Intracerebral Hemorrhage Triggers Interleukin-6 and Interleukin-10 Release in Blood

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Background and Purpose—Acute brain insult can cause systemic anti-inflammatory response, including anti-inflammatory cytokine release. The goal of this study was to determine the serum level of interleukin-6, interleukin-10, and interleukin-13 in patients with intracerebral hemorrhage and to correlate cytokine concentrations with stroke severity.

Methods—Thirty patients with intraparenchymal hemorrhage and 16 control subjects were included. Serum samples were collected on the second day of hemorrhagic stroke. Cytokine level was measured with the enzyme-linked immunosorbent assay method.

Results—Increased serum levels of interleukin-6 and interleukin-10 were detected in stroke patients. Interleukin-6 and interleukin-10 levels were significantly correlated with Glasgow Coma Scale score. In addition, interleukin-6 level correlated with blood volume and mass effect.

Conclusions—Intracerebral hemorrhage is associated with systemic release of anti-inflammatory cytokines. (Stroke. 2002; 33:2334-2335.)

Key Words: cytokines • interleukins • intracerebral hemorrhage • stroke

Experimental studies have shown that acute brain injury can induce a systemic anti-inflammatory response, including monocyte inactivation and decrease in cellular immune response (reviewed in Reference 1). Increased expression of anti-inflammatory cytokines in blood plays an important role in brain-mediated immunodepression in the periphery.

In this study we tested the hypothesis that an acute brain insult, such as intracerebral hemorrhage, triggers monocyte-derived (interleukin-6 [IL-6] and interleukin-10 [IL-10]) or T-cell-derived (interleukin-13 [IL-13]) anti-inflammatory cytokine release into blood. We also attempted to determine whether the production of these cytokines in blood is related to stroke severity, taking into account clinical and radiological findings.

Subjects and Methods

Thirty patients (17 men, 13 women; mean age, 61.6±14.7 years) with supratentorial, intraparenchymal cerebral hemorrhage and 16 control subjects, matched for age and sex, were enrolled. We excluded patients with history of recent infection (within 3 months before admission); with concurrent major cardiac, renal, hepatic, autoimmune, or cancerous disease; with history of previous stroke or head trauma; and who were taking immunosuppressive or anti-inflammatory drugs.

All patients underwent brain CT scans within 24 hours after stroke onset. To estimate the magnitude of brain injury we used 2 parameters: volume of hematoma and mass effect. The latter depends not only on the size but also on the site of the hematoma. The volume of the hematoma was calculated from standard CT scans with the use of the largest perpendicular diameters and slice thickness. The degree of mass effect was assessed as follows: 0, no effect or effacement of cortical sulci; 1, minor effacement of lateral ventricle; 2, complete effacement of lateral ventricle; and 3, shift of the midline. In all patients, angiography and/or angiographic CT of the cerebral vessels was performed.

With regard to intracerebral hemorrhage etiology, 22 patients had primary intracerebral hemorrhage; in 4 patients hemorrhage was due to rupture of arteriovenous malformation; in 2 patients hemorrhage occurred in the course of antithrombotic therapy; and in 2 patients we were not able to determine stroke etiology definitively.

Neurological deficit was assessed on admission (day 1) with the use of the Glasgow Coma Scale.

The blood of patients and controls was drawn through the antecubital vein on the second day at 10 AM. The mean delay from the onset of stroke to the blood sample was 24 hours (range, 19 to 27 hours). Samples were centrifuged at 2000g for 10 minutes, and sera were stored at -80°C until used. Serum levels of IL-10, IL-6, and IL-13 were measured with commercially available quantitative “sandwich” enzyme-linked immunosorbent assay kits obtained from R&D Systems for IL-6 and IL-10 and from BioSource International for IL-13. Sensitivity of the assay was 0.7 pg/mL for IL-6, 3.9 pg/mL for IL-10, and 12.0 pg/mL for IL-13.

The study protocol was approved by the local bioethics committee.

For statistical analysis, the Mann-Whitney test and Spearman rank correlation were used as appropriate. Results are expressed as mean±SEM. Values were considered significant at P<0.05.
**Results**

IL-6 and IL-10 levels were significantly higher in patients with intraparenchymal hemorrhage than in the control group: 59.5 ± 94.7 versus 3.1 ± 3.0 pg/mL (P = 0.0001) and 16.7 ± 31.6 versus 1.4 ± 5.4 pg/mL (P = 0.00006), respectively. IL-13 was not detectable in either group. The mean volume of hematoma was 39.7 ± 36.5 mL.

IL-6 level correlated with Glasgow Coma Scale score on admission (r = −0.62, P = 0.0002), total blood volume (r = 0.63, P = 0.003), and mass effect (r = 0.49, P = 0.007). IL-10 level correlated only with Glasgow Coma Scale score (r = −0.52, P = 0.007). We also found a correlation between IL-6 and IL-10 level (r = 0.60, P = 0.001).

Because the inclusion of 2 patients treated with anticoagulants could interfere with the final results, in the next analysis we excluded these patients; however, this did not change our results significantly.

**Discussion**

Monocytes and the cytokines released by them can be a target for the brain in modulating systemic immune response.1 We found an elevated level of monocyte-derived (IL-6 and IL-10) cytokines. IL-10 has prominent anti-inflammatory properties. Although initially thought to be a proinflammatory cytokine, recent findings suggest that IL-6 has many anti-inflammatory and immunosuppressive effects and may negatively regulate the acute phase response.2 Previously, Ferrarese et al3 observed, in 11 patients with hemorrhagic lesions, increased IL-6 secretion after ex vivo stimulation of blood samples with endotoxin.

The mechanisms leading to increased release of anti-inflammatory cytokines in patients with intracerebral hemorrhage remain unclear. It was shown in an animal model of brain trauma that systemic IL-10 release was mediated by the sympathetic nervous system and catecholamines.4 In addition, IL-6 secretion can be triggered by sympathetic neurons.5

In our study IL-6, but not IL-10, level correlated with parameters of brain damage (volume of hematoma and mass effect). Fassbender et al6 found a clear relationship between IL-6 level and volume of brain lesion in ischemic stroke patients.

Patients with elevated concentrations of anti-inflammatory cytokines may have an increased risk of infection. Further studies are needed to establish the relationship between anti-inflammatory cytokine level and infections in stroke patient. Our preliminary study protocol, approved by the bioethics committee, assumed only 1 cytokine measurement. In the future we plan to perform serial measurements to obtain an insight into cytokine kinetics in the course of intracerebral hemorrhage.

Our results support the idea that damaged brain can influence systemic immune response.

**References**

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