Role of cell adhesion molecules in acute ischemic stroke

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BACKGROUND AND OBJECTIVES: The expression of soluble adhesion molecules inter-cellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), besides activation of endothelial cells and transendothelial migration of leukocytes, play an important role in inflammation and progression of ischemic injury after acute stroke. The aim of this study was to determine serum levels of soluble ICAM-1 and VCAM-1 in patients with acute ischemic stroke and controls and correlate them according to etiological subtypes (thromboembolic or lacunar stroke), stroke severity and disability after acute stroke.

PATIENTS AND METHODS: Hospital-based prospective study of acute stroke patients hospitalized between December 2008 and September 2009 at the University Hospital Sestre Milosrdnice in Zagreb, Croatia.

METHODS: We enrolled 110 patients with acute ischemic stroke and 93 healthy individuals as controls. Serum concentrations of VCAM-1 and ICAM-1 were determined by means of quantitative sandwich enzyme immunoassay. Patients were classified according to etiological subtype, clinical severity of stroke and disability after stroke.

RESULTS: There was no significant difference between levels of soluble adhesion molecules VCAM-1 and ICAM-1 in patients and in controls. Levels of VCAM-1 were significantly higher in patients with thromboembolic stroke than in controls. There was no significant correlation between levels of soluble adhesion molecules VCAM-1 and ICAM-1 and stroke severity and disability. There was marked biological interindividual variability in all patient groups.

CONCLUSION: This study confirms the role of adhesion molecule VCAM-1 in the pathogenesis of acute thromboembolic stroke.

Many risk factors have been found for the appearance of a stroke and new factors are continually recognized.[1,2] The awareness that atherosclerosis is partially an inflammatory disease has lead to the acceptance of inflammation and its markers as new and significant risk factors for the development of cardiovascular and cerebrovascular diseases. The results of many recent studies suggest that the role of inflammation in the occurrence and development of ischemic brain damage is an important one.[3] Molecular adhesion and the development of cytokines occur in the early stage of ischemia and reperfusion, and they represent the foundation for an ischemic injury evolving into an inflammatory one.[4-7]

Acute stroke patients demonstrate alterations in the concentration of ICAM-1 and lymphocyte adhesion molecule 1 (L-selectin) similar to those seen in patients with vascular risk factors.[8] Former studies have demonstrated that acute stroke patients have increased levels of lymphocyte function-associated antigen 1 (LFA-1) and macrophage 1 antigen (Mac-1) on leukocytes.[9] Today, as thrombolytic therapy has become available outside of clinical studies, a decrease in reperfusion damage has become a promising therapeutic goal. The application of anti-adhesion therapy can prolong the time frame for the application of recombined tissue plasminogen, which could increase the effectiveness of thrombolytic therapy in the treatment of acute ischemic stroke.[10]

The objectives of this research were defining and comparing the serum levels of adhesive VCAM-1 and ICAM-1 molecules in patients who had an acute ischemic stroke and a control group, comparing the VCAM-1

and ICAM-1 levels in the thromboembolic and lacunar ischemic stroke and comparing the VCAM-1 and ICAM-1 levels with the severity of the stroke and the outcome of the patients with acute ischemic stroke. By discovering the role of the inflammation in the occurrence and development of the acute ischemic stroke, it might be possible to recognize patients at a high risk of stroke and applying anti-inflammatory therapeutic strategies to decrease the ischemic brain damage and restrict the neurological damage to the patient.

PATIENTS AND METHODS

The research was performed at the Neurology department, Sestre Milosrdnice, University Hospital, which is the Reference Centre for Neurovascular Disorders of the Ministry of Health of the Republic of Croatia. We consecutively included 110 acute stroke patients hospitalized in the period between December 2008 and September 2009. For each patient, we obtained the anamnesis, determined the somatic and neurological status and performed computerized brain tomography (CT), color Doppler sonography of carotid arteries and electrocardiograph (ECG). In patient blood samples, we defined the serum concentrations of adhesion molecules VCAM-1 and ICAM-1, the complete blood picture, the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and the blood sugar. Only patients with acute ischemic stroke hospitalized within 24 hours from the occurrence of symptoms were included in the study.

