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Vascular

Serum inflammatory adhesion molecules and high-sensitivity C-reactive protein correlates with delayed ischemic neurologic deficits after subarachnoid hemorrhage☆

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Abstract

Background: The purpose of the present study was to investigate the relationship between serum concentrations of the immunoglobulin-like superfamily, selectins, hsCRP, and the development of DIND in patients with aneurysmal SAH.

Methods: Serum ICAM-1, VCAM-1, E-selectin, P-selectin, L-selectin, and hsCRP were measured in 33 patients with SAH who underwent aneurysmal clipping within 48 hours of the onset of symptoms. Serum samples were obtained during the early period (day 0) and the late period (day 7).

Results: The serum concentrations of ICAM-1 (P = .009), VCAM-1 (P = .0383) and hsCRP (P = .0014) during the early period were significantly higher in patients with SAH than in control patients. Further, serum hsCRP concentration during the late period was significantly higher in patients with SAH than in control patients (P = 0033). Finally, serum concentrations of ICAM-1, VCAM-1, and hsCRP during the early (P = .0055, P = .0266, and P = .0266) and late (P = .0423, P = .0041, and P = .0004) period were significantly higher in patients with DIND than in patients without DIND.

Conclusions: Serum levels of ICAM-1, VCAM-1 and hsCRP during the early and late period following SAH correlate with DIND.

Keywords: Adhesion molecule; High-sensitivity C-reactive protein; Subarachnoid hemorrhage; Delayed ischemic neurological deficit

1. Introduction

Delayed ischemic neurological deficits resulting from cerebral vasospasm remains the leading cause of morbidity and mortality after aneurysmal SAH [17]. Recent studies in experimental animals and humans suggest that inflammatory adhesion molecules participate in the pathogenesis of DIND [2,5,8,18,20,22-24,27,29,31]. The inflammatory cells-endothelial adhesion process starts with capture and rolling of the inflammatory cells on the endothelium and is followed by adhesion of inflammatory cells to the endothelium. This results in diapedesis of inflammatory cells to the abluminal side and transmigration into local tissues, including the brain [6,28]. Inflammatory molecules include the E-selectin (CD62E), P-selectin (CD62P), L-selectin (CD62L), ICAM-1 (CD54), ICAM-2 (CD102), ICAM-3 (CD50), VCAM-1 (CD106), and platelet-endothelial adhesion molecules (CD31) [23].

Recent studies also suggest that serum levels of hsCRP, a marker of inflammation, can predict outcomes in patients with stroke [13] and other cardiovascular disorders [16].

Abbreviations: hsCRP, High-sensitivity C-reactive protein; DIND, Delayed ischemic neurological deficit; SAH, Subarachnoid hemorrhage; ICAM, Intercellular adhesion molecules; VCAM, Vascular cell adhesion molecule; CT, Computed tomography; CTA, CT angiography; IL, Interleukin; TNF, Tumor necrosis factor.

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Thus, the goal of the present study was to investigate the relationship between serum concentrations of selectins (E-, P-, and L-), the immunoglobulin-like superfamily (ICAM-1 and VCAM-1), hsCRP, and the development of DIND in patients with SAH.

2. Subjects and methods

2.1. Patient population

Between April 2005 and December 2005, 46 patients underwent aneurysmal clipping within 48 hours of SAH onset. Of these 46 patients, 33 (12 men and 21 women; age, 62.2 ± 10.8 years [mean ± SD]) with SAH scored as class III according to Fisher classification [4] and a ruptured aneurysm in the anterior circulation were enrolled in the present study. None of the enrolled patients had a history of chronic neurological disease, chronic inflammatory disease, surgical treatment for any kind of disease within 4 weeks before admission, or nosocomial infection (eg, hospital-acquired pneumonia). All patients underwent cerebral angiography with arterial catheterization or multislice CTA within 48 hours of SAH onset. Eighteen patients were scored as grade II (55%), and 15 patients were scored as grade III (45%) according to the classification of Hunt and Hess [15]. An additional 5 patients with unruptured cerebral aneurysms served as the control group.

