The relationship between concentration of Lp(a), changes in hemostatic system and severity of ischemic brain disease

Major Assist. Prof. **Ranko Raičević**[*], MD, PhD, Lt. General Prof. **Aco Jovičić**[*], MD, PhD, Assist. Prof. **Pavle Jović**[†], PharG, PhD, **Slavka Mandić-Radić**[†], BS, Major-General Prof. **Momčilo Krgović**[‡], MD, PhD, Lt. Col. **Ljubo Marković**[||], MD, MA, Capt. 1st Class. **Dragan Dinčić**[‡], MD, MA, **Dragana Đorđević**[*], MD, PhD

Military Medical Academy, [*]Clinic of Neurology, [†]Institute of Biochemistry, [‡]Clinic of Cardiology, [||]Institute of Radiology, **Belgrade**

Vascular brain disorders are ranked the third as the causes of morbidity and mortality in spite of the progress in diagnostic, therapeutical and preventive measures. Ischemic brain disease is the most frequent of vascular brain diseases and it represents the most severe final stage of cerebral artery atherosclerosis. Etiopathogenesis of atherosclerosis is still unclear and one of the acceptable hypothesis would be the one concerning the lipid oxidation. The main point of this hypothesis is the oxidative modification of LDL and Lp(a) including numerous physiopathological factors with the central role of reactive oxidative matters, and endothelial dysfunction as the central change leading to coagulation system disorder. According to these facts we have established the hypothesis that in patients with IBD were found the changes in hemostatic system, which were in positive correlation with the concentration of Lp(a) and the degree and severity of IBD. The study comprised 60 patients with acute ischemic brain disease (IBD). Control group was comprised of 30 patients with IBD of nonvascular genesis, the disease of the similar general features. We examined the correlation of changes in hemostatic system (platelet aggregation, antithrombin III, D-dimer, protein C and S, factor VIII and PAI-1) and the degree and severity of IBD and changes in concentration of Lp(a) in the mentioned groups of patients. Our results pointed out that in patients with IBD existed the significant increase of procoagulant factors. Also, significant correlation was found between the increase of these factors and the increase in concentration of Lp(a).

K e y w o r d s : **brain ischemia; lipoprotein(a); atherosclerosis; cerebral arteries; ischemic attack, transient; brain infarction; hemostasis; blood coagulation disorders.**

Introduction

Due to the rapid development of science and technology, medicine has a trend of creating highly specialized experts, who tend to have a tunnel vision. Frequently, we neglect the multidisciplinary approach as well as the fact that an organism is not only one organ, but a fine organization of inter-relationships (1).

Vascular brain diseases are ranked the third as the cause of morbidity and mortality in the majority of countries, independently of their medical technological progress and socio-economic status. Ischemic brain disease (IBD) is represented in 80% of the cases (2).

Primary disorder responsible for the development of IBD is the atherosclerosis of cerebral arteries. There are several hereditary and habitual factors influencing the pro-

gression of this process. Since etiopathogenesis of atherosclerosis is still unclear, this study deals with the actual processes leading to atherosclerotic cerebral changes, especially with hemorrheologic and coagulation disorders. Less frequently the cause is lacunar infarction occurring during fibrinoid degeneration of penetrating cerebral arteries due to hypertension or brain infarction faused by cardiac origin embolism (1–7).

Lipid oxidation is one of the theories explaining this process. Oxidation of LDL and Lp(a) occurs under the activity of free radicals and enzymatic reactions. This influences the modification of apo B 100 (apoprotein specific for LDL), which leads to uncontrolled uptake of LDL from monocytes and macrophages in which degradation and deposition of cholesterol with foamy cell formation occurs. This is the initial pathological process in atherogenesis and therefore responsible for IBD. This, we can say cascade system including extremly complex changes is responsible for atherosclerosis, which also leads to IBD – the most severe and final atherosclerotic brain complication. The main event in this system is the change in hemorrheologic mechanisms, primarily because we are dealing with the factors influencing cerebral microcirculation (1–2, 8–27).