The diagnosis of acute ischemic stroke was set based on clinical signs and symptoms of a sudden focal or global disorder of brain functions caused by an ischemic event and based on CT results.[2] The CT excluded the existence of cerebral hemorrhage and other possible causes of a brain damage (eg, a tumor) that can imitate the clinical picture of ischemic stroke. For patients who underwent CT within the first 12 hours from the occurrence of symptoms and had normal findings, a control screening was performed between the third and the fifth day of hospitalization. Patients with a transitory ischemic stroke, cerebral hemorrhage and those who during the admittance demonstrated increased ESR (>30 mm/h), increased body temperature (>37.5°C), increased values of C-reactive protein (>10mg/L) or clinical signs of respiratory, urinary of other system infection, were not included in the study.

The control group consists of 93 examinees of the same age and sex who suffered from headaches and/or dizziness. They were afebrile with no signs of respiratory, urinary or system infection, ESR or C-reactive protein were within the referential values and they had normal CT findings.

Patients with acute ischemic stroke were divided according to the pathogenic stroke form into two groups: patients with thromboembolic (TE) and patients with lacunar stroke.

The diagnosis and the determination of the pathogenic ischemic stroke form were performed by a neurologist experienced in diagnosing and treating the acute ischemic stroke based on anamnesis, somatic-neurological examination, CT, color Doppler sonography of carotid arteries and EKG. CT was read by a neuroradiologist experienced in the neuroradiological picture diagnostics of acute ischemic stroke. Patients with lacunar ischemic stroke caused by embolism from the internal carotid artery or heart were not included in the study.

All blood samples were taken into test tubes that contained ethylenediaminetetraacetic acid (EDTA) as anticoagulant and were centrifuged within 30 minutes after they had been taken and stored at the temperature of -20°C until the measuring procedure started. The serum concentrations of ICAM-1 and VCAM-1 were defined by quantitative enzyme immunoassay (RandD Systems, Minneapolis, USA).

The severity of a stroke was determined during the blood sampling, i.e. within 24 hours from the occurrence of stroke symptoms. The severity was determined based on neurological status that was evaluated according to the National Institute of Health Stroke Scale (NIHSS). The outcome of a stroke was determined on the tenth day after the disease had occurred according to the Barthel Index (BI).

For statistic analyses we used Statistical Analysis System (SAS) software (Institute Inc., Cary, North Carolina) for Windows 95/98/NT/Me/2000. As most of the variables did not follow the normal distribution, non-parametric tests were applied. For comparison of more than two groups the Kruskal-Wallis test was used, while the Mann-Whitney test with a correction was used for comparing pairs because of multiple testing. For comparing quantitative marks the chi-square test was applied. Numeric marks were graphically portrayed in "box-plot" form.

All ethical principles of the medical profession were followed according to the Helsinki Declaration and Good Clinical Practice. All examinees were informed in advance about the procedures that were to be used during the research and they signed an approval for the participation in the research. The Ethical Committee of the Clinical Hospital Sestre Milosrdnice concluded that the research followed the Good Clinical Practice and accepted the research protocol.

RESULTS

The research included 110 patients with acute stroke and 93 examinees as controls. The distribution of patients according to their age, stroke severity and its outcome, as well as the distribution of controls according to their age is shown in **Table 1**. The patient group included 62 men (56.4%) and 48 women (43.6%). The control group included 52 men (55.9%) and 41 women (44.1%). There was no significant differences between the two groups regarding age (P=0.815; Mann-Whitney test) and sex (P=.949; χ^2 test). There was no significant difference in the concentration of VCAM-1 and ICAM-1 in patients with acute ischemic stroke and examinees from the control group (**Table 2**). The patients with thromboembolic stroke included 67 examinees, 35 men and 32 women, whereas the the patients with lacunar stroke included 43 examinees, 27 men and 16 women. The patients with thromboembolic and lacunar stroke showed no statistically significant difference to the control group in age (P=.259; Kruskal-Wallis test) and sex (P=.552; χ^2 test). The serum concentrations of adhesion molecules in patients with thromboembolic or lacunar ischemic stroke are represented in **Table 3**. Serum values of VCAM-1 were statistically significantly higher (P=.023; Mann-Whitney test) in the group of patients with thromboembolic stroke than in the control group, but this was not the case when we compared serum values of ICAM-1 in these two groups (P=.204; Mann-Whitney test)

The group of patients with light stroke included 45 examinees, the group with moderate stroke included 37 patients and the group with severe stroke included 28 examinees. The values of serum concentrations of VCAM-1 and ICAM-1 did not differ significantly between the examined groups (**Table 4**).

