High-sensitivity C-reactive protein, lipoprotein-related phospholipase A2, and acute ischemic stroke

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Background: Serum biomarkers may be useful for early diagnosis of acute ischemic stroke, exclusion of other diseases that may mimic stroke, and prediction of infarct volume. We evaluated serum high-sensitivity C-reactive protein (hs-CRP) and lipoprotein-related phospholipase A2 (Lp-PLA2) in patients who had acute ischemic stroke.

Methods: In 200 patients who presented to an emergency service (acute ischemic stroke, 102 patients; control with no stroke, 98 patients), stroke patients were evaluated with the Canadian neurological scale and diffusion-weighted magnetic resonance imaging, and all patients were evaluated with the Glasgow coma scale and their serum hs-CRP level and Lp-PLA2 activity were assessed. The volume of stroke lesions was calculated from magnetic resonance images.

Results: Patients who had stroke had higher mean serum hs-CRP level (stroke, 7±6 mg/dL; control, mean ± standard deviation 1±1 mg/dL; P≤0.001) and Lp-PLA2 activity (stroke, mean ± standard deviation 113±86 nmol/min/mL; control, mean ± standard deviation 103±50 nmol/min/mL; P≤0.001) than control patients who did not have stroke. The mean hs-CRP level and Lp-PLA2 activity were higher in patients who had greater stroke severity (lower Canadian neurological scale score) and were higher in patients who had larger volume strokes.

Conclusion: Higher hs-CRP level and Lp-PLA2 activity are significantly associated with more severe neurologic impairment and larger infarct size in patients who have acute ischemic stroke. These biomarkers may be useful for rapid diagnosis and prediction of ischemic tissue volume in the early stage of ischemic stroke. These findings may be important for health care facilities that have limited access to emergency computed tomography scanning for the diagnosis of stroke.

Keywords: cerebrovascular accident, atherosclerosis, inflammation, biomarker

Introduction

Acute ischemic stroke is caused by sudden interruption of cerebral blood flow. The causes of acute ischemic stroke in most patients who have severe symptoms include embolic or thrombotic occlusion (70% to 80% of patients).1 Despite developments in treatment, acute ischemic stroke still is a leading cause of morbidity, mortality, and economic burden on society. Therefore, it is important to prevent acute ischemic stroke by determining and modifying risk factors. It is also important to minimize the duration from onset of symptoms to treatment to ensure effective reperfusion in patients who have acute ischemic stroke.

A major obstacle for patients suspected of having acute ischemic stroke is that diagnostic evaluation may not be provided quickly.2,3 Diagnosis and treatment of small
strokes may be delayed because symptoms may be absent. Computed tomography (CT) has low sensitivity and specificity in the early stage of acute ischemic stroke. Although CT or magnetic resonance imaging (MRI) of the brain can be performed within 30 minutes, enabling diagnosis in the early stage of acute ischemic stroke, these imaging methods require an experienced team and technical equipment that are not available in many hospitals in our country.4

Thrombolytic treatment with tissue plasminogen activator within 3 hours after early diagnosis of acute ischemic stroke may decrease patient mortality and improve quality of life. Thrombolytic treatment is more effective in younger patients who have low National Institutes of Health stroke scale score and low infarct volume in diffusion-weighted imaging.5 Early diagnosis and calculation of infarct volume are important in assessing suitability of thrombolytic therapy, and only 2% to 6% of patients diagnosed with acute ischemic stroke may be treated with tissue plasminogen activator.6

Acute ischemic stroke is diagnosed with physical examination, CT scan, and MRI scan. Missed diagnosis and delayed treatment may occur because the specificity and sensitivity of CT scanning are low in the early stage of acute ischemic stroke, and CT and MRI scans are not available in many health care facilities. Therefore, diagnostic serum biomarkers may be useful for early diagnosis of acute ischemic stroke, exclusion of other diseases that may mimic stroke, and prediction of infarct volume.

Inflammation may cause atherosclerosis and plaque rupture that may cause myocardial infarction and acute ischemic stroke.7 High-sensitivity C-reactive protein (hs-CRP) and other serum inflammatory markers may be helpful in predicting carotid atherosclerosis and acute ischemic stroke. Lipoprotein-related phospholipase A2 (Lp-PLA2) is a proinflammatory enzyme that may hydrolyze oxidized phospholipids and cause the release of lysophosphatidylcholine.8 High hs-CRP level and Lp-PLA2 activity may be complementary to established risk factors for the development of stroke.9,10

The purpose of the present study was to evaluate serum hs-CRP level and Lp-PLA2 activity in patients who had acute ischemic stroke and determine whether these factors may predict ischemic tissue volume.