Investigating these changes, we can get an insight in fine molecular changes at the level of ionic currents in ischemic tissue. Coagulation-anticoagulation system represents the dynamic balance allowing liquid blood state by cascade processes.

Apart from these facts, there is also an intensive lipid peroxidation in atherosclerotic lesions, reduction of prostacyclin production, increase in free radicals formation, during aging there is an increase of fibrinogen, antiplasmin, reduction of free heparin, increase in circulating catecholamines with altered reaction to stress. Actually all these factors are favorable for IBD development (1–3, 16–27).

On the other hand these processes make a disequilibrium in coagulation-anticoagulation system. Physiopathologically, increased thrombocyte activity is the earliest phase of atherogenesis in endothelial dysfunction.

So far, the significance of changes in coagulation-anticoagulation system in patients with IBD is not completely explained. Based on these facts we have established the following hypothesis:

1. In patients with acute IBD exist significant changes of coagulation-anticoagulation system;

These changes are in positive correlation with concentration of Lp(a) and severity of ischemic brain disease.

Methods

The study comprised 60 patients who were hospitalized in our clinic due to transient ischemic attack (TIA), reversible ischemic attack (RIA) and brain infarction (BI). Control group comprised 30 patients without symptoms and signs of atherosclerosis, immunologic, inflammatory, hematologic and malignant diseases.

Upon the check-up, in each patient we have determined the degree of neurologic (Canadian neurological scale) and functional deficiency (Bartel's daily activity scale).

Blood samples for determination of parameters of coagulation and anticoagulation activity (activated partial thromboplastin time-a PTT), euglobulin test, platelet aggregation, antithrombin III, fibrin degradation products, D-dimer, PAI-1, protein C and S, factor VII and VIII) and Lp(a) were taken from all patients with IBD and control group immediately after the admission or at least 72 hours after the clinical picture was revealed.

Between the third and tenth day after the onset of the disease, computerized brain tomography (CT) or magnetic resonance imaging (MRI) were performed and localization and size of ischemic lesion were determined.

After the acute phase, upon the neurologic examination and degree of functional recovery, as well as neuroradiologic findings, we have determined the degree of ischemic brain disease using Grotta scale (28) and analyzed the correlation of changes in coagulation-anticoagulation system with the changes in concentration of Lp(a) and severity of IBD. All patients with IBD received the same therapy. Results were analyzed using Student's test, biserial correlation, and linear regression analysis.

Coagulation-anticoagulation parameters were analyzed by the same analyst using Dade Behring reagens and Behring Coagulation Apparature. Only for D-dimer we used reagens from Boehringer Manheim and Diagnostica Stago.

Results

After the scoring of IBD severity we analyzed the correlation between all paremeters of hemostatic system and concentration of Lp(a). Patients in control group were almost 5 years younger than the patients with IBD, but due to the high standard deviation this was not significant.

No significant differences of general characteristics were found between the observed groups (Table 1).

Table 1

General characteristics of patients with IBD and control groups

	Sex		Age	Patients
	Male	Female	$\bar{x} \pm SD$	
IBD	39	21	64.56 ± 7.11	60
CD	19	11	59.98 ± 6.96	30

Significance of the association of changes in hemostatic factors, and concentration of Lp(a) in all examinees is presented in Tables 2, 3 and 4 and in Figures 1, 2 and 3.

2. Highly negative correlation was established between antitrombin III and Lp(a) ($p<0.001$), negative correlation between Lp(a), platelet aggregation ($p<0.01$), and protein C ($p<0.05$), respectively.