The patients with thromboembolic stroke included 67 examinees, 15 of whom had a light stroke, 27 suffered from a moderate one and 25 had a severe stroke. The group of patients with lacunar stroke included 43 examinees, 30 of whom had a light stroke, 10 suffered from a moderate one and three patients had a severe stroke. Serum concentrations of VCAM-1 and ICAM-1 did not differ significantly between the examined groups (**Table 5**). Poor recovery was observed among 43 of 110 patients (BI<60), 24 recovered partially (BI 60-84) and 43 patients recovered well after the stroke (BI≥85). The results of measuring serum concentrations of VCAM-1 and ICAM-1 did not differ significantly between the examined groups (**Table 6**). Patients with thromboembolic stroke included 67 examinees, 33 of whom had a poor functional recovery, 17 of them recovered partially and 16 patients recovered well. The group of patients with lacunar stroke included 43 examinees, 9 of whom had a poor functional recovery, 7 of them recovered partially and 27 patients recovered well. The results of measuring serum concentrations of VCAM-1 and ICAM-1 statistically did not differ significantly between the examined groups (**Table 7**).

Table 1. Distribution of patients according to age, stroke severity and outcome and distribution of examinees in the control group according to their age.

Feature	Patients group (n=110)			Control group (n=93)		
	Arithmetic mean	Standard deviation	Minimum	Arithmetic middle	Standard deviation	Minimum
	Maximum	Median	Extent	Maximum	Median	Extent
Age	70.2	9.6	36	70	9.5	47
	86	72	50	86	71	39
Stroke severity	11	6.6	2	-	-	-
	28	9.0	26	-	-	-
Outcome	58.2	35.5	0	-	-	-
	100	70.0	100	-	-	-

The patient group included 62 men (56.4%) and 48 women (43.6%). The control group included 52 men (55.9%) and 41 women (44.1%). There was no significant differences between the two groups regarding age (P=.815; Mann-Whitney test) and sex (P=.949; χ² test).

Table 2. Serum concentrations of adhesion molecules inter-cellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) in patients and controls.

Examinees	VCAM-1 ng/mL (range)	ICAM-1 ng/mL (range)
With acute stroke (n=110)	717.5 (90-1810)	375.55 (14.80-745.4)
Control group (n=93)	688 (555-850)	385.7 (213.7-463.9)

ICAM-1= Inter-cellular adhesion molecule 1; VCAM-1= Vascular cell adhesion molecule 1

Table 3. Serum concentrations of adhesion molecules inter-cellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) in examinees according to stroke type and controls.

Feature	Lacunar stroke (n=43)		Thromboembolic stroke (n=67)		Controls (n=93)	
	Minimum	Extent	Minimum	Extent	Minimum	Median
	Maximum	Median	Maximum	Median	Maximum	Extent
VCAM-1 ng/mL	445	765	90	1720	555	688
	1210	675	1810	730	850	295
ICAM-1 ng/mL	14.80	658.2	40.5	704.9	213.7	385.7
	673	358.3	745.40	376.5	463.9	250.2

ICAM-1= Inter-cellular adhesion molecule 1; VCAM-1= Vascular cell adhesion molecule 1

Table 4. Serum concentrations of adhesion molecules Inter-cellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) according to stroke severity.

Examinees	VCAM-1 ng/mL (range)	ICAM-1 ng/mL (range)
Light stroke (n=45)	710 (445-1210)	374.7 (14.8-637)
Moderate stroke (n=37)	730 (295-1520)	374 (135.3-662.2)
Severe stroke (n=28)	712.5 (90-1810)	376.9 (163.7-745.4)

ICAM-1= Inter-cellular adhesion molecule 1; VCAM-1= Vascular cell adhesion molecule 1

Table 5. Serum concentrations of adhesion molecules Inter-cellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) according to stroke type and severity.

