A Longitudinal Prospective Study of Soluble Adhesion Molecules in Acute Stroke

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Background and Purpose—Activation of endothelial cells is a consequence of cerebral ischemia and leads to the expression of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin, which can be released into the blood. This study aimed to define the kinetics of soluble adhesion molecule serum levels after cerebral ischemia and their correlation with the extent of neurological deficits, clinical outcome, and infarct volume as measured on CT scans.

Methods—Plasma levels of soluble (s) ICAM-1, sVCAM-1, and sE-selectin were repeatedly determined by ELISA in 38 patients during a period of 14 days after acute cerebral ischemia.

Results—Soluble adhesion molecule levels demonstrated considerable variability. Overall, concentrations revealed characteristic and significant changes after completed strokes but not after transient ischemic attacks. In patients with completed stroke (n = 26) but not in patients with transient ischemic attacks (n = 12), sICAM-1 peaked within 24 hours (P = 0.04), sVCAM-1 reached a maximum after 5 days (P = 0.02), and sE-selectin levels decreased after 5 days (P = 0.002). There was no clear-cut correlation of soluble adhesion molecule levels with infarct volume or clinical disability. The initial increase of sE-selectin levels was higher in more disabled patients (P = 0.02). sICAM-1 levels were higher in patients with signs of infection (n = 9; P = 0.03).

Conclusions—As a result of large interindividual variability influenced by ischemia-independent factors, soluble adhesion molecules are not reliable candidates as surrogate markers in acute cerebral ischemia. The characteristic profile of individual soluble adhesion molecules after completed stroke supports prior hypotheses of their involvement in the pathogenesis of acute cerebral ischemia, but this needs to be clarified in detail. (Stroke. 1998;29:2129-2135.)

Key Words: cell adhesion molecules cerebral ischemia, transient selectins stroke

There is increasing evidence that inflammatory processes are involved in acute cerebral ischemia. In experimental animal models of stroke, peripheral blood leukocytes migrate into the brain parenchyma within the first 12 hours after ischemia. Migration of peripheral blood leukocytes requires prior adhesion to cerebral endothelial cells, which is mediated by adhesion molecules on the surface of cerebral endothelial cells and peripheral blood leukocytes. Upon activation by several stimuli, these cells secrete a multitude of different cytokines, chemokines, and other inflammatory mediators. Most of them are thought to induce cell damage and significantly contribute to reperfusion injury. Therefore, therapeutic interventions are currently investigated that antagonize these inflammatory processes at different levels, e.g., by blocking cell adhesion that has already been at least partially effective in animal models. Because most adhesion molecules are not only expressed on cell surfaces but are also released into the circulation, they can easily be quantified, e.g., by ELISA in peripheral blood.

In cerebral ischemia at least 3 different adhesion molecules have merited special interest so far. Intercellular adhesion molecule 1 (ICAM-1), which is responsible for adhesion of mononuclear cells and granulocytes, was found to be expressed on microvessels in areas of infarction in human autopsy tissue and was elevated in the peripheral blood after stroke. Vascular cell adhesion molecule 1 (VCAM-1) predominantly mediates adhesion of monocytes and was also raised after stroke. E-selectin is only expressed by endothelial cells and facilitates adhesion of monocytes and granulocytes. Increased serum levels of this adhesion molecule have also been reported after acute stroke.

Beyond this current knowledge, the exact pathogenetic role of each adhesion molecule during cerebral ischemia in humans has not yet been defined in detail. It is not known whether the extent of adhesion molecule expression correlates with clinical disability and outcome in a single patient. The time course of adhesion molecule expression during stroke is not exactly known in humans. It is unclear whether serum levels of different adhesion molecules correlate with stroke volume or territory. In addition, the question of differences in adhesion molecule expression between transient ischemic attack (TIA) and completed stroke remains to
be clarified. Answers to these open questions could not only have implications for future therapeutic strategies directed against adhesion molecules but may also be important for clinical practice, since there is still a lack of reliable surrogate markers for stroke volume, outcome, and the differentiation of TIA from completed stroke during the initial phase of cerebral ischemia. To detect impending tissue damage early in an individual patient becomes more important with the rise of effective but potentially dangerous treatments such as thrombolysis.12,13 These therapies may not be applied to patients with TIA or with a spontaneously favorable outcome.

