during 1 year after stroke (21). In that study IL-6 and CRP levels declined gradually after stroke. Longitudinal concentrations of both IL-6 and CRP were markedly elevated compared with healthy elderly but not compared with risk factors group.

Increased level of interleukin-6 in blood was also observed in patients with intracerebral hemorrhage (5, 6, 22). CRP level rose significantly during first 24 hours in most of patients with intracerebral hemorrhage (Dziedzic *et al.*; unpublished observation).

The results of studies measured the kinetics of fibrinogen during stroke are not unequivocal. Some researchers found higher level of fibrinogen in acute stroke patients compared to stroke-free control group (9, 12, 13). In the study of Beamer *et al.* levels of fibrinogen were elevated up to 1 year after acute stroke compared to healthy control subjects (21). In some studies fibrinogen level rose during stroke course (12) whereas in other studies no evidence of time trend was seen (13, 19).

The concentration of interleukin-1, the protein involved in regulation of the APR, increased significantly in cerebrospinal fluid on the 3rd day after stroke onset and then dropped successively during the following days (3). The increased production of this protein was observed only in patients with major stroke. Serum interleukin-1 level did not change significantly during stroke and was similar to this cytokine level in control group.

Several issues should be taken into account when one interprets the results of above mentioned studies. First, the increase of CRP and IL-6 concentration is determined largely by the intensity of ischemia. Second, several factors could confound the results of human studies. The important group of factors significantly elevating IL-6 and CRP level constitutes vascular risk factors and diseases: hypertension, diabetes mellitus, obesity, smoking, coronary artery disease. On the other hand different drugs (aspirin, statins, ACE-inhibitors) used in stroke patients could potentially reduce IL-6 and CRP level. When a stroke patient group is compared with healthy subjects, it is difficult to separate the changes in IL-6 and CRP level triggered by stroke from those related to the vascular risk factors and medications (23). Third, infections prior to stroke onset and nosocomial infections during hospitalization elevate the levels of APPs. Fourth, time of samples collection after stroke is a critical factor in analysis of kinetics APPs. Fifth, genetic factors could influence the level of APPs during stroke (9,24). Sixth, the significance of inflammatory process in stroke patients may depend on stroke etiology. Inflammatory reaction by promoting atherosclerosis may be particularly linked to stroke caused by large artery disease.

4. RELATIONSHPI BETWEEN ACUTE PHASE PROTEINS AND SEVERITY AND COURSE OF STROKE

In numerous studies IL-6 and CRP level correlated with stroke severity measured in different clinical scales (7, 9, 11, 18, 20, 25, 26) and with infarct size (9, 11, 14, 20, 25, 27, 28): higher IL-6 and CRP, greater degree of neurological deficit on admission and larger infarct volume. In the study of Ferrarese *et al.* serum interleukin-6 was unrelated to stroke size and severity (6). Also Tarkowski *et al.* found no correlation between serum IL-6 level and brain lesion volume measured 2 months or later after stroke (3). In one study serum IL-6 level showed a significant inverse correlation with infarct size measured at days 4-7 (29).

Stroke severity was positively correlated with fibrinogen level measured on days 1, 14, and 90 after stroke (12). In patients with intracerebral hemorrhage serum IL-6 concentration measured on the day 2 after stroke onset was significantly correlated with Glasgow Coma Scale on admission and hematoma volume (22).

Interleukin-6 acts as important endogenous pyrogen. It could also activate hypothalamo-pituitary-adrenal axis. Both hyperthermia and hypercortisolemia are associated with poor outcome in stroke patients. During ischemic stroke plasma levels of IL-6 were significantly higher in the group of patients with hyperthermia than in the normothermic group (30). Blood IL-6 level correlated significantly with cortisol level in stroke patients (10, 31). Also urine albumin excretion, another marker of prognosis in acute ischemic stroke, was related to serum interleukin-6 (32).

In patients with ischemic stroke plasma IL-6 level was an independent factor for early clinical worsening during first 48 hours (27).

In patients with intracerebral hemorrhage high fibrinogen and IL-6 levels were associated with early growth of hematoma (33). Moreover, serum fibrinogen level >523 mg/dL was also associated with early neurological deterioration (34).

5. ACUTE PHASE PROTEINS AND OUTCOME AFTER STROKE

Multiple studies demonstrated that CRP concentrations are predictive of future cardiovascular events, death, and poor functional outcome in stroke patients. Muir *et al.* showed that CRP is an independent predictor of survival after ischemic stroke (35). The study group consisted of 228 consecutive ischemic stroke patients. CRP level was measured within 72 hours after symptoms onset (in most patients within 24 hours). Median follow-up was 959 days. Survival in those with CRP>10.1 mg/L was significantly worse than in those with CRP≤10.1 mg/L. Cardiovascular disease accounted for 76% of deaths in those with CRP>10.1 mg/L and 63% of deaths in those with CRP≤10.1 mg/L. Higher CRP concentration was an independent predictor of mortality (HR: 1.23, 95%CI: 1.13 – 1.35).

