Impact of Early Leukocytosis and Elevated High-Sensitivity C-Reactive Protein on Delayed Cerebral Ischemia and Neurologic Outcome After Subarachnoid Hemorrhage

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BACKGROUND: **The role of inflammatory response in the pathophysiology of subarachnoid hemorrhage (SAH) is being increasingly recognized. This study analyzed the impact of cellular and biochemical markers of early inflammatory response to ictus on outcome after SAH.**

METHODS: **Patients with SAH were prospectively studied for markers of early cellular, biochemical, and cytotoxic inflammatory response, including total leukocyte count (TLC), high-sensitivity C-reactive protein (hs-CRP), and lactate dehydrogenase. The relationship of these markers to delayed cerebral ischemia (DCI), new infarct, and Glasgow Outcome Scale (GOS) score at 3 months was studied.**

RESULTS: **The study comprised 246 patients. Of patients, 94 who developed DCI had a significantly higher TLC [± SD] (11.2 × 10^3/mm^3 [± 4.0] vs. 9.4 × 10^3/mm^3 [± 2.9], P = 0.001) and 62 with new infarct had significantly higher TLC (11.0 × 10^3/mm^3 [± 3.6] vs. 9.8 × 10^3/mm^3 [± 3.4], P = 0.05). GOS score had a significant inverse relationship to TLC at admission. The mean TLC [± SD] was 12.7 × 10^3/mm^3 [± 4.2], 11.7 × 10^3/mm^3 [± 3.1], 10.2 × 10^3/mm^3 [± 3.4], and 9.3 × 10^3/mm^3 [± 2.8] among patients with GOS scores of 1, 3, 4, and 5 (P < 0.001). hs-CRP showed a trend of an inverse relationship to GOS score in univariate analysis. Lactate dehydrogenase had no relationship with any outcome parameter. In multivariate analysis, higher admission TLC had a significant association with DCI (P = 0.01) and poorer GOS score (P < 0.001), and higher hs-CRP had a significant association with poorer GOS score (P = 0.05).**

CONCLUSIONS: **A leukocytosis response to ictus seems to have a significant independent association with both DCI and poor GOS score, and hs-CRP level had a significant independent association with poor GOS score, indicating preeminence of early cellular response in SAH pathophysiology.**

INTRODUCTION

Subarachnoid hemorrhage (SAH) has high morbidity and mortality despite improvements in diagnostic modalities, better intensive care unit facilities, and advancements in microsurgical and endovascular techniques.[1-3] Delayed cerebral ischemia (DCI) is the largest contributor to high mortality and morbidity.[4-6] Inflammation has been thought to play a major role in the causation of DCI.[1,4,7-10]

Various studies on early cellular (total leukocyte count [TLC]) and biochemical (C-reactive protein) markers of inflammation in SAH have shown inconsistent associations with DCI and neurologic outcome.[7-10] Biochemical assessment of inflammation using high-sensitivity assay of C-reactive protein (hs-CRP) in conjunction with cellular (TLC) and cytotoxic (lactate dehydrogenase [LDH]) inflammatory response to ictus has not been studied. The aim of the present study was to analyze the relationship of levels of

Key words
- DCI
- Early inflammatory response
- GOS
- hs-CRP
- Ictus
- New infarct
- Outcome
- TLC

Abbreviations and Acronyms
CT: Computed tomography
DCI: Delayed cerebral ischemia
GOS: Glasgow Outcome Scale
hs-CRP: High-sensitivity C-reactive protein
LDH: Lactate dehydrogenase
SAH: Subarachnoid hemorrhage
TLC: Total leukocyte count
WFNS: World Federation of Neurosurgical Societies

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early inflammatory markers (TLC, hs-CRP, and LDH) to DCI, new infarct, and neurologic outcome after SAH.

MATERIALS AND METHODS

Appropriate ethics approval was obtained for this study. All adult patients with spontaneous SAH reporting within 24 hours of ictus to the neurosurgical emergency department of a tertiary care hospital were included in the study. All patients were assessed using the World Federation of Neurosurgical Societies (WFNS) SAH grading scale. At this stage (i.e., hospital admission), blood was sent for routine hematologic and biochemical parameters. Serum samples were also sent for measurement of the following inflammatory markers: TLC, hs-CRP, and LDH.

TLC was analyzed on ethylenediaminetetraacetic acid blood samples using the Sysmex KX-21N Automated Hematology Analyzer (Sysmex America, Inc., Lincolnshire, Illinois, USA) based on direct current detection method, after validating 50 samples with manual counting. The clotted blood samples after centrifugation were analyzed for serum LDH based on enzymatic colorimetric assay using an Hitachi Automated Analyzer (Roche Diagnostics, Indianapolis, Indiana, USA), and hs-CRP was measured using particle-enhanced immunonephelometry with the Nephstar protein analysis system (Goldsite Inc., Shenzhen, China).