Table 2

Hemostatic factors (IBD and control groups)

Hemostatic factors	IBD			CG		
	$\bar{x}$	±	SD	$\bar{x}$	±	SD
PAI-1	4.45	±	1.23^{***}	2.68	±	1.22^{***}
D-dimer	3.30	±	1.34^{***}	1.79	±	1.35^{***}
AT III	0.84	±	0.098^{*}	1.19	±	0.11^{*}
F VIII	1.39	±	0.12^{*}	0.98	±	0.13^{*}
Plat. agg.	7.89	±	1.45^{*}	8.96	±	1.78^{*}
Protein C	0.87	±	0.08^{**}	1.39	±	0.09^{***}

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$

Table 3

Relationship of the concentration of Lp(a) between IBD and control groups

	Significance of correlation
TIA	p=0.032 r=0.376
RIA	p<0.0087 r=0.401
BI-M	p<0.00034 r=0.523
BI-S	p<0.00023 r=0.554

TIA-transient ischemic attack; RIA-reversible ischemic attack; BI-M – brain infarction-moderate; BI-S – brain infarction-severe

Table 4

Relationship between concentration of Lp(a) and severity of IBD (linear regression analysis)

	Significance of correlation
IBD-total	p<0.05; r=0.396
TIA	p=0.67; r=0.265
RIA	p<0.05; r=0.387
BI-M	p<0.05; r=0.399
BI-S	p<0.01; r=0.414

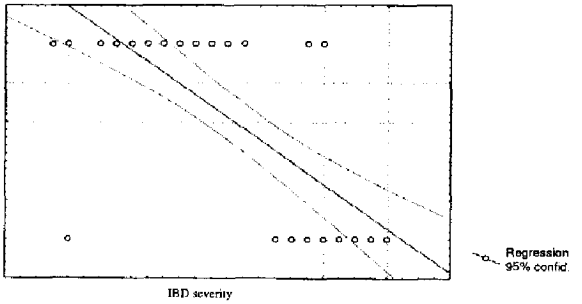

Fig. 1 – Correlation of Lp (a) and IBD severity

1. Highly positive correlation was established between PAI-1 and Lp(a) ($p<0.001$), positive correlation between Lp(a) and D-dimer ($p<0.01$) and border-line positive correlation between Lp(a) and F VIII ($p=0.059$);

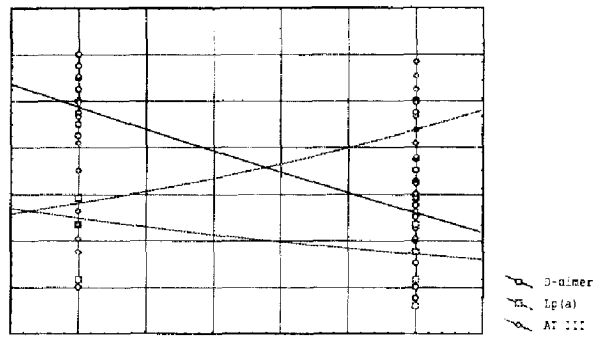

Fig. 2 – Relationship of Lp(a), AT III and D-dimer

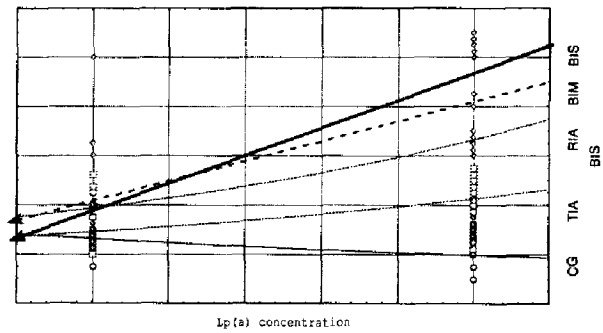

Fig. 3 – Relationship of Lp(a) – CG–TIA and BIS

Discussion

Vascular brain diseases are ranked the third as the cause of morbidity and mortality in most countries independently of medical technological progress and socioeconomic status. IBD is represented in 80% of cases (1, 2).