Materials and methods

Study design

Patients who presented to Selçuk University School of Medicine Hospital Emergency Service from June 2012 to August 2013 were considered for inclusion in this prospective study when they presented within 24 hours after onset of symptoms, were aged >18 years, and had findings in the initial history and physical examination that were consistent with acute ischemic stroke. The 102 patients who were included in the study group were diagnosed with acute ischemic stroke with diffusion-weighted MRI performed within 24 hours after presentation. The 98 patients who were included in the control group had presented to the emergency service with various complaints; were evaluated with physical examination, laboratory tests, and imaging studies; and were diagnosed with conditions other than acute ischemic stroke. Patients were excluded for cerebral hemorrhage, subdural hematoma, space-occupying lesion, cerebrovascular damage caused by trauma (detected on CT images performed in the emergency service), symptoms of infection, immunologic disease, malignancy, or pregnancy. All stroke and control patients gave informed consent before enrollment in the study. The study was approved by the Selçuk University School of Medicine Research Ethics Committee.

Evaluation

Patients who had acute ischemic stroke were evaluated with physical examination, neurologic examination, Glasgow coma scale, and Canadian neurological scale. The Glasgow coma scale was determined for patients in the control group, but the more detailed Canadian neurological scale was not determined for control patients. Severity of impaired level of consciousness was rated with the Glasgow coma scale score as mild (15), moderate (8 to 14), or severe (3 to 7). Severity of impaired neurologic status was rated by Canadian neurologic scale score as mild (8.5 to 10), moderate (2.5 to 8), or severe (0 to 2). In addition to routine laboratory tests such as biochemistry tests and complete blood count, the stroke and control patients were tested for hs-CRP level, Lp-PLA2 activity and underwent a 12-lead electrocardiogram.

Biochemistry

Blood samples were collected in plain plastic tubes during the emergency service admission. After standing for 30 minutes, the blood samples were centrifuged for 5 minutes at 3,000 rpm. The sera were separated and allocated to tubes (Eppendorf, Hamburg, Germany) and stored at −80°C until assay. The Lp-PLA2 activity was determined with a commercial kit (DiaDexus, South San Francisco, CA, USA) and analyzer (Architect C8000; Abbott Laboratories, Abbott Park, IL, USA). Calibration and control procedures were performed, samples were dissolved, and enzyme activity (nmol/min/mL) was determined from absorbance at
412 and 524 nm. Serum Lp-PLA$\text{}_{2}$ activity was defined as low (<100 nmol/min/mL), medium (100 to 150 nmol/min/mL), or high (>150 nmol/min/mL).

The hs-CRP level was determined with a commercial kit (Abbott Laboratories) and analyzer (Architect C8000; Abbott Laboratories). After the samples were dissolved, a commercial test was performed (Denka Seiken, Tokyo, Japan) and validated by a commercial method (Dade Behring; Siemens Healthcare, Erlangen, Germany) and analyzed with a spectrophotometric method. The hs-CRP level was reported in mg/dL (reference range <0.5 mg/dL). Plasma hs-CRP level was defined as low (<3 mg/dL), medium (3 to 15 mg/dL) or high (>15 mg/dL). The assays were performed at the Selçuk University School of Medicine Biochemistry Laboratory.

**Imaging**

MRI scans were performed with a 1.5-T scanner (Aera; Siemens Healthcare). Diffusion-weighted imaging was performed with single-shot, echo-planar imaging (TE, 89 ms; TR, 6,300 ms; matrix, 128×128; b values, 0 and 1,000 seconds/mm$^2$; slice thickness, 5 mm; gap, 1 mm; 20 slices). All MRI data were analyzed by an experienced radiologist who was blinded to clinical and laboratory information about the patients and location and number of hyperintensities on diffusion-weighted imaging. The lesion volumes were calculated off-line after the images were transferred to an image postprocessing software package (syngo Via, Siemens Healthcare). The areas of diffusion hyperintensity were drawn manually by two observers, and the volume was determined by multiplying the areas of diffusion hyperintensity by the interslice gap. Infarcts were classified as nonlacunar or lacunar.

**Statistical analysis**

Data analysis was performed with statistical software (SPSS Statistics for Windows, version 20.0; IBM Corporation, Armonk, NY, USA). Data were evaluated with descriptive statistics, variance components analysis, and $\chi^2$ test. Average results were reported as mean ± standard deviation. Differences between the groups were analyzed with one-way analysis of variance. In addition, differences between stroke and control patients were assessed with cross tabulation and $\chi^2$ test. Statistical significance was defined by $P\leq0.05$.