Examinees	Stroke severity	VCAM-1 ng/mL (range)	ICAM-1 ng/mL (range)
Thromboembolic stroke (n=67)	Light (n=15)	720 (605-970)	400.9 40.5-641.1
	Moderate (n=27)	755 (295-1520)	375.2 172.10-662.2
	Severe (n=25)	720 (90-1810)	376.4 163.7-745.4
Lacunar stroke (n=43)	Light (n=30)	697.5 (445-1210)	374.1 (14.8-673)
	Moderate (n=10)	662.5 (450-1190)	284.35 (135-531.9)
	Severe (n=3)	650 (595-1090)	377.4 (267-595.2)

ICAM-1= Inter-cellular adhesion molecule 1; VCAM-1 = Vascular cell adhesion molecule 1
The group of patients with thromboembolic stroke included 67 examinees, 15 of whom had a light stroke, 27 suffered from a moderate one and 25 of them had a severe stroke. The group of patients with lacunar stroke included 43 examinees, 30 of whom had a light stroke, 10 suffered from a moderate one and three patients had a severe stroke. Serum concentrations of VCAM-1 and ICAM-1 did not differ significantly between the examined groups.

Table 6. Serum concentrations of adhesion molecules Inter-cellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) according to recovery after stroke.

Examinees	VCAM-1 ng/mL (range)	ICAM-1 ng/mL (range)
Poor recovery n=43	720 (90-1520)	375.9 (83.5-745.4)
Partial recovery n=37	722,5 (540-1810)	370.85 (40.5-618)
Good recovery n=28	705 (295- 1210)	407.5(14.8-767.3)

ICAM-1= Inter-cellular adhesion molecule 1; VCAM-1= Vascular cell adhesion molecule 1
Poor recovery was observed among 43 out of 110 patients (BI<60), 24 recovered partially (BI 60-84) and 43 patients recovered well after the stroke (BI≥85). The results of measuring serum concentrations of VCAM-1 and ICAM-1 did not differ significantly between the examined groups (Table 6).

DISCUSSION

In this research, serum concentrations of soluble adhesion molecules VCAM-1 and ICAM-1 in patients with acute ischemic stroke were not significantly different statistically from serum concentrations of VCAM-1 and ICAM-1 in the control group. Regarding the pathogenetic type of ischemic stroke, serum concentrations of VCAM-1 were significantly higher in patients with thromboembolic ischemic stroke than in the control group. Serum concentrations of adhesion molecules VCAM-1 and ICAM-1 in patients with acute ischemic stroke statistically showed no significant difference with respect to the severity and outcome of the stroke. As to the pathogenetic type of ischemic stroke, serum concentrations of adhesion molecules VCAM-1 and ICAM-1 statistically showed no significant difference with respect to the severity and outcome of thromboembolic and lacunar stroke.

In all patients, in subgroups of patients with thromboembolic and lacunar ischemic stroke and in patients according to the severity and outcome of the stroke, as well as in the subgroups of patients with thromboembolic and lacunar stroke, depending on the severity and outcome of a stroke, a higher biological interindividual variability in serum concentrations of soluble adhesion molecules VCAM-1 and ICAM-1 was noticed than among the examinees from the control group.

Many authors have examined the role and significance of soluble adhesion molecules in the cascade flow of etiopathogenetic events during ischemic brain damage. The results published so far are very heterogenous and it is still not possible to draw a conclusion that would generalize all current findings. The most significant reason for that is probably the inability of standardizing the research conditions in order for the obtained results to be scrutinized by means of unified measuring standards and be interpreted in the same way. The selection criteria for patients are often not the same and different authors also define the controls (healthy examinees) in various ways.[11-13]

This study excluded all patients with acute ischemic stroke who within the first 24 hours from the occurrence of symptoms showed clinical signs of a respiratory, urinary or another system infection, had an increased body temperature (>37.5°C), leukocytosis or an increased ESR. In this way the possibility that increased concentrations of adhesion molecules VCAM-1 and ICAM-1 indicate the existence of a systemic inflammation and not local ischemic brain damage was eliminated. In the research of Bitsch and colleagues,[14] in which a significant increase in concentrations of adhesion molecules ICAM-1 and VCAM-1 appeared in patients with acute ischemic stroke,

the patients who showed signs of a system inflammation were recognized, but not excluded from the research.