Therefore, we prospectively determined the levels of the soluble (s) adhesion molecules sICAM-1, sVCAM-1, and sE-selectin in patients with TIA and completed strokes within the first 2 weeks after onset of neurological symptoms to define their prognostic value.

Subjects and Methods

Thirty-eight consecutive patients with clinical signs of cerebral ischemia were included in the study at their admission to the Department of Neurology, Georg August University, Göttingen, Germany. The study had been approved by the ethical committee of the medical faculty of the university. Informed consent was obtained from all patients before study entry. Patient recruitment was performed prospectively. The sudden emergence of a focal neurological deficit of ≤12 hours’ duration was the criterion for inclusion. Patients with intracranial bleeding, hypoglycemia, and inflammatory central nervous system diseases were excluded. The observation period was 14 days in patients with completed stroke (see below) and 5 days in those with TIA because hospital stay normally did not exceed 1 week after TIA. The characteristics of the study population are summarized in Table 1. All diagnoses were made prospectively during hospitalization of the patients.

Clinical examination was performed at study entry and after 5 and 14 days (except for TIA patients) in a standardized way. At each time point, scores were assessed according to the Scandinavian Stroke Scale (SSS) (no disability = 46), the National Institutes of Health Stroke Scale (NIHSS) (no disability = 0), and the Barthel Index (BI) (no disability = 100). These 3 scales of neurological deficits and disability have been used in many stroke trials and were found to be reliable and valid measures.12,13 Clinical and laboratory signs of infection were determined routinely at admission. During the hospital stay, body temperature was recorded twice per day. Patients were interviewed and clinically examined for symptoms and signs of infection once per day. If there was evidence of infection, blood and urine analyses were performed. Results of these routine procedures were drawn from the medical records at the end of the study. The items of interest included fever (>38.5°C), signs of respiratory tract infection on physical examination, elevated white blood cell count, erythrocyte sedimentation rate, C-reactive protein, and inflammatory findings on urine analysis.

Cerebral ischemia was classified as follows: A neurological deficit with a duration of ≤24 hours was designated as TIA. If the deficits persisted for >24 hours, the patient was classified as having a completed stroke. The affected vascular territory was defined on the basis of cranial CT (CCT) scans. If imaging did not show any recent vascular lesion, classification was based on clinical findings. For definition of pathogenetic categories, each patient underwent a diagnostic workup that included blood pressure measuring (repeated), Doppler ultrasonic examination of cervical and cerebral vessels, transthoracic echocardiography, electrocardiography, and laboratory screening for vasculitis and coagulopathy.

CCT scans were performed without contrast at study entry and after 5 days. The volume of cerebral infarction was estimated by a recently described procedure with good interrater agreement.14 The volume in milliliters was calculated as an ellipsoid by multiplication of the longest diameter through the hypodense area on CCT scans of the longest diameter through the hypodense area on CCT scans

| TABLE 1. Clinical Data of the Study Population (n=38) |
|---------------------------------|--------|--------|
| Sex                             | Male   | 25     |
|                                 | Female | 13     |
| Age range, y                    | 35–90  |        |
| Mean                            | 64.4   |        |
| Median                          | 64     |        |
| Patient history                 |        |        |
| Arterial hypertension           | 18     |        |
| Diabetes mellitus               | 8      |        |
| Hypercholesterolemia            | 5      |        |
| Atrial fibrillation             | 4      |        |
| Nicotine abuse                  | 4      |        |
| ICA occlusion                   | 2      |        |
| Alcohol abuse                   | 2      |        |
| Prior cerebral ischemia         | 14     |        |
| Type of ischemia                |        |        |
| TIA                             | 12     |        |
| Completed stroke                | 26     |        |
| Type of infarction              |        |        |
| Territorial                     | 17     |        |
| Lacunar                         | 9      |        |
| Pathogenesis                    |        |        |
| Atherothrombotic/arterio-arterial embolism | 28     |
| Cardiac embolus                 | 6      |        |
| Others*                         | 4      |        |

ICA indicates internal carotid artery; VB, vertebrobasilar territory. Values (except age) are number of patients.