**Results**

The patients who had or did not have stroke had similar sex, mean age, Glasgow coma scale score, and systolic blood pressure (Table 1). Patients who had stroke had higher mean

| Table 1 Demographic and clinical characteristics of patients who had or did not have stroke |
|---------------------------------------------|
| **Characteristic** | **Stroke** | **Control** | **P-value** |
| Number of patients | 102 | 98 |  |
| Sex, male | 58 (57) | 45 (46) | NS |
| Age (years) | 68±14 | 64±15 | NS |
| Glasgow coma scale | 14±2 | 15±2 | NS |
| Canadian neurological scale | 8±3 | Not determined |  |
| Blood pressure (mmHg) | | | |
| Systolic | 138±25 | 130±31 | NS |
| Diastolic | 82±10 | 76±14 | 0.02 |
| Symptoms | | | |
| Walking impairment | 75 (74) | 24 (25) | 0.001 |
| Speech impairment | 54 (59) | 32 (33) | 0.003 |
| Impairment in consciousness | 24 (24) | 15 (15) | NS |
| History | | | |
| Hypertension | 41 (40) | 34 (35) | NS |
| Diabetes mellitus | 24 (24) | 10 (10) | 0.01 |
| Coronary artery disease | 27 (27) | 19 (19) | NS |
| Recurrent stroke | 20 (20) | 13 (13) | NS |
| Electrocardiogram | | | |
| ST segment changes | 39 (38) | 30 (31) | NS |
| Arrhythmia | 37 (36) | 20 (20) | 0.01 |
| Normal sinus rhythm | 27 (27) | 47 (48) | 0.001 |
| Laboratory tests | | | |
| hs-CRP (mg/dL) | 7±6 | 1±1 | 0.001 |
| Lp-PLA$\text{}_{2}$ (nmol/min/mL) | 113±86 | 103±50 | 0.001 |

**Notes:** Data reported as number (%) or mean ± standard deviation. Statistical significance was defined as $P\leq0.05$.

**Abbreviations:** hs-CRP, high-sensitivity C-reactive protein; Lp-PLA$\text{}_{2}$, lipoprotein-related phospholipase A$\text{}_{2}$; NS, not significant ($P>0.05$).
diastolic blood pressure, higher frequency of walking and speech impairment, higher frequency of diabetes mellitus and arrhythmias, and higher mean hs-CRP level and Lp-PLA₂ activity than control patients (Table 1).

Increased severity of neurologic status rated by the Canadian neurological scale was associated with lower mean Glasgow coma scale, larger volume of nonlacunar or lacunar stroke, and higher hs-CRP level and Lp-PLA₂ activity (Table 2). Increased impairment of consciousness rated by Glasgow coma scale was associated with lower mean Canadian neurological scale score and higher hs-CRP level but not infarct size or Lp-PLA₂ level (Table 3). Higher hs-CRP level and Lp-PLA₂ activity were significantly associated with larger volume of nonlacunar and lacunar infarcts, except medium Lp-PLA₂ levels were associated with highest mean volume of lacunar infarcts (Tables 4 and 5).

Discussion

The present results showed that higher hs-CRP level and Lp-PLA₂ activity were significantly associated with more severe neurologic impairment and larger infarct size in patients who had acute ischemic stroke (Tables 2 to 5). These biomarkers may be useful in assessing patients who are suspected of having acute ischemic stroke, especially in the emergency service when thrombolytic treatment is being considered. A widely-used, rapid, and sensitive biomarker for acute ischemic stroke has not previously been available. A specific biomarker that can be detected in blood in the early stages of stroke may facilitate accurate diagnosis in emergency situations, especially in smaller centers that do not have CT or MRI scanners available.

The ideal biomarker for acute ischemic stroke should increase in the early stage, rapidly diffuse into the blood circulation from the ischemic tissue, have a half-life of several hours, and be specific for ischemic nerve tissue. Most (87%) acute strokes are caused by atherothrombotic events. Atherosclerosis, an important and preventable risk factor for acute ischemic stroke, develops after a long asymptomatic period, and the first sign of the presence of atherosclerosis may be an acute event such as myocardial infarction or stroke. Acute ischemic stroke is a preventable disease because risk factors and inhibitors are well described. Inflammation is important in the development of atherosclerosis that precedes an ischemic event. The studies conducted by using protein biomarkers in patients who have ischemic cerebrovascular disease are focused on pathophysiology, diagnosis,