Primary disorder responsible for the development of IBD is the atherosclerosis of cerebral arteries. There are several hereditory and habitual factors influencing the progression of this process. Since etiopathogenesis of atherosclerosis is still unclear, this study deals with the actual processes leading to atherosclerotic cerebral changes, especially with hemorrheologic and coagulation disorders (1–15).

Etiology and pathogenesis of cerebral atherosclerosis and atherosclerosis in general are still not clearly defined. On the other hand, numerous epidemiologic studies enabled the identification of multiple factors, which contributed to the development of atherosclerosis and scale of their importance was established. These factors are known as atherosclerotic risk factors (1–3): arterial hypertension, dyslipoproteinemia, diabetes and smoking. Smoking on the other hand is not frequently associated with IBD.

In the most recent studies was shown that functional characteristics of endothelial cells probably have the most important role in atherogenic effects (1–3, 29–34).

According to the obtainable literature data the leading physiopathological events in cerebral atherosclerosis are the disorders of lipids and their interaction with functional and structural integrity of endothelial cells in arterial wall (1–3, 31–46).

Degree of lipoprotein influx into arterial wall is the product of lipoprotein concentration in plasma and degree of permeability of arterial endothelium. Lipoprotein influx is in linear correlation with lipoprotein plasma concentration, while permeability of arterial endothelium is individually variabile (1–3, 29–46).

Important determinants are: size of lipoprotein particle and integrity of endothelial surface. Mechanical trauma, immunological lesion and chemical trauma (smoking) are the factors influencing these determinants (31–46).

According to recent studies, increased Lp(a) plasma concentration and low A1 (apo A1) and apo B are the most intensive atherogenic factors for the development of cerebral atherosclerosis as well as IBD as its most serious complications (1–3, 47–54).

Oxidative hypothesis could be one of the explanations. Under the influence of reactive oxidative products and enzymatic processes, oxidation of LDL and Lp(a) occurs, which results in modification of apo B 100. The consequence is uncontrolled monocyte/macrophage intake of LDL in which LDL degradation and cholesterol deposition occurs with formation of foamy cells leading to initiation of atherogenesis (1–3, 47–54).

This, we can say cascade system including extremly complex changes, is responsible for atherosclerosis, which also leads to IBD, the most severe and final atherosclerotic brain complication. The main event in this system is the change in hemorrheologic mechanisms, primarly because we are dealing with the factors influencing cerebral microcirculation (1–3, 47–69).

Investigating these changes, we can get an insight in fine molecular changes at the level of ionic currents in ischemic tissue. Coagulation-anticoagulation system represents the dynamic balance allowing liquid blood state by cascade processes.

It is important to understand that during endothelial dysfunction as a factor in development of atherosclerosis, three main components influencing platelet activation are released: platelet activation factor (PAF), thrombin and collagen contact. Further more, platelet factor 3 representing thrombocinase, which can initiate coagulation process is released. Thus, thrombosis is a complex interaction between platelet activation and coagulation cascade with endothelial dysfunction as the inittial trigger (1–3, 31–46).

Dynamic balance of these processes which creates liquid state of the blood is the role of anticoagulation system including antithrombin III, protein C and S, as well as fibrinolytic system (31–46).

Hypercoagulabile state is defined as a state in which changes of coagulation, platelet activity and anticoagulation mechanisms favour thrombogenesis.

These processes lead to the activation of hemostatic system. Activated platelets release platelet factor 3 (active thrombocinase), which activates Hageman's factor. This process leads to the formation of thrombin, a strong platelet activator.

In addition, if fibrinolytic failure is present, there is no possibility to remove microthrombotic layers in endothelial lesions. The consequence is endothelial proliferation (1–2, 60–75).

Lipoprotein (a) has an important role in hemostatic dysfunction. Lp(a) is composed of LDL connected to specific apo disulphide bonds. It has high affinity for scavanger macrophage receptors and there is a close correlation between its plasma concentration and deposition in atherosclerotic lesions, more expressed then for apo B (1–3, 31, 76–90).