*Polyglobulia (hemoglobinoathy, Minneapolis type), hypertensive crisis, β-adrenoreceptor antagonist–induced vasospasm, unknown (each n = 1).

(A), the longest diameter at right angles to A (B), and the thickness of the infarction area (C). The product was divided by the factor of size reduction on CCT scans compared with in vivo dimensions (D) and by the factor of 2 to approximate the volume of an ellipsoid. Stroke was designated as lacunar if the maximum lesion diameter was <20 mm15 or if there was a persistent neurological deficit for >24 hours without visible infarction on CCT scans. Territorial infarctions had a minimum diameter of ≥20 mm.

EDTA-anticoagulated peripheral blood was drawn from each patient at study entry and after 12 hours, 24 hours, 5 days, and 14 days (not in TIA patients). In most TIA patients the first blood sample was collected when neurological symptoms had already disappeared. The median time between disappearance of symptoms and first blood drawing in TIA patients was 2 hours (range, 0 to 6 hours). Plasma was immediately separated by centrifugation and stored in aliquots at −20°C until analysis. The levels of sICAM-1, sVCAM-1, and sE-selectin were determined by commercially available ELISA (R&D Systems). ELISAs were performed according to manufacturer’s instruction. Each sample was analyzed in duplicate, and the mean value of both measures was taken for analyses. The mean intra-assay coefficients of variation for sICAM-1, sVCAM-1, and sE-selectin were 5.61%, 6.38%, and 4.81%, respectively.

Statistical analysis was performed with the intention (1) to determine the possible influence of other than stroke-related factors on soluble adhesion molecule levels; (2) to identify differences in
adhesion molecule levels depending on stroke subtypes, pathogenesis, and vascular territory; (3) to define fluctuations of adhesion molecule levels over time after stroke; and (4) to correlate adhesion molecule levels to infarction volume and clinical disability. Results are expressed as mean ± SD. Although all data columns passed the test for gaussian distribution (Kolmogorov-Smirnov test), statistical analysis was based on the assumption of a nonparametric distribution of data because of the small numbers of patients. The Wilcoxon signed rank test and the Mann-Whitney test were used for the comparison of 2 paired or unpaired groups, respectively. For nonparametric correlative analyses, the Spearman rank correlation coefficient ($r$) was calculated. All $P$ values are 2-tailed and were considered significant if <0.05. In case of multiple comparisons, a correction was performed by application of the Bonferroni test. If $P$ values rose to >0.05 after correction, this is indicated in the text. In these cases, $P$ values before correction are also mentioned. For all statistical analyses, GraphPad PRISM software (version 2.0, GraphPad Software, Inc) was used.

Results

Soluble Adhesion Molecules in Patients With Acute Cerebral Ischemia

Soluble adhesion molecules were measurable in each sample that was collected from patients with acute cerebral ischemia during the first 2 weeks after onset of symptoms. Mean (range) values of sICAM-1, sVCAM-1, and sE-selectin from all patients were 254.8 (33 to 600), 708.8 (296 to 1770), and 38.3 (13 to 121) ng/mL, respectively. There was a correlation between each of the adhesion molecules (sICAM-1/sVCAM-1: $r=0.29$, $P=0.0003$; sICAM-1/sE-selectin: $r=0.37$, $P=0.0003$; sVCAM-1/sE-selectin: $r=0.24$, $P=0.006$; $P$ values corrected for multiple comparisons).

Correlation of Soluble Adhesion Molecule Levels With Parameters Other Than Cerebral Ischemia

In patients with cerebral ischemia, mean and maximum sICAM-1 levels during the study period were on average higher in older than in younger patients (Figure 1a). Analyzed without correction for multiple comparisons, there was a statistically significant correlation of sICAM-1 levels with age ($r=0.42$, $P=0.02$). After correction, the $P$ value was >0.05. sVCAM-1 and sE-selectin levels were found independent of age.