All good-grade patients (WFNS grades I–III) underwent urgent computed tomography (CT) angiography. Poor-grade patients (WFNS grades III and IV) underwent CT angiography after initial resuscitation. Patients with no aneurysm on CT angiography were excluded. A further decision on securing the ruptured aneurysm by surgical clipping or endovascular coiling was made depending on aneurysm architecture as well as taking into account patients' preferences for treatment.

In the postocclusion period, the patients were managed in the intensive care unit on oral nimodipine. The patients were closely monitored for development of DCI. DCI was diagnosed based on "occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]), which was not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, imaging of the brain, and appropriate laboratory studies."[11] New infarct was defined as the presence of hypodensity on noncontrast CT scan, which may or may not have manifested clinically, occurring 48 hours after aneurysm occlusion.

Patient demographics, comorbidities (hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease), WFNS and Fisher grades, and treatment details were noted in a prospective database and followed. The development of DCI or infarcts was documented during the hospital stay. The outcome was also assessed 3 months after presentation by the Glasgow Outcome Scale (GOS). GOS scores 1–3 were considered unfavorable outcomes, and scores 4 and 5 were considered favorable outcomes.

Statistical Analysis

IBM SPSS Statistics version 21 software (IBM Corporation, Armonk, New York, USA) was used for statistical analyses. Univariate analyses of continuous variables across binary categories were compared using the independent samples t test. The bivariate relationship between 2 continuous variables was assessed using the Pearson correlation coefficient. Proportions were compared using χ^2 or Fisher exact test wherever appropriate. Two-sided significance tests were used throughout, and the significance level was kept at $P < 0.05$. Multivariate analyses were conducted using binary logistic regression with mandatory significance of the model coefficient being <0.05 for validity of outcome prediction after adjusting for known prognostic factors, such as age, sex, serious systemic disease, WFNS grade, Fisher grade, and definitive treatment, in relation to TLC, hs-CRP, and LDH levels. Several threshold levels were analyzed for the purpose of studying the relationship of TLC, hsCRP, and LDH with DCI, new infarct, or GOS.

RESULTS

The study comprised 246 patients (117 men and 129 women). The mean age was 49.8 years (range, 20–85 years). Of 246 patients, 72 patients had systemic illnesses, including hypertension, diabetes, chronic obstructive pulmonary disease, and others. At presentation, 137 patients were WFNS grade I, 50 were grade II, 15 were grade III, 40 were grade IV, and 4 were grade V. Five patients were Fisher grade 1, 30 were grade 2, 110 were grade 3, and 101 were grade 4. Surgical clipping of the aneurysm was performed in 189 patients, and endovascular coiling was performed in 23 patients; 34 patients refused any intervention.

The levels of inflammatory markers with respect to baseline characteristics are shown in Table 1. TLC level was significantly higher in patients with systemic disease and higher Fisher grades. TLC levels were also elevated in patients with WFNS grades IV and V, but this did not reach statistical significance. Similarly, hs-CRP levels trended higher in patients with poor-grade subarachnoid hemorrhage.

Of 246 patients, 94 (38.21%) developed DCI, and 62 patients (25.21%) experienced new-onset infarcts during their hospital stay. Mean TLC [± SD] was found to be higher in the DCI group compared with the non-DCI group ($11.2 \times 10^3/mm^3$ [± 4.0] vs. $9.4 \times 10^3/mm^3$ [± 2.9]). This finding was statistically significant as a continuous variable ($P = 0.001$) (Table 2). However, no categorical threshold value for TLC could be found for defining the relationship with DCI or outcome. There was no significant difference in mean hs-CRP levels between patients with DCI and other patients (5.0 mg/L vs. 7 mg/L). Mean LDH level also had no significant association with DCI.

Mean TLC [± SD] was significantly higher in patients who developed infarcts compared with patients without infarcts ($11.0 \times 10^3/mm^3$ [± 3.6] vs. $9.8 \times 10^3/mm^3$ [± 3.4], $P = 0.05$). However, hs-CRP values did not show any relationship to the development of new infarct (Table 2). Also, mean LDH values showed no significant association with development of new infarct.

Outcome could be assessed for 221 patients at 3 months. Mean TLC [± SD] was $12.7 \times 10^3/mm^3$ [± 4.2], $11.7 \times 10^3/mm^3$ [± 3.1], $10.2 \times 10^3/mm^3$ [± 3.4] and $9.3 \times 10^3/mm^3$ [± 2.8] among patients with GOS scores of 1, 3, 4, and 5 ($P < 0.001$) (Figure 1 and Table 2). Thus, admission TLC had a significant inverse relationship with GOS score. The mean hs-CRP was 14.1 mg/L, 8.0 mg/L, 4.6 mg/L, and 3.7 mg/L among patients with GOS

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