

THE ROLE OF CONVENTIONAL AND SOME LESS CONVENTIONAL RISK FACTORS IN THE PATHOGENESIS OF ACUTE ISCHEMIC STROKE

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SUMMARY – The aim of the study was to determine the role of some conventional and some less conventional risk factors for stroke, such as inflammatory adhesion cell molecules, in the pathogenesis of ischemic stroke, and their relationship. Sixty-seven subjects with acute ischemic stroke and 76 healthy controls were enrolled in the study. On admission, the concentration of soluble adhesion molecules, C-reactive protein, erythrocyte sedimentation rate and total leukocyte count were determined. The concentrations of soluble adhesion molecules were determined using quantitative sandwich enzyme immunoassay. On the next morning, fasting blood glucose, triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol concentrations were determined in patient sera. Results showed the mean levels of sICAM-1, sVCAM-1 and sE-selectin to be higher, and that of sL-selectin lower in patients with acute ischemic stroke than in controls. In patients, soluble adhesion molecule levels did not differ with respect to carotid atherosclerotic disease, smoking status, hypertension and hypercholesterolemia. Some soluble adhesion molecules correlated with blood glucose, lipid parameters and markers of inflammation.

Key words: *Cerebrovascular disorders – etiology; Brain ischemia – pathophysiology; Risk factors; C-reactive protein analysis; Leukocyte count*

Introduction

Stroke is the third leading cause of death worldwide and the first leading cause of death in Croatia. It is also the leading cause of long-term disability, both worldwide and in Croatia^{1,2}. It poses an enormous financial burden and has a major financial impact on the healthcare system. Due to its unacceptably high morbidity and mortality, it is extremely important to understand the pathophysiology of acute stroke as well as the role of all known and some less known risk factors for stroke.

Stroke is an etiologically heterogeneous disease, but atherosclerosis contributes to a large proportion of cases either directly *via* aortic, cervical or intracranial large artery atherosclerosis, or indirectly by cardioembolism, e.g., as the re-

sult of cardiac arrhythmias caused by coronary heart disease or emboli after myocardial infarction. Atherosclerosis is today perceived as a chronic inflammatory vascular condition, and infectious disease are believed to contribute to its pathophysiology.

A key pathophysiological event in the development of ischemic lesion in acute stroke is the upregulation of inflammatory cell adhesion molecules and subsequent transendothelial migration of leukocytes to the site of injury.

Cell adhesion molecules are cell surface proteins that serve as mediators of cell-cell and cell-extracellular matrix interactions³. They are thought to be involved in cellular responses that occur as a consequence of hypoxia and subsequent reoxygenation. Soluble adhesion molecules may appear in the blood as the result of cell activation due to end proteolytic cleavage. Human E-selectin and L-selectin are members of the selectin family. E-selectin expression is found on endothelium within several hours of cytokine stimulation, whereas L-selectin is expressed on leukocytes.

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They both mediate rolling and tethering of leukocytes to the vascular endothelial cells, which is the first phase of transendothelial migration of leukocytes to the site of inflammation. Both human intracellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) belong to the immunoglobulin superfamily. They are expressed by activated endothelium and play an important role in leukocyte transendothelial migration by mediating firm adhesion of leukocytes to the vascular endothelium. In addition to this, weak expression of ICAM-1 is also found on leukocytes, epithelial and resting endothelial cells, whereas VCAM-1 is expressed in a wide variety of cell types³.

In this study we tried to show the role of some conventional risk factors for stroke and of inflammatory parameters in the pathogenesis of ischemic stroke, and their relationship with conventional risk factors for stroke. We also tried to determine whether upregulation of adhesion molecules and other markers of inflammation correlated with each other.

Subjects and Methods

Sixty-seven patients admitted to Emergency Unit of the University Department of Neurology, Sestre milosrdnice University Hospital, Zagreb, Croatia, within 24 hours of the onset of acute ischemic stroke were included in the study. The diagnosis was made on the basis of patient history, neurologic examination and cerebral computed tomography (CT). Demographic characteristics (age, sex) and risk factor profile (diabetes mellitus, carotid disease, smoking status, hypertension, total blood cholesterol) were collected for each patient. Diabetes mellitus, smoking status and hypertension were ascertained from patient personal history. Seventy-six apparently healthy volunteers asymptomatic for vascular disease served as a control group. Exclusion criteria

for cases and controls was the presence of inflammation and malignant disease.