Maximum and mean sICAM-1 but not sVCAM-1 or sE-selectin levels were higher in patients with clinical or laboratory signs of infection ($P=0.003$ and $P=0.03$; $P$ values corrected for multiple comparisons) (Figure 1b). These patients (n=9) suffered from lower urinary tract or respiratory tract infections, respectively.

Levels of soluble adhesion molecules did not differ in patients with a known history of arterial hypertension (n=18) compared with patients with normal blood pressure before cerebral ischemia (n=20). A history of cerebral ischemia (n=14) did not correlate with initial soluble adhesion molecule levels. Initial sICAM-1 levels in patients with known arteriosclerosis in any vascular territory, arterial hyperten-

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**Table 2. Levels of Soluble Adhesion Molecules During the First 5 Days After Completed Stroke and TIA**

<table>
<thead>
<tr>
<th></th>
<th>TIA (n=12)</th>
<th>Completed Stroke (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sICAM-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial levels at admission</td>
<td>252 (121)</td>
<td>241 (88)</td>
</tr>
<tr>
<td>Maximum levels</td>
<td>291 (116)</td>
<td>287 (89)</td>
</tr>
<tr>
<td>Mean levels</td>
<td>252 (118)</td>
<td>250 (72)</td>
</tr>
<tr>
<td>sVCAM-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial levels at admission</td>
<td>622 (155)</td>
<td>691 (292)</td>
</tr>
<tr>
<td>Maximum levels</td>
<td>782 (171)</td>
<td>884 (334)</td>
</tr>
<tr>
<td>Mean levels</td>
<td>661 (135)</td>
<td>725 (237)</td>
</tr>
<tr>
<td>sE-selectin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial levels at admission</td>
<td>47 (33)</td>
<td>35 (13)</td>
</tr>
<tr>
<td>Maximum levels</td>
<td>50 (33)</td>
<td>39 (15)</td>
</tr>
<tr>
<td>Mean levels</td>
<td>46 (32)</td>
<td>35 (13)</td>
</tr>
</tbody>
</table>

Values are mean (SD), expressed in nanograms per milliliter. Differences were not statistically significant.
Dependence of Soluble Adhesion Molecule Levels on Pathogenesis and Type of Cerebral Ischemia

There was no significant difference of initial, maximum, or mean levels of soluble adhesion molecules between completed stroke and TIA during the first 5 days (Table 2) or territorial and lacunar infarctions during 2 weeks of observation. When we compared the ratios of adhesion molecule levels at 12 hours after admission divided by levels at admission, there was also no difference between completed stroke and TIA. Levels of soluble adhesion molecules were similar in patients with different pathogenesis of cerebral ischemia. There were no significant differences between different vascular territories.

Longitudinal Time Course of Soluble Adhesion Molecule Levels

There was a large interindividual variability of levels of each soluble adhesion molecule at study entry and during the first 2 weeks after cerebral ischemia. Overall, sICAM-1 levels showed 1 distinct peak within 24 hours after symptom onset (Figure 2a). Levels after 12 hours were significantly higher than at study entry (P=0.04, corrected for multiple comparisons) (Figure 2a). This sICAM-1 peak was found in 68% of all patients. sVCAM-1 levels revealed a monophasic course with a peak after 5 days (P=0.02, corrected for multiple comparisons), which was observed in 79% of patients (Figure 2c). sE-selectin levels decreased significantly (P=0.002, corrected for multiple comparisons) after 5 days in 87% of all cases.
Correlation of Soluble Adhesion Molecule Levels With Infarct Volume

The infarct volume on CCT scans at admission was 0 mL in each patient, indicating patient recruitment early after onset of cerebral ischemia. On the second CCT scan performed at day 5, infarct volume ranged from 0 mL, predominantly in TIA patients to 180 mL (mean, 29 mL) in patients with completed stroke. There was no significant correlation of soluble adhesion molecule levels with infarct volumes calculated from CCT scans of patients with completed stroke. Increases of sVCAM-1 or sICAM-1 levels at any time during the first 2 weeks after stroke did not correlate significantly with CCT findings. Two patients died from malignant infarctions in the total middle cerebral artery territory. These patients did not have higher levels of soluble adhesion molecules than some patients with TIA.