Di Napoli *et al.* observed 128 patients with first-ever ischemic stroke (36). They excluded patients with history of recent clinical infection. CRP and fibrinogen

level was measured within 24 hours after symptoms onset. Primary end point was a combination of death of any cause and any new nonfatal vascular events (transient ischemic attack, myocardial infarction, unstable angina) during the 1-year follow-up. The probability of end point rose with tertiles of CRP and fibrinogen. In multiple logistic regression analysis higher CRP level, but not fibrinogen level, was independently associated with an end point. Both CRP on admission and CRP at discharge were predictors of the end point, however, CRP at discharge was the stronger marker of adverse outcome. In the next study the same researchers confirmed their own results on larger group of patients (37).

Winbeck *et al.* have found a significant higher rate of death and new cardiovascular events in stroke patients with CRP concentration ≥0.86 mg/dL measured within 24 hours after correction for other risk factors (17). CRP levels measured within 24 hours and within 48 hours, but not within 12 hours after symptoms onset, were associated with unfavorable functional outcome (Barthel Index <85) after 1 year.

Elkind *et al.* conducted the prospective study investigating the relationship between CRP and long-term outcome in 476 patients with first ischemic stroke (26). CRP level was measured in most of patients within 72 hours after symptoms onset. Median follow-up was 4 years. After adjusting for confounders CRP was associated with risk of death (adjusted HR: 2.11, 95%CI: 1.18 – 3.75), but not with risk of recurrent stroke or myocardial infarction.

In the study of Christensen and Boysen, CRP level correlated significantly with stroke outcome measured in modified Rankin Scale 3 months and 1 year after stroke (18). Higher CRP was associated with poorer functional outcome. In multivariate logistic regression analysis CRP concentration >10 mg/L was independently related to 1-year mortality.

In the retrospective study, Ceccarelli *et al.* demonstrated that CRP level measured within 12 hours after stroke onset in 288 elderly patients correlated with 30-day mortality, disability at discharge, and the rate of re-hospitalization for secondary stroke (38).

Anuk *et al.* have found a significant correlation between CRP measured within 24 hours after stroke symptoms onset and neurological deficit determined by modified Rankin Scale 8-12 months after stroke (39).

CRP predicts further ischemic events (brain infarction, transient ischemic attack, myocardial infarction) in first-ever transient ischemic attack or stroke in patients with intracranial large-artery occlusive disease (40).

Silvestri *et al.* studied the population of 647 consecutive elderly patients with ischemic stroke and presence of >50% stenosis of common or internal carotid artery (41). Plasma IL-6 and CRP levels were measured within 12 hours of admission. IL-6 and CRP on admission were predictors of future in-hospital and 3-months cerebrovascular events. IL-6 level was a stronger predictor of new cerebrovascular events than CRP. High CRP and IL-6 levels at baseline were not associated with poor 1-year prognosis.

Plasma fibrinogen level was predictive of vascular events in both stroke group and risk factors group and remained independently significant in a multivariate model only for stroke patients (21). Elevated fibrinogen level measured within 48 hours after stroke symptoms onset was associated with increased risk of death during 1 year after stroke (42).

On univariate analysis blood IL-6 level measured in acute stroke correlated with less favorable prognosis assessed in modified Rankin Scale or Barthel Index 3 or 12 months after stroke (7, 11, 25, 28).

In patients with medium to large spontaneous supratentorial intracerebral hemorrhage lower fibrinogen and CRP levels were associated with good outcome defined as modified Rankin Scale ≤2 at 3 months and on multivariate analysis fibrinogen concentration remained independent predictor of outcome (43).

6. PERSPECTIVE

Taking together the APR accompanies acute stroke and increased level of APPs in acute stroke is related to poor prognosis. It is still unknown why CRP and other APPs concentrations are predictive of outcome. Their concentrations could reflect both the degree of stroke severity and the burden of atherosclerotic lesions. In myocardial infarction CRP deposits are found within necrotic tissue and co-localized with complement components (2). In the rat model of myocardial infarction, the size of infarction is determined by complement mediated inflammation. It is unknown if CRP is also an active player in tissue destruction in human stroke.

Some drugs used in stroke patients (aspirin, statins, angiotensin converting enzyme inhibitors) could decrease level of IL-6 and CRP, however, it is unclear if attenuation of inflammatory response could be beneficial for stroke patients. In one study concomitant treatment with angiotensin converting enzyme inhibitors at the time of acute stroke was associated with lower CRP level and better long-term outcome (44).

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Abbreviations: IL-6: interleukin-6; CRP: C-reactive protein; APR: acute phase response; APP: acute phase protein; SAA: serum amyloid A

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