On admission, the concentration of soluble adhesion molecules, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and total leukocyte count were determined. The concentrations of adhesion molecules, sICAM-1, sVCAM-1, sE-selectin and sL-selectin, were determined by the commercially available quantitative sandwich enzyme immunoassay (R&D Systems, Minneapolis, USA). On the next morning, fasting blood glucose, triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol concentrations were determined in patient sera, using standard enzymatic methods on an Olympus AU600 analyzer.

Data were analyzed for normality using Kolmogorov-Smirnov test prior to further analysis. Data are presented as mean \pm SD and median (range) for normal and non-normal distribution, respectively. Differences between data sets were tested using the parametric Student's t-test for normally distributed data sets, and nonparametric Mann-Whitney rank sum test for data sets that were not normally distributed. A $p < 0.05$ value was required for a difference to be considered significant. Spearman rank order correlation test was used to measure the strength of association between variables rising from the distributions that were not normal.

Results

Study populations

There were 67 acute stroke patients and 76 healthy volunteers as a control group, mean age 72 (45-88) and 52 \pm 16 years, 55% and 32% male, respectively. Biochemical parameters and risk factor profile according to the National Stroke Association (NSA) Stroke Prevention Guidelines of the patient and control group are presented in Tables 1 and 2, respectively.

Table 1. Biochemical parameters of study populations

Parameter	Acute stroke (n=67)	Controls (n=76)	p
Glucose (mmol/L)	6.9 (4.5 – 20.9)	5.7 (4.4 – 17.2)	<0.001
Triglycerides (mmol/L)	1.33 (0.53 – 7.22)	1.2 (0.2 – 7.1)	0.410
Total cholesterol (mmol/L)	5.6 \pm 1.3	6.0 \pm 1.3	0.050
HDL-cholesterol (mmol/L)	1.1 \pm 0.4	1.4 (0.6 – 2.2)	<0.001
LDL-cholesterol (mmol/L)	3.6 \pm 1.1	3.8 \pm 1.0	0.170
Erythrocyte sedimentation rate (mm/h)	15 (2 – 90)	10 (1 – 35)	0.002
Total leukocyte count (x10 ⁹ /L)	8.8 (5.1 – 38.7)	6.67 \pm 1.8	<0.001
C-reactive protein (mg/L)	5.1 (0.5 – 183.8)	3.7 \pm 2.2	0.063

Table 2. Stroke risk factors in patient group

Clinical data	Acute stroke (n=67) n (%)
Arterial hypertension	58 (87)
Hypercholesterolemia (total cholesterol >5.2 mmol/L)	30 (45)
Stenosis >50% of at least one carotid artery	17/60 (28)
Previous stroke history	18 (27)
Diabetes mellitus	14 (21)
Atrial fibrillation	10 (15)
Previous or current smoking	8 (12)

Levels of soluble adhesion molecules in patients and controls

The mean levels of sICAM-1, sVCAM-1 and sE-selectin were higher, whereas sL-selectin was lower in patients than in controls. The observed differences were statistically significant for all four adhesion molecules. The highest sICAM-1 (1188 ng/mL), sVCAM-1 (462 ng/mL) and sE-selectin (2205 ng/mL) levels and the second highest sL-selectin (2390 ng/mL) level were observed in a female patient who was admitted with the diagnosis of acute stroke, developed cerebral death, and died within a few hours from admission.

The mean concentrations in patients and controls and p values are summarized in Table 3.

Relationship of soluble adhesion molecule concentrations with stroke risk factors

In the patient group there were 14 (21%) diabetic patients whose soluble adhesion molecule levels generally did not differ from those in nondiabetic patients, with the ex-

ception of sL-selectin. The mean levels of sL-selectin were higher in diabetic (1180 ± 409 ng/mL) than in nondiabetic (906 ± 375 ng/mL) patients. The difference was statistically significant ($p=0.004$). The patients were divided into three subgroups according to their duplex ultrasonography findings. Group 1 consisted of patients who had no evidence of vascular disease (6/60, 10%), group 2 of patients with >50% stenosis of at least one carotid artery (17/60, 28%), and group 3 of patients in whom duplex ultrasonography provided some evidence of atherosclerotic changes, without a significant vascular lumen reduction (37/60, 62%). These subgroups were tested for difference in the levels of soluble adhesion molecules. There was no statistically significant difference in the levels of adhesion molecules according to the severity of atherosclerotic changes in the carotid vasculature.