Correlation of Soluble Adhesion Molecule Levels With Severity of Clinical Symptoms

Patients with completed stroke at admission had mean clinical scores of 34 (SSS), 9 (NIHSS), and 49 (BI). After 2 weeks 3 patients had died, 2 from malignant middle cerebral artery infarction and 1 from sepsis. The survivors had mean clinical scores of 38 (SSS), 6 (NIHSS), and 82 (BI). There was a weak correlation between initial sVCAM-1 levels and initial SSS scores ($r=0.32$, $P=0.047$) in patients with completed stroke. After correction for multiple comparisons, the $P$ value became nonsignificant. There was no correlation between sVCAM-1, sICAM-1, or sE-selectin levels at any other time of the study and the extent of neurological deficits.

An initial rise of sE-selectin levels within the first 24 hours correlated with worse SSS, NIHSS, and BI scores ($r=-0.36/0.39/0.33$, $P=0.02/0.02/0.04$, respectively). A decrease of sE-selectin levels from day 0 to day 5 correlated with a better clinical status as measured by BI ($r=0.42$, $P=0.02$). After correction for multiple comparisons, all $P$ values regarding sE-selection dynamics and clinical scores were >0.05. Increases of sVCAM-1 or sICAM-1 did not show any correlation with clinical findings.

Discussion

Adhesion molecules are involved in the pathogenesis of cerebral ischemia.1 Cerebral endothelial cells express high levels of ICAM-1, VCAM-1, and E-selectin after in vitro simulation of ischemia.16 In knockout mice that lack the ICAM-1 gene, infarct volume is significantly reduced after transient middle cerebral artery occlusion compared with normal animals.17 These findings strongly suggest a pathogenic role of leukocyte adhesion and migration in acute cerebral ischemia. However, the role of adhesion molecules in acute stroke in humans thus far is only incompletely understood. Longitudinal studies in human peripheral blood after cerebral ischemia are rare. Therefore, knowledge of the time course of soluble adhesion molecule serum concentrations and their correlation to clinical or radiological findings is limited.

This study demonstrates that levels of soluble adhesion molecules are highly variable between patients after acute cerebral ischemia. Other investigators also found a large range of soluble adhesion molecule concentrations in stroke patients, with a considerable overlap with normal individuals.18 The present study was not designed to answer the question of whether adhesion molecule concentrations are elevated after cerebral ischemia compared with those in healthy controls. We were not able to determine basal levels before stroke or TIA because of the study design. Because it is not known at which point after cerebral ischemia adhesion molecule levels reach basal levels again, we are not able to conclude that levels turned to normal at the end of the observation period in our study. Data from control groups that were published in the literature indicate the normal range of sICAM-1, sVCAM-1, and sE-selectin to be <310, 670, and 35 ng/mL, respectively.10,11,18,19 At least concerning sICAM-1, there is a considerable overlap of these normal ranges with data obtained from our patients. However, absolute concentrations may vary between studies because of different test systems and heterogeneous control groups. This may also explain the fact that data on soluble adhesion molecules after cerebral ischemia have been contradictory, at least in part. In 1 study, sE-selectin and sP-selectin were increased in patients within 24 hours after stroke and several weeks after a transient neurological deficit, compared with normal controls.18 In contrast, sICAM-1 and sVCAM-1 did not show any changes.18 Other investigators measured adhesion molecule levels within 24 hours after ischemic stroke and demonstrated sICAM-1 levels to be elevated compared with healthy controls, whereas E-selectin was unchanged.10 Clark and coworkers9 even reported decreased levels of sICAM-1 in acute stroke patients compared with controls or individuals with vascular risk factors.