2.2. Postoperative management

The rate of intravenous fluid infusion was adjusted in an attempt to maintain the central venous pressure in the range of 5 to 10 cm H_2O. Dobutamine and/or dopamine, hyperosmolar fluids (mannitol and glycerol), and blood products were not used. When the serum glucose level increased to >200 mg/dL, insulin therapy was initiated with subsequent close monitoring of blood glucose levels. All protocols were reviewed and approved by the institutional ethics committee, and informed consent was obtained from all patients or their next of kin.

2.3. Clinical evaluation

Neurological status was assessed postoperatively every 3 hours until 14 days after the onset of SAH. DIND caused by cerebral vasospasm after SAH was defined as the onset of confusion or disorientation, decline in level of consciousness, or any focal neurological deficit occurring 3 to 14 days after the onset of SAH without CT, laboratory, or clinical evidence of other causes (eg, rebleeding, hydrocephalus, electrolyte disturbances, surgical morbidity, hypoxia, seizures). All patients underwent repeated cerebral angiography with arterial catheterization or multislice CTA [25] on day 7, and arterial narrowing due to cerebral vasospasm was evaluated using the scale of Schneck and Kricheff [30], as follows: none, mild (up to 30% reduction in lumen diameter), moderate (31%-60% reduction), and marked (at least 60% reduction). In the present study, moderate or marked arterial narrowing was defined as angiographic vasospasm.

2.4. Analysis of serum adhesion molecules and hsCRP

In SAH patients, blood samples were collected by venipuncture on Day 0 (ie, the day of SAH onset) and Day 7. In the control group, samples were collected via venipuncture on the day of admission to the hospital and 7 days postoperatively. In both groups, initial samples were always obtained before craniotomy. Each 5-mL sample was centrifuged at 1500 rpm for 10 minutes, and the resulting supernatant was collected and stored at −80°C until it was assayed. Serum ICAM-1, VCAM-1, E-selectin, P-selectin, and L-selectin levels were assessed with a commercially available enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minn). The hsCRP levels were determined using an enzyme-linked immunosorbent assay kit (Dade Behring Marburg GmbH, Tokyo, Japan).

2.5. Statistical analysis

Data are expressed as the mean ± SD. Differences in adhesion molecule and hsCRP levels between control patients and SAH patients were determined using the Mann-Whitney *U* test. Pairwise correlations between each adhesion molecule in the early and late periods were assessed using the Spearman correlation coefficient. Difference in adhesion molecule and hsCRP levels between patients with and without DIND was determined using the Mann-Whitney *U* test. Differences were deemed statistically significant if $P < .05$.

3. Results

Table 1 shows serum concentrations of the immunoglobulin-like superfamily, the selectins, and hsCRP in patients with SAH and control patients. The serum concentrations of ICAM-1, VCAM-1, and hsCRP during the early period were

Table 1
Serum concentrations of the immunoglobulin-like superfamily, the selectins, and hsCRP in patients with SAH and in control patients

	Control (n = 5)	All (n = 33)	*P*
Early ICAM-1 (ng/mL)	96 ± 32.4	189.2 ± 67.4	$P < .01$
Late ICAM-1 (ng/mL)	178.2 ± 96.7	218.8 ± 94.4	NS
Early VCAM-1 (ng/mL)	276 ± 89.4	381.3 ± 129.1	$P < .05$
Late VCAM-1 (ng/mL)	310.6 ± 73.4	416.9 ± 119.6	NS
Early E-selectin (ng/mL)	35.6 ± 18.0	48.3 ± 21.5	NS
Late E-selectin (ng/mL)	28.4 ± 13.5	43.8 ± 15.5	NS
Early P-selectin (ng/mL)	315.2 ± 237.3	425.4 ± 239.9	NS
Late P-selectin (ng/mL)	364.8 ± 284	502.5 ± 221.8	NS
Early L-selectin (ng/mL)	515.2 ± 150.6	702.4 ± 192.3	NS
Late L-selectin (ng/mL)	588.4 ± 242.9	615.7 ± 161.5	NS
Early hsCRP(ng/mL)	363.6 ± 178.3	7252.6 ± 10115.9	$P < .01$
Late hsCRP(ng/mL)	2016 ± 929.3	34651.5 ± 43932.3	$P < .01$

Early, the early period (day 0; the day of SAH onset); late, the late period (day 7).