Apo a is structurally similar to plasminogen and the consequence is competitive effect against the same substrate with reduction of plasmin production (1–3, 85–99).

Considering the microcirculation, human brain has specific autoregulatory mechanisms of hemostatic system. On the other hand, this system is not completely independent on the changes in hemostatic system in systemic circulation (1–3, 85–101).

In states leading to the development of IBD of atherothrombotic etiology, there are conditions for disorders of hemostatic system with predomination of procoagulation mechanisms (1–3).

In this study, we have begun with the fact that physiopathology of atherosclerosis and IBD, respectively, cannot be assesed according to individual disorders responsible for its evolution. The aim was to point out the significance of chain-cascade reaction. Our idea was to show the significance of laboratory findings, especially because they represented relatively easy and economic methods.

We have registered high concentrations of D-dimer, which is a sensitive marker for active coagulation and PAI-1 as a marker for the activated inhibition of fibrinolysis.

This correlation is the most important in patients with IBD ($p<0.001$) for both parameters. Besides we have registered positive correlation for rapid platelet aggregation, as well as for low concentrations of antithrombin III.

These results point that these parameters in acute phase of IBD, especially in the few first days, influence the increased activation of plasma coagulation factors.

In the acute phase, conditions for pro-coagulation were created, which was shown in our results. Also, it is important to mention that these changes are in the significant correlation with the increased concentration of Lp(a) and severity of IBD.

Conclusion

There is a significant increase in the concentration of pro-coagulant factors in patients with IBD.

Also, comparing the observed parameters using the linear regression analysis we have found significant correlation between changes in hemostatic system (procoagulant factors) and increased concentration of Lp(a) and severity of IBD.

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Апстракт

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ПОВЕЗАНОСТ КОНЦЕНТРАЦИЈА Lp(a) СА ПРОМЈЕНАМА У ХЕМОСТАЗНОМ СИСТЕМУ И СТЕПЕНОМ ТЕЖИНЕ ИСХЕМИЈСКЕ БОЛЕСТИ МОЗГА

Васкуларне болести мозга су на трећем месту по морталитету и морбидитету независно од напретка у дијагностичким, терапијским и превентивним процедурама. Исхемијска болест мозга представља болест са највећом учесталошћу међу васкуларним болестима мозга и представља најтежи и посљедњи стадијум церебралне атеросклерозе. Етиопатогенеза атеросклерозе још није довољно јасна али је најприхватљивија хипотеза да липидна пероксидација има у томе најзначајнију улогу. Срж ове хипотезе представљена је чињеницом да оксидативна модификација LDL и Lp(a) укључује бројне патофизиолошке факторе са централном улогом реактивних оксидативних материја уз дисфункцију ендотела као централног поремећаја што води поремећају коагулационог система. Полазећи од овога, формулисали смо хипотезу да код болесника са исхемијском болешћу мозга постоје промјене у хемостазном систему које су у позитивној корелацији са концентрацијом Lp(a) и степеном тежине исхемијске болести мозга (ИБМ). Испитивањем је обухваћено 60 болесника са акутном исхемијском болешћу мозга, и 30 болесника (контролна група) са неваскуларном генезом обољења сличних општих карактеристика. Ми смо испитивали корелацију промјена у хемостазном систему (агрегација тромбоцита, антитромбин три, D-димер, протеина C и S, фактори 7 и 8 и инхибитор-1 активатора плазминогена (*plasminogen activator inhibitor-1*) (PAI-1) у односу на степен тежине ИБМ и промјене у концентрацијама Lp(a) у испитиваним групама. Резултати су показали да код болесника са ИБМ постоји значајан пораст прокоагулантних фактора. Такође, постоји значајно изражена позитивна корелација између пораста ових фактора и повећаних концентрација Lp(a).

Key words: **mozak, ishemija; lipoprotein(a); ateroskleroza; aa. cerebri; mozak, prolazna ishemija; mozak, infarkt; hemostaza; krv, poremećaji koagulacije.**