In our patient group, there was no difference in the mean levels of adhesion molecules between smokers and non-smokers, hypertensive patients and those with normal blood pressure, or hypercholesterolemic patients and those with normal levels of blood cholesterol.

Discussion

The conventional stroke risk factors, including hypertension, diabetes mellitus, smoking, and cardiac disease, do not fully account for the risk of stroke, and stroke victims, especially young subjects, often do not have any of these factors.

Inflammatory parameters and chronic and acute infectious diseases have been considered to modify stroke risk independently of conventional risk factors. Although the roots of this topic go back as far as the 19th century, the discussion has strongly intensified during the last 5 to 10 years, with many new insights being gathered almost every month. However, results are often conflicting, and it appears increasingly difficult to keep abreast of this rapidly advancing field.

Table 3. Levels of soluble adhesion molecules in patients and controls

Group	sICAM-1 (ng/mL)	sVCAM-1 (ng/mL)	E-selectin s (ng/mL)	L-selectin s (ng/mL)
Acute stroke	361 ± 190	698 ± 289	75 ± 56	963 ± 395
Controls	342 (180–1188)	660 (225–2205)	62 (28–462)	890 (490–2530)
p	<0.001	0.034	0.002	0.043
P ^a	<0.001	0.046	0.003	0.028
P ^b	0.001	0.083	0.003	0.030

^ap values when the patient with maximal values was excluded from analysis; ^bp values after excluding two patients from analysis

Autopsy evidence of young children has revealed early fatty streaks in blood vessels in association with infiltration of foam cells and T cells, although this does not necessarily produce atherosclerosis. Increasing evidence supports the concept that migration of inflammatory cells to the vascular wall is intimately associated with the cause of vascular conversion leading to atherosclerosis⁴.

According to the response-to-injury hypothesis proposed by Ross and Glomset^{5,6}, atherosclerosis is initiated by the so-called damaging agents (high blood cholesterol, high homocysteine concentrations, cigarette smoking related components, tissue protein changes secondary to diabetes and aging, and some others), which in some way cause injury to the endothelium or dysfunctional endothelial response to these stimuli. The event secondary to the endothelial injury is infiltration of inflammatory cells to the site of injury. The cellular mechanisms involved in leukocyte-endothelium interactions include a wide variety of cell adhesion molecules.

Upregulation of some adhesion molecules has been described in patients with acute stroke, however, these data are still contradictory.

In this study, we confirmed some earlier reports mentioned above, that acute stroke is associated with elevated levels of soluble ICAM-1, VCAM-1 and E-selectin.

The link between traditional stroke risk factors and potential risk factors as adhesion molecules was also studied.

To measure the exact impact of these risk factors, a carefully designed prospective age-, sex-, and risk factor-matched study in a large cohort is needed. Some authors have reported on a significant correlation of soluble adhesion molecule levels with plasma concentrations of some biochemical parameters.

As expected, adhesion molecules strongly correlated with other markers of inflammation, such as ESR, total leukocyte count and CRP concentration in patients. While sICAM-1 and sVCAM-1 correlated with all three markers, sE-selectin correlated only with total leukocyte count and sL-selectin with CRP. The increase in the levels of soluble adhesion molecules and inflammatory markers indicated that inflammatory processes occurred in acute ischemic stroke. Namely, elevated plasma concentration of the markers of inflammation, upregulation of adhesion molecules, and infiltration of inflammatory cells occur as the result of abundant cytokine production in the area of cerebral ischemia and tissue injury.

Total leukocyte count, ESR and CRP are not absolutely specific markers of inflammation. They may also be elevat-

ed in some other conditions and diseases. Even smoking, obesity and aging were found to be associated with a moderate increase of CRP when measured with a high sensitivity method⁷. Since plasma levels of soluble adhesion molecules clearly indicate endothelial activation, with the exception of L-selectin which reflects neutrophil activation, we have hypothesized that soluble levels of adhesion molecules should have a high discriminating power in differentiating between acute ischemic stroke patients and healthy individuals.

Based on the results obtained, we conclude that acute ischemic stroke is associated with elevated plasma levels of inflammatory adhesion molecules sICAM-1, sVCAM-1 and E-selectin, independently of age, sex and other recognized stroke risk factors. That increase is an indicator of inflammatory process and is most probably transient in nature. The levels of sL-selectin are decreased in stroke patients and may be influenced by age, sex, and blood glucose levels.