The mean levels of sICAM-1, sVCAM-1, and sE-selectin in our cohort were within the range that was reported from patients after ischemia in prior studies.10,11,18 The large variability may have its cause in individual conditions before the ischemic event or in different pathogenetic processes during ischemia and therefore limits the validity of absolute concentrations. Infections significantly increase sICAM-1 levels and therefore interfere with ischemia-induced changes, since ICAM-1 is particularly involved in many inflammatory processes.20 Additionally, sICAM-1 levels were slightly higher in older patients and in the presence of arteriosclerosis. These differences were small and not significant after correction for multiple comparisons. Therefore, their pathogenetic or biological significance remains open. However, the benefit of
Adhesion Molecules in Acute Stroke

adjustment for multiple comparisons is controversial because the probability of a type II error is markedly increased. Nevertheless, others also described an increase of siCAM-1 with age, and ICAM-1 mRNA and protein were both shown to be expressed within arteriosclerotic plaques of the internal carotid artery in humans. In a recent study siCAM-1 levels were increased in patients at high risk of myocardial infarction. Patient numbers in our study were probably too small to yield highly significant results.

Beyond individual variability, our study indicates characteristic profiles of soluble adhesion molecule levels after cerebral ischemia. siCAM-1 peaked within the first 24 hours, which is in agreement with others. This short-lived peak is supported by findings in animal models and in human autopsy tissue. In a baboon stroke model, ICAM-1 was expressed in postcapillary microvessels for only 4 hours after reperfusion. After photochemically induced stroke in the rat, ICAM-1 was demonstrated until day 4 in the penumbral area. In humans, ICAM-1 expression was found until day 8 after stroke in cerebral microvessels within the area of infarction. These differences may be due to the variable times of reperfusion in different models of ischemia. Reperfusion may lead to an increased cleavage and solubilization of the extracellular domain of adhesion molecules. As in human stroke, the extent and timing of reperfusion largely vary between patients; this may be another reason for interindividual variability of soluble adhesion molecule levels.

In the present study more than half of the patients revealed a second peak of siCAM-1 levels at the end of the second week, which did not reach statistical significance in the whole study population. However, it possibly indicates a second phase of endothelial activation in the later course of stroke pathogenesis, which may be related to cytokine-induced tissue remodeling. For example, tumor necrosis factor- is capable not only of inducing adhesion molecule levels between patients with completed stroke and those with TIA (Table 2), nor did others. However, the characteristic courses of each soluble adhesion molecule over time after cerebral ischemia were only found in patients after completed stroke but not after TIA. This may reflect the pathogenetic differences between these 2 conditions with respect to a more prominent endothelial activation and subsequent adhesion molecule expression in stroke compared with transient ischemia. The increases of siCAM-1 and sVCAM-1 in particular were absent in TIA but pronounced in severe infarctions.

Overall, our data indicate that measurement of soluble adhesion molecules after acute cerebral ischemia seems not to offer sufficient surrogate markers for the estimation of infarct size and clinical disability or outcome in individual patients. However, specific time courses of sE-selectin levels seemed to be linked to the clinical course. Although not significant after correction, the initial increase was slightly higher in patients with poor prognosis and the final decrease was more pronounced in patients with less disability. As mentioned above, E-selectin is involved in the rolling of granulocytes on the endothelial surface, which is the first step of leukocyte adhesion. From animal models it is suggested that this may
lead to the so-called no-reflow phenomenon, which refers to insufficient reperfusion because of intravascular granulocyte deposits. Treatment with antiadhesion receptor antibodies in a primate stroke model was capable of reducing the no-reflow phenomenon. Therefore, the pronounced expression of adhesion molecules such as E-selectin may lead to a no-reflow state in cerebral microvessels after acute stroke and worsen prognosis.

In conclusion, this longitudinal study shows that levels of soluble adhesion molecules after cerebral ischemia vary significantly between patients. In the majority of patients each soluble adhesion molecule shows a characteristic course in completed stroke but not in TIA. sICAM-1 peaks within the first 24 hours, whereas sVCAM-1 has its maximum after 5 days. In contrast, sE-selectin levels decrease within 5 days after cerebral infarction. Since there was no clear-cut correlation of soluble adhesion molecule levels with clinical findings and infarct size, we do not regard these molecules as candidates for surrogate markers that would allow prognostic allocation of patients. Concentrations are influenced by additional factors independent from ischemia. Our data provide further evidence that adhesion molecules are involved in the pathogenesis of stroke. However, the exact role of each adhesion molecule remains to be defined in detail. This is of particular importance in view of the therapeutic strategies in stroke, which are directed against adhesion molecules.

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References

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http://stroke.ahajournals.org/content/29/10/2129