In this study, the control group included examinees with normal morphological CT results who had no clinical or laboratory signs of a system infection. However, examinees with hypertension and diabetes, smokers, overweight examinees and examinees with a heart or vascular disease were not excluded from the research. The existence of vascular risk factors of atherosclerosis in these examinees allows for the possibility that their concentrations of adhesion molecules VCAM-1 and ICAM-1 are increased.[15] Research of Frijns and colleagues,[16] and DeGraba and colleagues[17] showed that in humans endothelial cells above the atherosclerotic plaque extensively produce adhesion molecules P-selectin, ICAM-1 and VCAM-1. This could be one of the reasons why our research failed to show any increase in concentrations of adhesion molecules VCAM-1 and ICAM-1 in patients with acute ischemic stroke.

Increased concentrations of serum inflammatory adhesion molecules VCAM-1 and ICAM-1 were noticed in patients with ischemic stroke, although the results are contradictory. The research of Bitsch and authors[14] showed that ICAM-1 concentrations reached their highest values within 24 hours from the moment of occurrence of acute ischemic stroke, whereas VCAM-1 values reached highest levels after five days. In the research performed by Šimundić and authors[18] the values of VCAM-1 and ICAM-1 were increased in patients with acute ischemic stroke, but the research did not exclude patients with laboratory or clinical signs of inflammation. Fassbender and colleagues[19] demonstrated increased concentrations of ICAM-1 in patients who had risk factors for the development of vascular diseases, but a statistically significant difference between this group of examinees and patients with acute ischemic stroke was not proved. Clark and colleagues[20] did not prove the increase of concentrations of ICAM-1 in patients with ischemic stroke; the reason could be the fact that blood samples were taken within 72 hours from the moment when symptoms occurred.

Possible explanations for contradictory results include the differences between control groups, laboratory tests and time frames of blood sampling. Various drugs can also alter the expression of adhesion molecules, e.g. aspirin, corticosteroids and non-steroid anti-inflammatory drugs. In the research performed by Fassbender and colleagues[19] patients with acute ischemic stroke were treated by heparin and did not receive acetylsalicylic acid, which has anti-inflammatory effects

Table 7. Serum concentrations of adhesion molecules inter-cellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) according to stroke type and recovery after stroke.

Stroke type	Stroke recovery	VCAM-1 ng/mL (range)	ICAM-1 ng/mL (range)
Thromboembolic stroke	Poor (n=33)	730 (90-1520)	387.5 (83.50-745.4)
	Partial (n=17)	730 (540-1810)	367.7 (40.5-618)
	Good (n=16)	725 (295-1125)	430.55 (172.1-641.1)
Lacunar stroke	Poor (n=9)	675 (450-1190)	267 (176.9-611.7)
	Partial (n=7)	655 (595-845)	457.1 (135.3-612.6)
	Good (n=27)	690 (445-1210)	358.3 (14.8-673)

ICAM-1= Inter-cellular adhesion molecule 1, VCAM-1= Vascular cell adhesion molecule 1

and alters the response of an organism to an inflammation. The existence of other diseases, e.g. infections, diabetes or some system disease could affect the results.[21] Increased levels of ICAM-1 and VCAM-1, along with normal levels of E-selectin, were found in patients suffering from diabetes, especially those with silent stroke detected by MRI.[22]

The MITICO study[23] and study by Pinto and colleagues[24] have shown that, respectively, values of Interleukin-6 (IL-6), VCAM-1 and tumor necrosis factor (TNF-alpha), Von Willebrand factor (vWF), but not VCAM-1, are predictors of a new, recurrent vascular event. However, in this research we determined levels of VCAM-1 and ICAM-1 in acute stroke patients and it was not designed to assess the risk of recurrence of vascular disease.

The significance of this research can be related to the fact that the connection between the adhesion molecule VCAM-1 and the pathogenesis of thromboembolic acute ischemic stroke was proven. Due to a large inter-individual variability there are no indications in the current clinical practice that would determine these molecules as markers of a local inflammatory event within the acute stroke. The clinical significance of the role of these molecules in the inflammatory response after the acute ischemic stroke opens a new therapeutic area in treating acute ischemic stroke by means of combined effects of anti-inflammatory anti-adhesion therapy that would be able to prolong the time frame for the application of reperfusion-thrombolytic therapy.

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