Ridker *et al.*⁸ correlated ICAM-1 with fibrinogen, HDL-cholesterol, homocysteine, triglycerides, tissue type plasminogen-activator antigen and CRP in a large prospective cohort. Steiner *et al.*⁹ found E-selectin to correlate with LDL-cholesterol in a case-control study of 70 patients with type 2 diabetes.

In our group of stroke patients, adhesion molecules correlated significantly between each other, with the exception of the sVCAM-1 *vs.* sE-selectin and sE-selectin *vs.* sL-selectin pairs. This may point to some common mechanisms shared among various types of adhesion molecules, which induce their expression.

In healthy subjects, there was no correlation between the concentrations of various adhesion molecules, indicating the distribution of the adhesion molecule concentrations in this group to be exclusively due to inter-individual variability and to some extent only moderately influenced by some other factors. The population of healthy subjects was not exposed to any of the stimulating factors the contribution of which to the overall increase in the adhesion molecule concentrations could have been comparable with the impact of acute ischemia in stroke patients.

Patient levels of sICAM-1 and sL-selectin as well as the levels of sICAM-1, sVCAM-1 and sE-selectin in healthy controls correlated with blood glucose concentration. A study performed by Morigi *et al.*¹⁰ offers the possible explanation of the causal relationship between glucose concentration and soluble adhesion molecule levels. They found hyperglycemia to augment the leukocyte-endothelial interactions through upregulating the cell surface expression of adhesive proteins in an NF-kappa B dependent fashion.

Interestingly enough, in our stroke patients the concentrations of soluble adhesion molecules did not correlate with any of the lipid parameters tested, i.e. total serum cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides. We believe that this finding does not exclude the possibility that lipid parameters may have an impact on the adhesion molecule expression. Instead, we emphasize again that this should most probably be explained by the current difficulty to differentiate which fraction of the soluble adhesive molecule concentration has occurred in response to acute ischemia and which due to stimulation with plasma lipid components.

In our control group the increase in the concentrations of sICAM-1, sVCAM-1 and sE-selectin adhesion molecules paralleled the increase in the concentration of triglycerides, whereas the concentration of sVCAM-2 correlated with the concentration of cholesterol. In contrast to acute ischemia in stroke patients, in healthy subjects there is no obvious reason for the significant increase in the adhesion molecule concentrations. Thus, any increase in the concentration of soluble adhesion molecules in normal subjects clearly occurs due to stimulation with other factors, e.g., glucose, lipids, changes in blood pressure, etc. In stroke patients, this increase is probably masked by the effect of ischemia. We consider that certain plasma lipid components must have an atherogenic action stimulating vascular endothelium for adhesion molecule expression, and that their overall contribution to the increase in the adhesion molecule concentrations is measurable though low in comparison with the increase due to acute ischemia.

An interesting aim of this study was to evaluate the correlation of adhesion molecules with stroke risk factors. Our interest was focused on whether or not the presence of diabetes mellitus is associated with an additional increase in the serum level of adhesion molecules. As expected, our stroke patients with diabetes (14/67) as an underlying disease had increased concentrations of adhesion molecules, compared to stroke cases without diabetes (53/67). However, the difference reached statistical significance only in case of sL-selectin ($p=0.002$). The increased concentration of sL-selectin in diabetic subjects might also be a late consequence of the autoimmune destruction of the pancreatic Langerhans islets. The more so, some authors propose that consecutive measurement of sL-selectin concentration may prove useful in the follow-up of the course of disease and therapeutic effect in type 1 diabetes¹¹. Other stroke risk factors have also been examined for the possible association with plasma levels of soluble adhesion molecules. The levels of soluble adhesion molecules did not differ significant-

ly between patients with and without the presence of high cholesterol, smoking, hypertension, infection and evidence for vascular disease as diagnosed by duplex ultrasonography.

Arterial hypertension is perhaps the most extensively studied risk factor; accordingly, antihypertensives are most potent in stroke prevention. The association of chronically or acutely elevated blood pressure with markers of inflammation is well documented. Circulating levels of sICAM-1, sVCAM-1 and sE-selectin have been reported to be increased in patients with essential hypertension¹². Risk factors may perturb vascular function through additive, "ping-pong", or even synergistic effects, which involve systemic inflammation. Indeed, cross-sectional observations are consistent with the hypothesis that abnormal vascular function in type 2 diabetes in hypertensive subjects is at least in part secondary to increased inflammation, with associated EC and platelet activation¹³.