**Table 2** Relationship between neurologic status rated by the Canadian neurological scale and outcome parameters in patients who had acute ischemic stroke

| Parameter                      | Total | Mild | Moderate | Severe | P-value |
|-------------------------------|-------|------|----------|--------|---------|
|                               | Number of patients | Number of patients | Number of patients | Number of patients |         |
| Canadian neurological scale   |       |      |          |        |         |
| Glasgow coma scale            | 102   | 69   | 14;±0.3  | 3      | 11;±4   | 0.001 |
| Nonlacunar infarct volume (mL)| 3     | 23   | 20;±3    | 17     | 51;±6   | 0.05  |
| Lacunar infarct volume (mL)   | 54    | 46   | 3;±3     | 3      | 2;±2    | 0.009 |
| hs-CRP (mg/dL)                | 102   | 69   | 5;±6     | 20     | 8;±6    | 0.001 |
| Lp-PLA₂ (nmol/min/mL)         | 102   | 69   | 96;±88   | 20     | 143;±78 | 0.008 |

Notes: Data reported as number or mean ± standard deviation. Statistical significance was defined as P=0.05.

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; Lp-PLA₂, lipoprotein-related phospholipase A₂.

**Table 3** Relationship between level of consciousness rated by the Glasgow coma scale and outcome parameters in patients who had acute ischemic stroke

| Parameter                      | Total | Mild | Moderate | Severe | P-value |
|-------------------------------|-------|------|----------|--------|---------|
|                               | Number of patients | Number of patients | Number of patients | Number of patients |         |
| Canadian neurological scale   |       |      |          |        |         |
| Nonlacunar infarct volume (mL)| 102   | 76   | 9;±2     | 22     | 6;±3    | 0.4;±0.4 | 0.001 |
| Lacunar infarct volume (mL)   | 54    | 46   | 3;±3     | 7      | 5;±6    | 0.4;±0.4 | 0.001 |
| hs-CRP (mg/dL)                | 200   | 166  | 3;±5     | 28     | 7;±7    | 0.4;±0.4 | 0.001 |
| Lp-PLA₂ (nmol/min/mL)         | 200   | 166  | 134;±71  | 28     | 126;175 | 0.4;±0.4 | 0.001 |

Notes: Data reported as number or mean ± standard deviation. Statistical significance was defined as P=0.05.

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; Lp-PLA₂, lipoprotein-related phospholipase A₂; NS, not significant (P>0.05).
and prognosis of stroke. Therefore, many biomarkers such as basal plasma brain natriuretic peptide, N-terminal probrain natriuretic peptide, cortisol, copeptin, D-dimer, interleukin 18 (IL-18), S100B, hs-CRP, and Lp-PLA₂ have been evaluated for utility in detecting acute ischemic stroke, but there is no globally accepted biomarker available. 

Plasma D-dimer level is increased with higher National Institutes of Health stroke scale score and infarct volume. Levels of IL-18 increase significantly in patients who have acute ischemic stroke, but there is no significant relationship between infarct volume and IL-18 level. In contrast, increase in S100B protein level is associated with increased infarct diameter and poorer prognosis.

Previous studies showed that inflammatory indicators such as hs-CRP and proinflammatory cytokines are associated with early neurologic deterioration or poor functional results after stroke. Inflammatory processes likely contribute to cerebral ischemia, and ischemic brain damage is characterized by changes in acute local inflammation and inflammatory cytokines such as hs-CRP. Increased stroke risk is associated with increased hs-CRP levels. The acute phase protein CRP serves as a biological marker of systemic inflammation, and hs-CRP is associated with vascular inflammation. Increased hs-CRP levels are a predictive indicator of atherosclerosis and are associated with ischemic stroke. In a previous study performed with patients who presented to the emergency service and were diagnosed with acute ischemic stroke, increased hs-CRP levels were associated with an increase in ischemic volume. Furthermore, risk of mortality is increased in patients who have hs-CRP levels increased within 72 hours after onset of acute ischemic stroke. In a long-term study (4-year follow-up) of patients who had acute ischemic stroke, increased hs-CRP levels were associated with increased mortality, but hs-CRP levels were not associated with recurrent acute ischemic stroke.

During the inflammatory process, the intracellular phospholipase enzyme Lp-PLA₂ hydrolyzes the ester bonds of lipoproteins and oxidizes phospholipids on cell membranes. This enzyme causes the release of lysophosphatidylcholine, which has proinflammatory features by metabolizing low-density lipoprotein cholesterol. The level of Lp-PLA₂ may increase after ischemic events, and increased Lp-PLA₂ levels are associated with stroke in healthy middle-aged adults, healthy adults aged >55 years, and patients who have recurrent strokes. When a first stroke or strokes occur within 6 months after a transient ischemic attack, increased Lp-PLA₂ may be associated with recurrence of acute ischemic stroke but not mortality.