Cigarette smoking is generally held to be immunosuppressive, and in association with a prohemostatic risk factor, smoking may be a proinflammatory factor. Smoking increased circulating levels of sICAM-1 and decreased the number of activated circulating monocytes, which may indicate augmented cell-cell adhesion. In a population already harboring ischemic cerebrovascular disease, those who smoked had increased levels of sICAM-1 and sE-selectin¹⁴. Cross-sectional studies also showed associations between vascular risk factors, including diabetes mellitus, smoking, and hyperlipidemia, and inflammatory indexes such as leukocyte count, C-reactive protein and fibrinogen¹⁵.

Increased concentrations of triglycerides, cholesterol and glucose are related to moderately elevated concentrations of adhesion molecules in asymptomatic individuals pointing to chronic inflammatory activation of endothelium. Additional studies are needed to elucidate the exact causal relationship of the observed phenomenon and to predict the possible effect of administration of antibodies against adhesion molecules on the ischemic cell damage after transient or permanent cerebral artery occlusion in humans¹⁶.

In contrast to the previous report by Fassbender *et al.*¹⁷, our observation was that the increased number of risk factors in an individual did not tend to increase the levels of soluble adhesion molecules in the patient group. Bitsch *et al.*¹⁸ found no difference either in the levels of soluble adhesion molecules between patients with and without history of arterial hypertension, history of cerebral ischemia, and evidence for atherosclerosis in any vascular territory. It is not questionable whether some risk factors can influence the concentration of adhesion molecules, but the question is how to identify the proportion in the circulation which is due to acute ischemia and which to vascular risk factors.

This study was one more attempt to establish a connection between chronic infection and stroke. On the basis of current knowledge, chronic infections appear to be risk factors that may act in cooperation with conventional risk factors and genetic predisposition, and are neither necessary nor sufficient for disease development. The role of chronic infection and inflammation in stroke pathogenesis is still incompletely defined. Future studies need to investigate whether inhibition of inflammation or long-standing antimicrobial therapies will reduce the risk of ischemic stroke to offer effective adjuncts to platelet inhibitors, anticoagulants, and statin therapies already in clinical use.

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Sažetak

ULOGA KONVENCIONALNIH I NEKIH MANJE KONVENCIONALNIH RIZIČNIH ČIMBENIKA U PATOGENEZI AKUTNOG ISHEMIJSKOG MOŽDANOG UDARA

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Cilj istraživanja bio je utvrditi ulogu konvencionalnih i nekih manje konvencionalnih rizičnih čimbenika za moždani udar, poput upalnih adhezijskih staničnih molekula, u patogenezi ishemijskog moždanog udara, kao i njihov međuodnos. Šezdesetsedmoro bolesnika s akutnim ishemijskim moždanim udarom koji su bili primljeni na Kliniku za neurologiju, KB „Sestre milosrdnice“ u razdoblju od ožujka 2000. do ožujka 2001. godine, te 76 zdravih dobrovoljaca iz Doma zdravlja "Centar" bilo je uključeno u istraživanje. Pri dolasku je svim bolesnicima određena koncentracija adhezijskih molekula, C-reaktivnog proteina te ukupan broj leukocita u serumu. Koncentracija topljivih adhezijskih molekula određena je kvantitativnim enzimskim imunotestom. Dan nakon dolaska određena je serumska koncentracija glukoze, triglicerida, ukupnog kolesterola, HDL-kolesterola. Rezultati su pokazali da su vrijednosti konvencionalnih čimbenika u bolesnika značajno veće nego u kontrolnoj skupini. Odds omjer bio je 15,8 (95% CI 6,69-37,36) za hipertenziju, 12,6 (95% CI 2,78-56,85) za stenozu karotida >50%, 2,6 (95% CI 0,98-6,9) za šećernu bolest, 6,5 (95% CI 1,36-30,79) za atrijsku fibrilaciju, te 1,6 (95% CI 0,51-4,81) za pušenje. Vrijednosti unutarstaničnih adhezijskih molekula -1 (ICAM-1), vaskularnih staničnih adhezijskih molekula -1 (VCAM-1) i E-selektina bile su više u bolesnika nego u kontrolnih osoba ($p < 0,001$, 0,034, 0,002), dok je vrijednost sL-selektina bila niža u skupini bolesnika ($p = 0,043$).

Ključne riječi: *Cerebrovaskularne bolesti – etiologija; Moždana ishemija – fiziopatologija; Rizični čimbenici; Analiza C-reaktivnog proteina; Broj leukocita*