In the present study, we evaluated the relationship between serum hs-CRP level and Lp-PLA₂ activity, ischemic tissue volume, and severity of disease in patients who had acute ischemic stroke. Patients who had stroke had higher mean serum hs-CRP levels and Lp-PLA₂ activity than control patients who did not have stroke (Table 1). Further-

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**Table 4** Relationship between high-sensitivity C-reactive protein level and infarct volume in patients who had acute ischemic stroke

| Stroke type                        | Total | hs-CRP level (mg/dL) | P-value |
|------------------------------------|-------|----------------------|---------|
|                                     |       | Low                  | Medium  | High    |
|                                     |       | Number of patients   | Number of patients | Number of patients |
| Nonlacunar infarct volume (mL)     | 48    | 13 ± 9               | 25 ± 65 | 10 ± 37 |
| Lacunar infarct volume (mL)        | 53    | 31 ± 6               | 19 ± 5  | 3 ± 1   |

Notes: Data reported as number or mean ± standard deviation. Statistical significance was defined as P ≤ 0.05.

**Abbreviation:** hs-CRP, high-sensitivity C-reactive protein.

**Table 5** Relationship between lipoprotein-related phospholipase A₂ activity and infarct volume in patients who had acute ischemic stroke

| Stroke type                        | Total | Lp-PLA₂ level (nmol/min/mL) | P-value |
|------------------------------------|-------|-----------------------------|---------|
|                                     |       | Low                          | Medium  | High    |
|                                     |       | Number of patients           | Number of patients | Number of patients |
| Nonlacunar infarct volume (mL)     | 48    | 12 ± 5                      | 8 ± 40  | 28 ± 60 |
| Lacunar infarct volume (mL)        | 53    | 34 ± 1                      | 5 ± 12  | 14 ± 43 |

Notes: Data reported as number or mean ± standard deviation. Statistical significance was defined as P ≤ 0.05.

**Abbreviation:** Lp-PLA₂, lipoprotein-related phospholipase A₂.
more, patients who had stroke had a significant relationship between hs-CRP level and Lp-PLA₂ activity, infarct volume, and stroke severity (Canadian neurological scale) (Table 2). Higher mean hs-CRP level was associated with lower level of consciousness (Glasgow coma scale) (Table 3). In addition, higher hs-CRP level and Lp-PLA₂ activity were associated with increased nonlacunar and lacunar infarct volumes (Table 4 and 5). Therefore, increased hs-CRP level and Lp-PLA₂ activity in stroke patients may be an indicator of poor prognosis. Although some studies showed that high hs-CRP levels in patients with ischemic stroke are associated with poor clinical outcomes, other studies have shown opposite findings.¹⁹,³¹ The present study confirmed the findings of other studies that showed an association between Canadian neurological system, Glasgow coma scale, and infarct volume; lower scores (indicating greater severity of neurologic impairment or level of consciousness) in patients who have acute ischemic stroke are associated with significant increase in infarct volume detected with diffusion-weighted imaging, duration of hospital stay, morbidity, and mortality.²²⁻³⁴ In the present study, decreased Canadian neurological scale scores were associated with increased nonlacunar and lacunar infarct volumes (Table 2). The finding that medium levels of Lp-PLA₂ were associated with the largest mean lacunar infarct volumes may have been caused by the small number of patients (five) who had medium Lp-PLA₂ levels and lacunar infarct (Table 5).

Limitations of the present study included the small sample size, especially when patients who had stroke were divided into subgroups according to stroke severity level. The stroke severity was determined by physical examination and infarct diameter, but long-term follow-up for morbidity and mortality was not performed; therefore, the association between hs-CRP level, Lp-PLA₂ activity, and morbidity and mortality was not assessed. In addition, ischemia volumes were measured in the diffusion-weighted magnetic resonance images obtained during the initial presentation of the patient, and increase in infarct size may have occurred subsequently. Nevertheless, the present results provide justification for future studies with more patients to evaluate the correlation between hs-CRP level, Lp-PLA₂ activity, and ischemia volumes noted on diffusion-weighted magnetic resonance images.

In summary, we detected a relationship between serum hs-CRP level and Lp-PLA₂ activity, ischemic tissue volume, and severity of acute ischemic stroke. Therefore, hs-CRP and Lp-PLA₂ may be useful as possible biomarkers for the diagnosis of acute ischemic stroke. However, they probably will not replace CT or MRI because the latter provide anatomic information not available from a blood test. Further study is warranted to evaluate these biomarkers as possible convenient and cost-effective diagnostic studies for acute ischemic stroke.

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Disclosure
The authors report no conflicts of interest in this work.

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